STUDIES IN DEFICIENCY DISEASE

Sir Robert McCarrison, M. D.

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STUDIES IN DEFICIENCY DISEASE

BY

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PREFACE

THE aim of this book is to present the reader with a consecutive account of the results of recent experimental researches into the nature of Deficiency Diseases, and to point out the application of these results to their prevention. The subject is one which, as I shall hope to show, concerns both the administrator and the practitioner of medicine.

My own investigations, on which this book is mainly based, were originally undertaken in 1914, at a time when I was engaged in a study of the thyroid gland and its disorders. My object then was to ascertain the effects of deficient food on this organ. These studies were interrupted at the outbreak of war, and it was not until my return to India from active service, early in 1918, that I was able to resume them. The scope of the inquiry was then extended to include an investigation of the effects of deficient and ill-balanced foods on all other organs of the body. It was hoped that, in the course of such an inquiry, facts might emerge which would not only explain some of the manifestations of deficiency disease, but throw light also on problems relating to the place of the endocrine glands in the human economy. The methods of study adopted were experimental, gravimetric, and histo-pathological; the last being held to be of especial importance. For however necessary a knowledge of the normal structure and function of the organs of the body may be, it is not less necessary to possess a knowledge of the structural and functional changes induced in them by so fundamental a factor as faulty food. I have thus approached the study of Deficiency Disease from an aspect differing somewhat from that of other students of this subject whose object, as a rule, has been the induction in animals, by means of specially-devised food mixtures, of such maladies as scurvy, beri-beri, rickets, and pellagra. My own method, on the other hand, has been to observe the more general symptomatic and pathological effects of faulty food on the animal body as a whole, and thereby to ascertain what forms of human illness might reasonably be attributed to it. In this way I have been brought to the conclusion that much of the gastro-intestinal disorder so common at the present day, and much of the endocrine disorder probably almost equally common, though less readily recognizable, are attributable to deficient and ill-balanced food.

The results reached in the course of my investigations have for the most part been published, during the years 1919 and 1920, in the *Indian Journal of Medical Research*, in a series of articles under the general title of " The Pathogenesis of

Deficiency Disease"; but certain observations relating to the adrenal glands and malnutritional œdemas have been communicated to the Royal Society. Abstracts of some of these papers appeared from time to time in the *British Medical Journal*, but the original papers are not readily accessible except to those having the facilities afforded by a large medical library. For this reason, and because there was considerable overlapping in the subject-matter of the papers as they originally appeared, I have taken the opportunity afforded by a period of leave to reconstruct them so that the results might be presented in a consecutive and more accessible form. Other and more cogent considerations, however, prompted me to undertake the task: the desire to reconsider the whole of my work after a period of absence from it, and the necessity of studying the recent literature of the subject (not available for reference in India during the progress of the investigations themselves) in order to collate my results with those of others, in the hope that in this way a just estimate might be made of their utility in practical medicine.

The book is divided into four parts. In the first the objects and scope of my inquiry are set out and the experimental methods used are described; in this part is given also a brief summary,[1] prepared from the literature, of the present state of knowledge of vitamins. The second part deals with the various factors which influence the onset of symptoms and with the symptoms themselves. The third relates to the morbid anatomical effects of faulty food and to special pathology. In the fourth an attempt has been made to indicate some of the more obvious practical applications of the results reached in the laboratory to the prevention and cure of disease.

Throughout the progress of my investigations, and during the preparation of this volume, I have been assisted by my wife, who has been untiring in her perusal of the literature, in search of matter relating to the investigations themselves and to their bearing on practical medicine. To the Hon. Major-General W. R. Edwards, C.B., C.M.G., Director-General, Indian Medical Service, I am indebted both for the opportunity to carry out the work and for the help and encouragement he has at all times afforded me. My thanks are also due to the Council, Royal Society, for permission to reproduce Fig. 74, and to the Governing Body, Indian Research Fund Association, under whose auspices my investigations were conducted, for their ready response to the demands I have made upon them and for permission to use some eighty of the illustrations which originally appeared in papers published in their official *Journal*. To Sir Dawson Williams I am indebted for reading my manuscript and for much helpful criticism.

R. McCarrison.

Oxford,
15*th March*, 1921.

[1] In this summary it has not been possible to take account of publications later than February 15, 1921.

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PART I

INTRODUCTION—VITAMINS—EXPERIMENTS

CHAPTER I

INTRODUCTION

CUSTOM has sanctioned the application of the term " deficiency disease " to a group of maladies the chief causal factor of which is deficiency in the food of certain substances, named " accessory food factors " by Gowland Hopkins, their discoverer. These substances are also spoken of as " growth determinants," " food hormones," " exogenous hormones," " advitants," or more commonly " vitamines " : the last term was applied to them by Casimir Funk. Neither the term " deficiency disease " nor " vitamine " is free from objection. The former is too restricted in its application, and should embrace disorders due to faulty and ill-balanced food deficient, either in quantity or quality, in any essential food requisite ; the term is used in this sense in this volume. " Vitamine " is a misnomer, since there is no evidence that accessory food factors are amines ; but as the word is in general use it is adhered to in this monograph. Following a suggestion made by Drummond,[1] that " the final ' e ' of ' vitamine ' be dropped, so that the resulting word ' vitamin ' may conform with the standard scheme of nomenclature adopted by the Chemical Society, which permits a neutral substance of undefined chemical composition to bear a name ending in ' in,' " accessory food factors will here be referred to as " vitamins." The word has been so spelt in certain American medical journals for some years past. For my own part, I should prefer to see the adoption of some such non-committal term as that suggested by Professor H. E. Armstrong, F.R.S., viz. " advitant," indicating simply that the substance is necessary to life.

The object of my studies has been twofold : first, to find out how the body goes sick in consequence of deficient and ill-balanced food ; and, second, to deduce therefrom what forms of sickness in the human subject may reasonably be attributed to, or connected in their origin with, such foods. It was recognized early in the course of these studies that deficient foods are in practice usually ill-balanced foods, and that the effects of avitaminosis are bound up with mal-adjustments both in quality and quantity of other essential requisites of the food. The method of investigation adopted was, therefore, to study the effects of vitamin deficiency in association with other food faults which may accompany it. It is rare that the food of human beings is totally devoid of any one vitamin ; it is more usual for the deficiency to be partial, and for more than one vitamin

[1] *Biochem. Jour.*, 1920 (Oct.), XIV, No. 5, p. 660.

to be partially deficient; it is more usual still for partial deficiency of vitamins to be associated with deficiency of suitable protein and inorganic salts and with an excessive richness of the food in carbohydrates. Consequently, the manifestations of disease resulting from the faulty food are compounded of the several effects of varying degrees of avitaminosis on the one hand, and of ill-balance of the food on the other. Nor is this all, for pathogenic organisms present in the body, during the period of its subjection to the faulty food, contribute their share to the general morbid result. For instance, a diet deficient in vitamins and disproportionately rich in starch leads to depression of digestive and gastro-intestinal function. If, then, these organs are exposed at the same time to the action of pathogenic micro-organisms, their depression, which is at first functional, may become accentuated or fixed by organic changes due to the pathogenic agent. Further, under conditions of food deficiency, the presence in the bowel—let us say—of such agents may determine the character of the morbid states initiated by the food deficiency, and even impart to them endemic or epidemic characters. In these circumstances the etiological significance of the underlying food defects, which have permitted the unhampered action of the pathogenic agent, may be obscured. Experiences illustrating these points are given in succeeding chapters, but it cannot be too strongly emphasized that many of the infectious scourges to which human beings are subject—such, for example, as infantile diarrhœa and tuberculosis—require consideration as much from this point of view as from that of the pathogenic organism to which they are due.

Other factors also, such as age, sex, individual idiosyncrasy, rate of metabolism, fatigue, cold, insanitary surroundings, overcrowding, the varying susceptibilities of different individuals, of different organs, and of the same organs in different individuals, all play a determining part in the production of the morbid result of food deficiency.

So it is that in practice the manifestations of deficiency disease are influenced by a number of factors apart from the actual food fault. It may be expected, therefore, that wide variations in the incidence, the time of onset, and the character of the symptoms will occur in human beings in whom the dietetic fault has been to all appearances the same.

My investigations have so far been concerned with this wider aspect of the effects of food deficiency. For I have thought it well to make a general survey of this largely unexplored territory of disease before attempting more detailed studies. Indeed, however important it is to be in a position to compare the effects of different food deficiencies in order to learn what is peculiar to any one, it is, in the present state of knowledge, of still greater importance to be aware of the extent and variety of the morbid change to which food deficiency in general may give rise, since this knowledge can at once be applied in practice. For whether these changes are the result of a peculiar deficiency or of several, they are amenable to the same remedy; the provision of a well-balanced food of good biological value and rich in vitamins of every class.

It is to this variety of morbid change that I desire to draw attention in this

monograph, since it seems to me to impart to the term " deficiency disease " a wider significance than has been attached to it hitherto. It is a curious fact that the nomenclature of vitamins has been responsible, in considerable measure, for the narrowness of outlook with regard to diseases which are either favoured in their origin or initiated by an insufficient supply of these substances. We speak, for instance, of " anti-neuritic " or " anti-beri-beri " vitamin, thus directing attention to one system of the body and to one disease syndrome while ignoring others. The effects on the nervous system of a dietary devoid of vitamins and disproportionately rich in starch, as observed in animals, have thus often been emphasized to the almost complete exclusion of other equally important, if less prominent, symptoms. Long before nervous symptoms supervene, others, such as loss of appetite, impaired digestion, diarrhœa, colitis, unhealthy skin, low temperature, slow respiration, cardio-vascular depression, progressive anæmia, and asthenia result from the deficient and ill-balanced food. Do not these form a disease syndrome which is, in children especially, as familiar as its cause is unrecognized? It is to my mind with these earlier evidences of disease—with these beginnings of morbidity—that we as physicians are mainly concerned in practice. It will be shown in the course of this book that such evidences of disease as those I have just recounted manifest themselves as certainly when partial deficiency is protracted over long periods as when more extreme deficiency is experienced over shorter periods. It is no doubt of great importance to be aware that food deficient in certain vitamins will ultimately cause nervous symptoms of a definite order. But since these are end-results, it is of still greater importance to realize that the same faulty food will give rise more early to gastro-intestinal disturbance and other forms of vague ill-health, and that these, like the nervous symptoms, can be prevented by supplying the necessary vitamins and adjusting the balance of the food.

Another matter of importance concerns us here: it is often stated that vitamins are so widely distributed amongst naturally occurring foodstuffs that the variety of foods consumed by European peoples protects them—in times of peace—from risk of any deficiency in these essential substances. If vitamins be considered solely from the point of view of the grosser manifestations of disease—beri-beri, keratomalacia, and scurvy—to which their want gives rise, then this statement is to a great extent true. But is it wholly true? Is not scurvy a common disorder of infants, and is it always recognized as such? [1] Is rickets rare? Are the forms of peripheral neuritis of undetermined cause so uncommon that without their study the food factor can be excluded as a possible cause of some of them? May it not be that, because we do not seek for alimentary neuritis, we do not find it? Pellagra has seemed to spread rapidly in America since 1902.[2] But is this due to comparatively sudden alterations in the dietetic habits of the people, or to more accurate diagnosis and the recognition of minor manifestations of this malady consequent on the increasing knowledge of the nutritional factor in its

[1] Comby, J., *Press Médicale*, 1918 (Sept. 19), XXVI, No. 37, p. 480.
[2] Roberts, S. R., *Jour. Am. Med. Assoc.*, 1920 (July 3), LXXV, No. 1, p. 21.

production? Is this disease, in its varying manifestations, as uncommon in the British Isles as is generally assumed? We know nothing of its true incidence, since the health of the people has not been considered in regard to it. But, apart from the incompleteness of knowledge as to the prevalence of the grosser evidences of deficiency disease in this country, are there no lesser manifestations due to the supply of vitamins and of suitable protein and salts in quantities insufficient for the needs of the body?

The statement above referred to might be true, also, were it a fact that Europeans invariably used naturally occurring foodstuffs in quantities sufficient for their needs. But do they? Is it not common knowledge that, disregarding nature's plan, the modern tendency is to rear infants artificially—on boiled or pasteurized milk and proprietary foods, which are all of them vastly inferior to mother's milk in substances essential to the well-being of the child—inferior not only in vitamins, but in thyroid derivatives and other essentials? Again, is not cow's milk—an important dietary constituent of young and old alike—gradually becoming a luxury reserved for the few? Vegetable margarines are replacing butter even among the richer classes. Fresh fruit is a comparative rarity, even on the tables of the rich. Green vegetables are scanty, and such as there are are often cooked to the point of almost complete extraction of their vitamin-content and salts. White bread has largely replaced wholemeal bread, and it is notorious that bread forms a high proportion of the dietaries of persons of limited means. It is notable that, despite the food restrictions imposed upon the people of Belgium during the late war, the infant mortality and infantile diarrhœa decreased greatly—a circumstance which was due to the organized propaganda encouraging mothers to nurse their infants, and to the establishment of national canteens which provided prospective mothers from the fifth month of pregnancy onwards with eggs, meat, milk, and vegetables.[1] Again, fresh eggs are so expensive as to debar the struggling masses from their use. Meat is at best but poor in vitamins, and its value in these essentials is not enhanced by freezing and thawing. Sugar is consumed in quantities unheard of a century ago, and sugar is devoid of vitamins which the cane juice originally contained.[2] The use of stale foods, involving the introduction of factors incidental to putrefaction, is the rule, that of fresh foods the exception. Can it, then, truly be said that the variety of natural foodstuffs consumed by Europeans protects them from any deficiency of vitamins? My own clinical experience justifies no such belief; rather does it point in the contrary direction. Nor does it appear to be the experience of the compilers of the *38th Report of the Medical Research Council*,[3] who write: "From a consideration of dietaries consumed by the poorer classes in the towns of this country, one is led to suggest that no inconsiderable proportion of the population is existing on a food-supply more

[1] Demoor and Slosse, *Bull. l'Acad. Roy. de Méd. de Belgique*, 1920: "L'alimentation des Belges pendant la guerre."

[2] Osborne, T. B., *New York State Jour. Med.*, 1920 (July), p. 209.

[3] *Report on the Present Position of Knowledge concerning Accessory Food Factors (Vitamins)*, Medical Research Committee, London, 1919.

or less deficient in fat-soluble factor"—deficient, that is to say, in a vitamin one of whose cardinal functions is to maintain the natural resistance of the subject against infections. Neither is it the experience of Osborne,[1] who asserts that a large part of the food eaten by civilized people has been deprived of vitamin B by "improvements" in manufacture; nor of Hess,[2] who emphasizes that latent and subacute forms of scurvy are common disorders of infancy. But the frequency with which deficient and ill-balanced foods are used is most apparent when the dietetic habits of persons in subnormal health are considered. It will surprise those who study them to find how many there are, of capricious appetite, who habitually make use of foods sometimes deficient in calories—for it is not the food presented to the subject that counts, but the food eaten and assimilated—and often dangerously deficient in one or more vitamins, in protein of good biological value, and disproportionately rich in starch or sugar or fats, or in all three. Infants fed on many of the proprietary foods in common use come within the category of the deficiently-fed, unless deficiencies are made good. The food of young children is commonly low in vitamin-content and suitable protein, while it is frequently disproportionately rich in starch and sugar—a circumstance which enhances the danger of vitamin-deficiency. It may, indeed, be accepted as an axiom that the vitamin-value of a child's food is reduced in proportion to its excessive richness in carbohydrates. But the ranks of the deficiently-fed do not include only infants and young children; they include also those whose food is composed mainly of white bread, margarine, tea, sugar, and jam, with a minimum of meat, milk, eggs, and fresh vegetables. Even amongst those whose diet is more perfectly balanced, the commoner articles of food, as they are prepared for the table, are so low in vitamin-value that, unless they are enriched with a sufficiency of natural foods in the raw state, they are prone to cause ill-health, and especially gastro-intestinal ill-health. Such is my experience in India, where this European patient "cannot digest vegetables or fruit," and never touches them "as they carry infection," or that one "suffers so from indigestion" that he or she lives chiefly on custards and milk puddings; where milk is, of necessity, boiled and reboiled until as a carrier of vitamins it is almost useless; where meat is made tender by the simple device of boiling it first and roasting it afterwards; where every third or fourth European child has mucous disease, the direct outcome of bad feeding. So it is that the forms of food which such as these so commonly adopt are those most calculated to promote the very disorder from which they seek relief. Access to abundance of food does not necessarily protect from the effects of food deficiency, since a number of factors—prejudice, penury, ignorance, habit—often prevent the proper use and choice of health-giving foods. Who in the ranks of practising physicians is not familiar, among the well-to-do classes, with the spoilt child of pale, pasty complexion and unhealthy appetite, of sluggish bowel, and often with mucous stools or enuresis, who, deprived of the wholesome

[1] Osborne, T. B., *New York State Jour. Med.*, 1920 (July), p. 209.
[2] Hess, A. F., *Scurvy Past and Present*, Philadelphia, 1920.

ingredients of a well-balanced natural food, craves for sweetmeats, chocolates, pastries, and other dainties as devoid of natural health-giving properties as their excessive use is common? Constantly one encounters the anxious mother of the "highly-strung," "nervous" child "of delicate digestion," whose ignorance of essential principles of feeding is only excelled by her desire to do what is best for her offspring; who, guided by the child's preferences, supplies the means to convert it into a static, constipated, unhealthy-skinned adolescent, equipped with digestive and endocrine systems wholly unfitted to sustain the continued exercise of healthy function. Here it is that overfeeding joins with underfeeding and vitamin-insufficiency in swelling the C_3 ranks of the nation. Or, again, who is not familiar with the overworked anæmic girl, static and with visceroptosis, acne or seborrhœa, and oftentimes with vague psychoses, who ekes out a paltry wage for teaching, sewing, or selling, satisfying the cravings of her tissues principally with white bread, margarine, and tea? Or with the languid lady, devoid of healthful occupation, who, living in the midst of plenty, deprives herself, for some imaginary reason, of substances essential to her well-being? Or with the harassed mother of children, oppressed with the constant struggle to make ends meet, stinting herself that others may not want, exhausted by childbearing and suckling, worry, and too little of the right food? What wonder that such a woman is dyspeptic, and that "every bite" she eats "turns on her stomach." Some there are, living in luxury, whom ignorance or fancy debars from choosing their food aright; others for whom poverty combines with ignorance to place an impassable barrier in the way of discriminating choice. It is for us so to instruct ourselves that we may instruct such as these, and use our newer knowledge to the end that customs and prejudices may be broken and a more adequate dietary secured for those under our care. I do not doubt that, if the practice I now follow of estimating the vitamin-value and qualitative balance of the food in every case that comes before me is followed by others, they will be impressed as I am with the vast importance of the food factor in the causation of disease.

In this connexion reference may be made to the experiences of the Danes during the late war, as narrated by Hindhede.[1] When, as was the lot of other countries, the food-supply of Denmark had to be conserved, and rationing was strict, it was considered that to feed cattle and swine with cereals and potatoes that might be used for human consumption was wasteful, since it meant a loss of approximately 80 per cent. in the nutritional value of the foods as compared with the yield in the flesh of animals. For this reason the potatoes and grain were reserved for the use of the people, and the stock of cattle and swine was reduced. The cereals and potatoes were taken "from the distillers, so that they could not make brandy, and one-half of the cereals from the brewers, so that the beer output was reduced one-half." The people received a sufficiency of potatoes, whole rye bread—containing wheat bran and 24 per cent. of barley-meal—barley porridge, grains, milk, abundance of green vegetables, and some

[1] *Jour. Am. Med. Assoc.*, 1920 (Feb. 7), LXXIV, No. 6, p. 381.

butter. In consequence of this enforced alteration in the dietetic habits of the Danish people, the death-rate dropped as much as 34 per cent., being as low as 10·4 per cent. when the regime had been in force for one year. Hindhede, therefore, concludes that " the principal cause of death lies in food and drink " ; and few will be disposed to doubt the justice of his contention in the face of an experiment so unequivocal. My own experience provides an example of a race, unsurpassed in perfection of physique and in freedom from disease in general, whose sole food consists to this day of grains, vegetables, and fruits, with a certain amount of milk and butter, and goat's meat only on feast days. I refer to the people of the State of Hunza, situated in the extreme northernmost point of India. So limited is the land available for cultivation that they can keep little livestock other than goats, which browse on the hills, while the food-supply is so restricted that the people, as a rule, do not keep dogs. They have, in addition to grains—wheat, barley, and maize—an abundant crop of apricots. These they dry in the sun and use very largely in their food. Amongst these people the span of life is extraordinarily long ; and such service as I was able to render them during some seven years spent in their midst was confined chiefly to the treatment of accidental lesions, the removal of senile cataract, plastic operations for granular eyelids, or the treatment of maladies wholly unconnected with food-supply. Appendicitis, so common in Europe, was unknown. When the severe nature of the winter in that part of the Himalayas is considered, and the fact that their housing accommodation and conservancy arrangements are of the most primitive, it becomes obvious that the enforced restriction to the unsophisticated foodstuffs of nature is compatible with long life, continued vigour, and perfect physique.

Although no statistics are available in this country as to the precise influence of malnutrition in contributing to the low standard of physique revealed during the later years of the war, there can be no doubt that the food factor is connected with it. In America during the years 1917–18 it was estimated that about 30 per cent. of the school-children were suffering from malnutrition.[1] This condition was not always limited to the poor, but was found to a certain extent among all classes. Chapin[2] remarks with regard to it that " the malnutrition was due to a failure in the proper selection and preparation of food materials in addition to poverty."

With increasing knowledge of nutritional problems, it has become apparent that our dietetic habits need remodelling, and that education of the people as to what to eat and why they eat it is urgently necessary. It is clear that green vegetables, milk, and eggs should form a far higher proportion of the food of the nation than is now customary. So far from curtailing the beneficent scheme whereby portions of land were made available to town-dwellers during the war for cultivation by allotment-holders, this scheme should be extended and facilities given to allotment-holders for the keeping of fowls. Municipalities and other public bodies should concentrate on the provision of an abundance of milk,

[1] Manny, F. A., *Jour. Am. Med. Assoc.*, 1918 (April 27), LXX, No. 17, p. 1257.
[2] *Jour. Am. Med. Assoc.*, 1920 (Aug. 7), p. 364.

eggs, and vegetables, for there is no measure that could be devised for improving the health and well-being of the people at the present time that surpasses this either in excellence or in urgency.

The experimental, symptomatic, and morbid anatomical evidence which I have now to bring forward will, I hope, aid a clearer comprehension of the manifestations of deficiency disease, using the term in its widest sense, both as regards their grosser and their lesser evidences. Especially do I direct attention to the effects of food deficiency on the digestive organs and on those endocrine organs concerned in the regulation of metabolic processes. These effects provide the pathological basis for attaching to food deficiencies a prominent etiological significance in regard to that great mass of ill-defined gastro-intestinal disorders and vague ill-health which throngs clinics at the present day, and concerning which we have hitherto known little or nothing.

It is necessary to emphasize that the problems of nutrition must not be viewed from a too " vitaminic " outlook. Vitamins have their place in nutrition : it is that of one link in a chain of essential substances requisite for the harmonious regulation of the chemical processes of healthy cellular action.

Before proceeding to a consideration of the experimental and other data on which these generalizations are based, it may be useful to give a brief summary of knowledge regarding vitamins, excluding all historical and experimental detail which is available from other sources.[1]

[1] *Report on the Present Position of Knowledge concerning Accessory Food Factors (Vitamins)*, Medical Research Committee, London, 1919.

CHAPTER II

VITAMINS

VITAMINS are not foods in the sense of tissue-builders or producers of energy: they have not been isolated, and their nature and composition are unknown. What is known of them has been learned from feeding experiments on animals. Two are essential to growth and maintenance; the third is necessary for normal nutrition and the prevention of scurvy. A properly constituted food must contain them in small but definite quantity and quality which vary with age, sex, species, and individual idiosyncrasy. Without vitamins the proximate principles of the food cannot sustain life; they are in a sense "dead" food. The function of vitamins in the animal economy is little understood; some conception of what this function is will emerge from the data to be presented in succeeding chapters, but need not be formulated until these data have been examined.

Vitamins are obtained from the vegetable kingdom. Plants appear to possess the power of synthesizing them, while the animal body does not. Man and animals derive them directly from the plants they eat, or indirectly from the flesh, fats, milk, and eggs of other animals. They are stored in the body in varying quantities and situation. One class is more abundant in cellular organs; a second in fatty tissues; and a third in muscle tissues and liver. Vitamins are present in abundance in the natural foods of man and animals—in young leaves and shoots; in grasses, grains, pulses, vegetables, fruits, tubers, and roots; and in eggs, milk, fresh meat, and animal fats. Like other essential requisites of the food, they exist in different quantity and quality in different foodstuffs, and it is essential to be familiar with their quantitative and qualitative distribution, since the amount of the several vitamins necessary for the maintenance of health is the outstanding feature in our knowledge of prevention and management of morbid states due to their deficiency. But the vitamin-value of food is often too low, owing either to insufficient intake of these natural foodstuffs or to their treatment prior to consumption. This value may be reduced by boiling, cooking, and pasteurization; by storage, oxidation, and decomposition; by subjection to heat or to the action of alkalis; by drying, canning, or other methods of preservation; and by various manufacturing and refining processes. Different classes of vitamins vary in their susceptibility to injury by these influences; and while one influence alone may

not greatly alter a food's total content of vitamin, the combined action of two or more may do so. Vitamins are absent, or comparatively deficient, in the refined foods of the modern food industry (Osborne and Mendel). In short, the degree of departure from the fresh raw natural foodstuffs is the measure of a food's deficiency in total vitamin-value.

Vitamins are of three orders :

1. Anti-neuritic or anti-beriberi vitamins, also called water-soluble B-growth factors,[1] hereinafter called " Vitamin B."
2. Fat-soluble or A-growth factors,[1] hereinafter called " Vitamin A."
3. Water-soluble anti-scorbutic vitamin, hereinafter called " Vitamin C."

The first is a constituent of all cells,[2] and is necessary for growth and maintenance; its absence from the food is an essential cause of beri-beri. The second, also a constituent of all cells,[2] is necessary for the promotion of growth in the young as well as for the maintenance of health in adults; its absence from the food is an essential cause of keratomalacia. The third is a constituent of growing tissues; its absence from the food is an essential cause of scurvy.

VITAMIN B

This vitamin is widely distributed throughout natural foodstuffs. Its richest sources[3] are the germs of seeds, eggs, yeast, wheat and rice bran, peas, beans, lentils, and cellular organs (such as liver, brain, sweetbreads, fish-roe, kidney and heart muscle).[4] Nuts are comparatively rich in it[3]; cow's-milk is less so.[3] Meat (beef and mutton) contain it in comparatively small amounts, and the flesh of fish is poor in it.[3] Vegetables and fruit contain it in larger amount than was formerly supposed.

In Eggs and Seeds the large deposits of this vitamin appear to be reserve stores for the nutrition of the young.[3] In the case of peas, beans, and other pulses, it is distributed throughout the seeds; but in cereals it is concentrated in the germ or embryo, and in the peripheral layers of the seed which are removed in the process of milling.[3] Wheat and rice germ is much richer in this vitamin than is the bran.[3] Germinated pulses or cereals are comparatively rich in it.[3] Soya-bean is of peculiar value because of its content of both growth vitamins and of the high physiological value of its protein. So also are ground-nuts, almonds, walnuts, filberts, Brazil nuts, chestnuts, hickory, and pinenut; the high value of nuts is due as much to the nutritive value of their protein as to their content of vitamin B.[5]

In Animal Tissues this vitamin is comparatively scanty, except in highly cellular organs such as the liver, kidney, brain, sweetbreads, fish-roe, and heart

[1] McCollum and Kennedy, *Jour. Biol. Chem.*, 1916, XXIV. 491.
[2] McCollum, *Newer Knowledge of Nutrition*, New York, 1919.
[3] *38th Rep. Med. Res. Com.*, London, 1919.
[4] Osborne and Mendel, *Jour. Biol. Chem.*, 1918, XXXIV. 17.
[5] Cajori, *Jour. Biol. Chem.*, 1920, XLIII. 583.

muscle. Actively-growing animal tissues do not contain it in appreciable amounts.[1] Desiccated pituitary body, thyroid, thymus, testicle, and ovarian tissues[1] are poor in it; the fresh endocrine organs, however, contain it more abundantly, especially those of most importance in developmental processes.[2]

In Milk this vitamin is present in relatively small amounts, weight for weight, as compared with eggs and seeds: raw cow's-milk, raw skim-milk, dried whole-milk, boiled milk, and sweetened condensed milk all appear to contain it in approximately the same quantity.[3]

Yeast is a valuable source of this vitamin,[3] and has the additional merits of being comparatively rich in protein and of improving the appetite.[4] It may occasionally be substituted for meat in the dietary with advantage. "Marmite" is a convenient form in which to introduce this vitamin into the food.

Fruit is comparatively rich in vitamin B. It is present in bananas, in fresh orange juice, lemon juice, and grape fruit juice. Apples, pears, and prunes also contain it.[5] The potency of fresh orange juice with respect to its content of this vitamin is, volume for volume, comparable with that of cow's-milk.[5] The efficacy of fruit juices, so far as this vitamin is concerned, is not lost by suitable methods of desiccation.[6] The tomato is of peculiar value, since it contains all three vitamins.[7] The value of fruits, therefore, as sources of vitamins ranks high, while their content of organic acids and of indigestible vegetable constituents —gums, waxes, and cellulose-like carbohydrates[8]—gives to them an added value in promoting the excretory processes of the kidney, and in maintaining the functional perfection of the gastro-intestinal tract.

In Vegetables this vitamin is found in cabbage, lettuce, spinach, carrots, and potatoes.[3] Spinach (dried), for instance, is richer in it than whole wheat, soya-bean, dried eggs, meat, milk, or potato.[9] Spinach leaves are also much richer in vitamin A than are most of the products in common use.[9] Osborne and Mendel conclude that "green vegetables supply an important addition to the diet of man, because the staple foods, such as cereals, meat, potatoes, fats, and sugar, probably furnish too small an amount of these vitamins to meet fully the requirements of an adequate dietary."[9] Onions, if they contain it at all, do so in small amount.

This vitamin is absent from polished rice, white flour, cornflour, sago, tapioca, arrowroot, custard powders, egg substitutes, peaflour, butter, cream, purified cod-liver oil, meat extract, distilled and malted liquors,[3] tea and coffee; and is very deficient or wholly lacking in the refined foods of the modern food industry. Its absence from polished rice—the staple food of many Eastern peoples—is

[1] Drummond, *Biochem. Jour.*, 1918, XII. 41.
[2] Swoboda, *Jour. Biol. Chem.*, 1920, XLIV, No. 2, p. 531.
[3] *38th Rep. Med. Res. Com.*, 1919.
[4] Schottelius, *Deutsch. Med. Wochenschr.*, 1915, XLI. 817.
[5] Osborne and Mendel, *Jour. Biol. Chem.*, 1920, XLII. 465.
[6] *Jour. Am. Med. Assoc.*, 1920 (Aug. 7), p. 418.
[7] Osborne and Mendel, *Jour. Biol. Chem.*, 1920, XLI. 454 and 549.
[8] *Jour. Am. Med. Assoc.*, 1920 (Aug. 7), p. 417.
[9] *Jour. Am. Med. Assoc.*, 1919 (April 12), p. 1077; *Proc. Soc. Exp. Biol. and Med.*, 1918, XVI. 15.

an important etiological factor in the causation of beri-beri. Its absence from white flour—the staple food of many Western people—is peculiarly significant. The value of a given foodstuff in this vitamin appears to run parallel with the content of the food in phosphorus. According to Fraser and Stanton,[1] rice containing less than 0·4 per cent. of phosphorus pentoxide is deficient in vitamin. Voegtlin and Myers[2] have found the same to be true of corn and wheat. The phosphorus-content of the soil on which these foods are grown may, therefore, be of considerable importance in determining their vitamin-value.

Properties.—Vitamin B is soluble in water and in alcohol, but not soluble, or but slightly, in ether or other solvents of fats.[3] It is adsorbed from solutions upon the surface of various adsorbents such as animal charcoal, Fuller's earth, and colloidal ferric hydroxide.[3] It is relatively stable and resistant to considerable degrees of heat, being slowly destroyed at 100° C. and much more rapidly at higher temperatures.[3] It is not likely to be much affected, therefore, in the ordinary processes of cooking. The high temperature to which tinned foods are subjected destroys this vitamin in great measure. Its solubility in water renders it liable to be dissolved out in the process of boiling, hence the importance of utilizing the water in which foods are boiled. It is largely destroyed by alkalis,[3] so that when these are present in proprietary foods or are added to milk,[4] or to the water in which foods are boiled, and when they are used for purposes of baking, the vitamin-value of the food is much reduced. If, however, the sodium bicarbonate so commonly used in baking be combined with buttermilk or tartaric acid, the alkali is neutralized and the vitamins are protected.[5]

It is generally believed that the water-soluble vitamin B and the anti-neuritic vitamin are identical. The distribution of both is similar; absence of the one frequently causes symptoms similar to those arising from absence of the other; their solubility appears to be identical; they have the same precipitants and adsorbents; their stability appears to be the same. H. H. Mitchell,[6] in advancing these arguments in favour of their identity, points out that, while they are generally true, there are notable exceptions, such as: (1) Cabbages are rich in the water-soluble but poor in the anti-neuritic vitamin. (2) Lack of anti-neuritic vitamin sometimes causes symptoms (e.g. paralysis) not caused by lack of the other. (3) Solubility in alcohol differs according to the source; while exceptions as to precipitants, adsorbents, and stability are known also. In this volume the two factors are spoken of as vitamin B, and it is emphasized that both gastro-intestinal and nervous symptoms may result from its absence, the former being the earlier manifestations.

The reserve stores of this vitamin in the body appear to be comparatively small[3]; the body is thus very dependent on the food for their adequate supply.

[1] *Studies for the Med. Research Inst. Fed. Malay States*, 1909, No. 10.
[2] *Pub. Health Rep.*, 1918, XXXIII. 647, 843, and 911.
[3] *38th Rep. Med. Res. Com.*, 1919.
[4] McCollum, *The Newer Knowledge of Nutrition*, New York, 1918.
[5] Voegtlin and Myers, *Pub. Health Rep.*, 1916, XXXI. 935.
[6] *Jour. Biol. Chem.*, 1919, XL. 399.

To ensure this supply, the dietary should include wholemeal bread or nuts, eggs, glandular organs, fresh fruit and green vegetables.

VITAMIN A

The primary sources of this vitamin are raw milk, animal fat, egg-yolk, green leaves, and the growing parts of plants. It is intimately associated in its distribution with certain plant pigments or lipochromes,[1] although it does not appear to be a member of the lipochrome class of pigments.[2] The distribution of vitamin A and lipochrome in a number of fats and plants runs parallel: those that are rich in lipochrome are also rich in vitamin A; those that are poor in lipochrome are also poor in vitamin A. Rosenheim and Drummond[1] remark on the significant fact that the occurrence of lipochromes in the animal body is most obvious in those organs and secretions which are connected with reproduction and the nutrition of the growing young (ovaries, eggs, and milk).

In Animal Tissues this vitamin is present in great abundance in liver, heart, and kidney; in salmon, herring, and other fat fish; it occurs also, but more sparingly, in lean meat, brain, sweetbreads, and fish-roe. Liver is of peculiar value because of its high content of all classes of vitamins and of the good biological quality of its protein.

In Milk.—The quantity of this vitamin in cow's-milk and butter is dependent on the supply of green fodder in the food. Young guinea-pigs grow better and are healthier on milk from a cow fed on green fodder than from a cow fed on dry fodder.[3] I have found that the butter made from the milk of cows fed on green fodder contains a substance which tends to protect pigeons from œdema resulting from an exclusive diet of autoclaved rice, whereas that made from the milk of cows fed on dry fodder contains this substance in much lesser quantity.[4] The importance of green food in relation to the value of cow's-milk, and to that of nursing mothers, in this vitamin is thus very great. It is less abundant in stale milk, in dried milk, and in boiled and pasteurized milk than in whole raw milk; it is absent from skim-milk and from skim-milk cheese; and present in small amount in sweetened condensed milk and in whole-milk cheese.[5]

In Fats and Oils.—Reference has been made to the presence of this vitamin in the butter made from the milk of grass-fed cows. Cream is less rich in it than butter.[5] Crude cod-liver oil contains vitamin A in great abundance, being 250 times as rich in it as butter or the refined oil.[6] Much of the potency of the crude oil is lost in consequence of oxidation during the refining process. Next to cod-liver oil and butter, its richest sources among fats are mutton fat, beef fat (suet), and fish oils (whale, herring, etc.).[6] It is absent, with few excep-

[1] Rosenheim and Drummond, *Lancet*, 1918 (April 17), p. 862.
[2] Drummond and Coward, *Biochem. Jour.*, 1920, XIV, No. 5, p. 668.
[3] Dutcher and Others, *Jour. Biol. Chem.*, 1920, XLV, No.1, p. 119.
[4] *Brit. Med. Jour.*, 1920 (Aug. 14), p. 236.
[5] 38*th Rep. Med. Res. Com.*, London, 1919.
[6] Zilva and Miura, *Lancet*, 1921 (Feb. 14), p. 323.

tions, from vegetable oils, such as olive oil, cotton-seed oil, coconut oil, cocoa-butter, linseed oil,[1] and in hardened or hydrogenated fats, whether of animal or vegetable origin.[1] Margarines made from vegetable oils do not contain it; those prepared from animal fats do so in proportion to the amount of animal fat the product holds.[1] The vegetable oils that are said to contain it are peanut or arachis oil [1] and palm oil.[2] Lard or bacon fat does not contain this vitamin,[1] owing both to the nature of the food on which pigs are fattened and to the processes to which it is subjected during manufacture.[3]

In Vegetables.—Green leaves and shoots are rich in this vitamin, especially spinach, lettuce, cabbage, and brussels sprouts.[4] Root vegetables—potatoes, carrots, beet, radish, turnip—are comparatively poor in it.[1] The fresher the vegetable the richer it is in both vitamin A and vitamin C.

In Grains.—The seeds and resting tissues of plants contain less of this vitamin than the leaves; soya-bean, however, contains it in considerable quantity, as do linseed or millet seed and maize. It is present in germinated pulses or cereals, although in relatively small amount.

In Fruits.—The distribution of this vitamin in fruits has not yet been properly worked out. It is known to be present in small amounts in bananas and in nuts—Brazil, Barcelona, peanut, walnut, almond, and butter-nut. A rich source of this vitamin is the tomato,[4] in which its presence is of great importance owing to its association with both of the other vitamins.[5] The tomato is not only easily cultivated, but is highly prized as a food by all classes of the community. It is said that it can be tinned without losing much of its total vitamin-value. The property which the raw tomato possesses of invigorating those fatigued by hunger and exertion (as, for example, in the case of long-distance cyclists) is perhaps related to its triple content of vitamin. The addition of tomato juice to the dietary of infants reared on pasteurized and boiled milk is rivalled in value only by that of orange juice—which contains vitamins B and C in abundance, and vitamin A in relatively small amount.[6] Pending further quantitative studies, it will be well to regard fruits and fruit juices in general as a source of vitamins of all classes.

In Eggs.—Vitamin A is abundant in egg-yolk, and here again its combination with other requisites essential for growth and maintenance is so perfect that this source of food should always be included in the dietaries of young and old alike. It has been said to be present in equal amount in dried eggs; but having regard to the readiness with which this vitamin is destroyed by exposure to atmospheric oxygen at temperatures ranging from 15° to 120°,[7] it seems improbable

[1] *38th Rep. Med. Res. Com.*, 1919.
[2] *Biochem. Jour.*, 1920, XIV, No. 5, p. 668.
[3] Drummond and Others, *Biochem. Jour.*, 1920, XIV, No. 6, p. 742.
[4] Osborne and Mendel, *Jour. Biol. Chem.*, 1920, XLI. 549.
[5] Idem, *Proc. Soc. Exp. Biol. and Med.*, 1919 (Nov.), XVII. 46; and *New York State Jour. Med.*, 1920, XX, No. 7.
[6] Idem, *Jour. Biol. Chem.*, 1920, XLII, No. 3, p. 465.
[7] Hopkins, *Biochem. Jour.*, 1920, XIV, No. 6, p. 725.

that dried eggs could be equivalent in vitamin-value to fresh eggs. The same comment applies to dried milk. It may be accepted as an axiom that no dried product can equal in vitamin-content that of the food in the fresh state.

This vitamin is absent [1] from vegetable oils, vegetable margarines, skim-milk, skim-milk cheese, white flour, pure cornflour, polished rice, custard powders, glucose, cane sugar, beetroot sugar, syrups, egg substitutes, meat extracts, proprietary foods, highly-refined foods, hydrogenated and hardened fats, and white fish.

Properties.—It is soluble in ether, ligroin, alcohol, and benzene; and slightly soluble in chloroform and carbon disulphide.[1] Its reactions and behaviour suggest that it may be of lipoid nature.[1] It easily undergoes oxidation under the influence of light and air. In butter-fat it is gradually destroyed by exposure to a temperature of 100° C. for four hours, the destruction being no doubt largely due to oxidation.[2] In vegetable materials it appears to be more resistant to heat; autoclaving for three hours at 15 pounds pressure does not destroy it in yellow maize, neither does this treatment cause any notable destruction of the vitamin in chard, carrots, sweet potatoes, and squash.[3] Experiments by Steenbock and Boutwell [3] demonstrate that this vitamin as found in the plant kingdom is comparatively stable at high temperatures. This stability is, however, mainly a question of freedom from oxidation. It appears also to be more resistant to alkalis than either of the other vitamins, but the chemical agents employed in hydrogenation and hardening of fats destroy it.[1] It is destroyed by exposure to ultra-violet rays [4]; this destruction is due to the oxidizing action of the ozone produced by the mercury quartz lamp. In this respect vitamin A is said to contrast with other vitamins, which do not appear to be so destroyed.[4] Sterilization of milk by ultra-violet rays imparts to it a peculiar taste, which Zilva [4] attributes to alterations in the butter-fat brought about by the exposure. It resists saponification by alkalis, whereby it is distinguished from true fats.[5] It does not appear to be destroyed by freezing.[6]

The reserves of this vitamin in the body are considerable. It is stored in the fats. It is particularly necessary to young and growing animals, which early exhibit the characteristic evidences of its deficiency in the food. Mature animals, since they have ceased to grow, are not so dependent upon it, but in them also it is necessary for the maintenance of health and of the powers of propagation. Its absence from the food gives rise to keratomalacia and to a " greatly lowered state of health resulting in abnormally high death-rate from

[1] *38th Rep. Med. Res. Com.*, 1919.

[2] Steenbock, Boutwell, and Kent, *Jour. Biol. Chem.*, 1918, XXXV. 517; Halliburton, Paton, Drummond, and Others, *Jour. Physiol.*, 1919, LII. 328.

[3] Steenbock and Boutwell, *Jour. Biol. Chem.*, 1920 (Feb.), XLI, No. 2, p. 163.

[4] Zilva, *Biochem. Jour.*, 1919, XIII. 164, and 1920, XIV. 740.

[5] Steenbock and Boutwell, *Jour. Biol. Chem.*, 1920 (May), XLII. 131.

[6] *Rep. Food Invest. Board for Year* 1919, London, 1920.

acute infections, particularly those affecting the lungs." [1] Insufficient supply of this vitamin, or of a substance closely allied to it, is thought to be an essential cause of rickets (Mellanby),[2] and also to be concerned in the production of osteomalacia.[3] A possible connexion between the inadequate provision of vitamin A and the occurrence of phosphatic urinary calculi has been suggested by Osborne and Mendel.[4] Its relation, or that of a substance allied to it, to malnutritional œdemas will be discussed in another chapter.

To ensure an adequate supply of this vitamin, the dietary should include whole-milk, butter, animal fat, egg, glandular organs, green vegetables, and fruit.

VITAMIN C

This vitamin occurs in nature in association with living tissues in which metabolic processes are still proceeding. When these cease, the vitamin disappears.[1] In the case of seeds, it is created anew during germination.[1] Its principal sources are thus fresh vegetable tissues and (to a much less extent) fresh animal tissues. In these tissues it is distributed in widely different amounts (Table I).

In Milk.—The value of milk in this vitamin is relatively low. This value depends, as in the case of vitamin A, on the character of the cow's food. Hart, Steenbock, and Ellis [5] have found that summer pasture milk is much richer in anti-scorbutic factor than " dry-feed milk or winter-produced milk, involving the use of a ration of corn silage or even sugar mangels " [5]; nearly twice as much of the latter being required to prevent the onset of scurvy in guinea-pigs. Dutcher and others [6] have also shown that scurvy develops more quickly in guinea-pigs fed on winter milk than in those fed on summer milk. The source of the food-supply of cows and of lactating women is thus, as in the case of the fat-soluble vitamin, of great importance in relation to infantile scurvy. This malady is not unknown in breast-fed infants.[7] Skim-milk appears to contain as much of this vitamin as whole raw milk,[1] but dried milk,[8] boiled milk, milk sterilized at 120° C. for ten minutes [8] or by means of hydrogen peroxide,[9] pasteurized milk,[8] sweetened condensed milk, and commercial unsweetened milk [8] are deficient in it. As has been emphasized by Chick, Hume, and Sketon,[10] whenever milk is heated or dried in any way, the resultant loss of anti-scorbutic property must be made good by the addition to the dietary of some anti-scorbutic, such as orange juice, tomato juice, or swede juice. An

[1] *38th Rep. Med. Res. Com.*, 1919.
[2] Mellanby, E., *Jour. Physiol.*, 1918; *Proc. Physiol. Soc.*, pp. xi and liii.
[3] *Brit. Med. Jour.*, 1920 (April 2), 477.
[4] *Jour. Am. Med. Assoc.*, 1917 (July), LXIX. 32.
[5] Hart, Steenbock, and Ellis, *Jour. Biol. Chem.*, 1920, XLII. 383.
[6] Dutcher, *Jour. Biol. Chem.*, 1919, XXXIX. 63.
[7] Hess, *Scurvy Past and Present*, Philadelphia and London, 1920, p. 35.
[8] Hart, Steenbock, and Smith, *Jour. Biol. Chem.*, 1919 (June), XXXVIII. 305.
[9] Still, *Brit. Med. Jour.*, 1920, II. 147.
[10] *Biochem. Jour.*, 1918, XII. 131.

appropriate amount of these anti-scorbutics is a teaspoonful daily for a baby one month old, increased to a tablespoonful for one of three months. They are best given diluted with water, between feeds, and sweetened if necessary.

In Vegetables and Fruits.—The value of vegetables and fruits in this vitamin varies greatly. In general, it may be said that green vegetables and fresh fruits are richest in it; tubers and roots poorest. This value is reduced by age and storage; freshly-plucked vegetables are richest in it.[1] Even the degree of maturation is not immaterial—ripe tomatoes, according to Hess,[1] contain more of this vitamin than those that are not completely ripe. It is thought that the soil on which vegetables are grown may not be without influence in determining their content of vitamin. Thus, while it is of the first importance to know the value of any vegetable food in units of vitamin, this value is dependent upon a variety of factors, which prevent the too rigid application of such evaluations. Since quantity and quality are the essential elements in the efficient use of vegetables as anti-scorbutics, it is important to be aware of the amounts of the vitamin in various foodstuffs. The results arrived at by the Lister Institute in London are incorporated in Table I, wherein the average value of 1 gram of lemon juice is taken as 100.

TABLE I

Fresh lemon juice, raw	100
Fresh orange juice, raw	100
Ripe onion	100
Fresh cabbage juice, raw	100
Fresh cabbage leaves cooked at 100° C. for 20 minutes	30
Fresh cabbage leaves heated to 70°–80° C. for 60 minutes	10
Germinated peas, beans, lentils, etc., raw	30
Fresh swede juice, raw	60
Fresh tomato juice, raw	60
Fresh turnip juice, raw	30
Fresh green beans, raw	30
Potato cooked at 100° C. for 30 minutes	7·5
Fresh carrot juice, raw	7·5
Fresh beetroot juice, raw	less than 7·5
Tamarind	7·5
Grape juice	5
Fresh beef juice, raw	less than 7·5
Fresh cow's milk, raw	1·5
Dry cow's milk	less than 0·5
Dry beans, peas, lentils, etc., raw	7·5

From Table I it is apparent that, if sufficient vitamin C for the needs of the body are to be provided within a reasonable bulk, fresh vegetables and fruit should be eaten raw. It is of particular importance to note the low value of milk and beef juice in this vitamin. Scurvy can be, and has been, prevented by

[1] Hess, *Brit. Med. Jour.*, 1920 (July 31), p. 154.

the use of fresh meat, as, for instance, among exploring parties in the Arctic, but it requires to be consumed in large amounts in a practically raw state to effect this purpose.

This vitamin is absent [1] from animal and vegetable oils, from tinned meats, and practically so from cereals and pulses or their food derivatives. It is absent also from yeast, and from distilled and malted liquors [2] made according to European methods.

Properties.—" This vitamin suffers destruction when the fresh foodstuffs containing it are subjected to heat, drying, or other methods of preparation. All dry foodstuffs are deficient in anti-scorbutic properties; such as cereals, pulses, dried vegetables, and dried milk. Tinned vegetables and tinned meat are deficient in anti-scorbutic principle. In the case of tinned fruits, the acidity of the fruit increases the stability of the vitamin, and prevents, to some extent, the destruction which would otherwise occur during the sterilization by heat and the subsequent storage." [1] Advantage has been taken by Hess and Unger [3] of the fact that canning does not wholly deprive tomatoes of anti-scorbutic potency, to utilize the juice of tinned tomato as a substitute for orange juice in the case of children fed on pasteurized milk where, for reasons of scarcity of the fruit or expense, orange juice was not available. They recommend its administration in doses of two tablespoonfuls daily for babies over three months of age. This vitamin is in general destroyed by heat in proportion to the degree of heat and the time of exposure to it; the latter being the more important of the two. Quick heating at 100° C. involves less destruction of the vitamin than does more prolonged heating at a lower temperature.[4] Whereas cabbage juice, when cooked at 100° C. for twenty minutes, loses two-thirds of its value in this vitamin, it loses nine-tenths of its value when heated to 70°–80° C. for sixty minutes.[4] The vitamin is rapidly destroyed in the presence of alkalis,[5] hence the danger of the common practice of adding sodium bicarbonate to the water in which vegetables are cooked. The effects of deprivation of this vitamin are thus often to be found, especially in children, where to all appearances a liberal supply of anti-scorbutic food is being provided. An interesting example of this nature has recently been published by Chick and Dalyell.[6]

Although in general this vitamin is destroyed by heat, fruit juices, no doubt because of their acidity, appear more resistant to heat than other vegetable products. Thus it has been shown by Chick and Rhodes [7] that orange juice loses little of its potency when heated to 100° C. for one hour. Advantage has been taken of the comparative resistance of orange juice to heat to prepare from

[1] 38*th Rep. Med. Res. Com.*, 1919.
[2] Harden and Zilva, *Jour. Inst. Brewing*, 1918, XXIV. 197.
[3] Hess and Unger, *Proc. Soc. Exper. Biol. and Med.*, 1918, XV. 96.
[4] Delf, *Biochem. Jour.*, 1918, XII. 416.
[5] Harden and Zilva, *Lancet*, London, 1918 (Sept. 7), p. 320; Hess and Unger, *Jour. Am. Med. Assoc.*, 1919, LXXIII, No. 18, p. 1353.
[6] Chick and Dalyell, *Brit. Med. Jour.*, 1920 (Oct. 9), p. 548.
[7] Chick and Rhodes, *Lancet*, London, 1918, II. 774.

it, by suitable modes of desiccation, an efficient anti-scorbutic in a dry form. Givens and McCluggage [1] succeeded in 1919 in preparing a dried orange juice of high anti-scorbutic value. More recently Harden and Robison [2] have found it possible to reduce orange juice to a dry residue by rapid evaporation at a low temperature without causing great depreciation of its anti-scorbutic potency. This dried product can be stored for periods as long as two years without losing more than 60 per cent. of its original anti-scorbutic vitamin. Bassett-Smith [3] has further elaborated the method in order to provide a portable anti-scorbutic in the form of a lozenge suitable for armies and navies. Dried preparations containing this vitamin, while they may prove useful as temporary expedients, should never be relied upon to take the place of fresh vegetables and fruit. An important method of rapidly providing anti-scorbutic substances when fresh vegetables are scarce depends on the discovery of Fürst [4] that this vitamin, while practically absent from dry grains, is generated when the grains germinate.[4] To my mind, this discovery is one of the most important in connexion with the subject of vitamins in general. It indicates that the processes of germination and growth cause substances to be generated that are requisite for the chemical reactions necessary for growth; just as the moving engine of an automobile causes to be generated the spark which ignites the fuel mixture. It emphasizes, too, how necessary are these anti-scorbutic vitamins for growth and metabolism; that, in short, they too are in some sense growth factors aiding in the chemical harmony of cells. In this connexion it is of interest to recall the experience of Alexis Carrel, who found that in growing animal tissue outside the body in blood-serum, the tissues, when placed in adult's blood-serum, would live a long time but would not grow, whereas, if placed in the blood-serum of young and growing animals, they did grow; this shows that substances necessary for growth were present in the blood of growing animals, but not in the blood of adults. The method of preparation of germinated grains has been described by Chick and her co-workers in the following terms:

"*The method of preparation* is as follows: The beans, peas, etc., are washed in water and left to soak for twenty-four hours at room temperature. They are placed in layers not exceeding 5 to 7 cm. in depth upon an ordinary kitchen sieve or other porous surface. They are kept moist by occasional sprinkling with water and with free access of air for 48 to 72 hours. At the end of this period rootlets varying from 0·5 to 1 cm. in length should be visible. The germinated seeds should not be allowed to become dry again, but should be cooked immediately. The cooking should be for as short a time as is necessary to render them soft and palatable. Placing in water for half an hour and then boiling for ten to fifteen minutes should suffice for small seeds such as peas and beans. The anti-scorbutic value of this germinated material has been determined by means of experiments with animals (guinea-pigs), and has been found, weight for weight, to possess about one-third the value of cabbage leaves in the raw condition." [5]

[1] Givens and McCluggage, *Am. Jour. Dis. Child.*, 1919, XVIII. 30.
[2] Harden and Robison, *Biochem. Jour.*, 1920, XIV, No. 2, p. 171.
[3] Bassett-Smith, *Lancet*, 1920 (May 22), p. 1102.
[4] Fürst, *Ztschr. f. Hyg. und Infektionskrankh.*, 1912, LXXII. 121.
[5] Chick and Dalyell, *Brit. Med. Jour.*, 1920 (Oct. 9), p. 546.

Germinated grains have been successfully used in the prevention and cure of scurvy among our troops in Mesopotamia.[1]

This vitamin is soluble in water and in alcohol, and is not adsorbed upon the surface of fine precipitates such as Fuller's earth or colloidal iron,[2] differing in this respect from vitamin B.

The reserve store of vitamin C in the body appears to be considerable, since in the human subject the depletion period prior to the onset of the symptoms of scurvy extends to several months.

To ensure an adequate supply of this vitamin, the dietary should include raw fruit and green vegetables.

CONCLUSIONS

The data afforded in this chapter have brought to light three facts as simple as their importance is great :

1. To ensure an adequate supply of vitamin B, the dietary should include wholemeal bread or nuts, eggs, glandular organs, fresh fruit, and green vegetables.
2. To ensure an adequate supply of vitamin A, the dietary should include whole-milk, butter, animal fats, eggs, glandular organs, fresh fruit, and green vegetables.
3. To ensure an adequate supply of vitamin C, the dietary should include fresh fruit and green vegetables.

Conversely, dietaries which do not include an adequate supply of wholemeal bread, or nuts, or eggs, or glandular organs; of whole-milk, or butter, or animal fat ; and of fresh fruit and green vegetables, are likely to be deficient dietaries. Further, they are likely to be deficient dietaries not only from the point of view of vitamins, but from that of protein of good biological value, and of salts of good biological value, as has been so clearly brought out by McCollum.[3] This observer speaks of milk, eggs, and leafy vegetables as " protective foods." To these I would add, from the point of view of vitamins, a proportion in the dietary of wholemeal bread or nuts, or glandular organs (such as liver), and of animal fats as an added safeguard.

Considering the whole question of nutrition from the point of view of every essential constituent of human food, McCollum[3] writes : " It is unwise to approach very closely the physiological minimum with respect to any dietary factor. Liberal consumption of all the essential constituents of a normal diet, prompt digestion and absorption, and prompt evacuation of the undigested residue from the intestine before extensive absorption of products of bacterial decomposition of proteins can take place, are the optimum conditions for the maintenance of vigour and the characteristics of youth. Such a dietary regime can be attained

[1] Willcox, *Brit. Med. Jour.*, 1920 (July 31), p. 158 ; *Proc. Roy. Soc. Med.*, 1920, XIII, No. 3.
[2] *38th Rep. Med. Res. Com.*, 1919.
[3] McCollum, E. V., *The Newer Knowledge of Nutrition*, New York, 1919.

only by supplementing the seed products, tubers, roots, and meat, which must constitute the bulk of the diet of man, with the *protective foods*." It is the purpose of this monograph to show how the body goes sick if these foods are not provided in adequate quantity. It does so, among other reasons, because loss of appetite interferes with " liberal consumption " of food, and because depressed function of the gastro-intestinal tract interferes with " prompt digestion and absorption " and with " prompt evacuation of the undigested residue from the intestine."

CHAPTER III

DESCRIPTION OF EXPERIMENTS

In the earlier stages of my experimental work pigeons were used; in the later, guinea-pigs and wild monkeys.

EXPERIMENTS WITH PIGEONS

Over 400 pigeons were employed; of these 150 were controls. Minute precautions were taken with regard to the control of the experiments in order that factors such as sex, varying ages, varying seasons of the year, and complicating infections might be, as far as possible, excluded or their influence appraised. Thus, in carrying out estimations of the epinephrine-content of the enlarged adrenal glands from cases of polyneuritis columbarum, similar estimations were invariably made in a healthy control killed at the same time as the diseased bird. The pigeons used were semi-wild—that is to say, they had not, with certain exceptions, been confined in cages or in animal rooms prior to the initiation of the experiments. This choice of birds was made with the object of using those whose previous food conditions and habits of life had been as natural as possible, and in order also to exclude so far as one could the effects of previous confinement on such organs as the thyroid and adrenal glands. The exceptions referred to related to certain young birds, bred in captivity in order that their ages might be known definitely; these were subsequently used for the purpose of ascertaining the effect of age as a determining factor in the onset of symptoms resulting from food deficiency. Even among pigeons living in the semi-wild state I found the incidence of tubercular disease to be over 2 per cent.; control birds being affected almost as frequently as those fed on deficient foods. Practically every bird among the 400 used had halteridium infection.

The experiments were conducted in specially constructed cages and in animal rooms which had not been used previously for animal experiments. The hygienic conditions were perfect. My laboratory was situated at a height of over 6,000 feet above sea-level.

Milled rice formed the basis of the experimental dietaries. Eight varieties of commercial rice in use among the people of India were employed, namely: rice imported from Bellary, from Rangoon, from Patna, from Mangalore, from Coimbatore, from Latura, from Masulipatam, as well as rice obtained from the local bazaar at Coonoor. These rices included one variety actually in use by sufferers from beri-beri; namely that from Masulipatam. Those from Patna and Rangoon were rather more effectively milled than the rest. In none was the polish so high as that seen in rice used in England. The majority of grains were devoid of germ and pericarp; but when the rice was treated with a solution of iodine in order to detect with greater ease portions of adherent pericarp, it was

found that minute fragments still adhered to a considerable number of the grains. The germ was absent. According to McCay [1] rice is the poorest of all cereals in protein (less than 7 per cent.). The percentage of starch is high—up to 80 per cent.; rice is deficient in fat. It absorbs three and a half times its weight of water when cooked; 1,000 grams of dry rice after cooking measured 2,800 c.c. The disproportionate richness in starch of a dietary composed mainly of rice hinders the absorption of protein and gives rise to excessive fermentation processes and increased peristalsis; thus inducing digestive disorders, and further hampering absorption by the rapid passage of food through the digestive tract. The amount of rice present in a diet influences in marked degree the quantity of urine excreted.[1]

Slight differences only were observed in the length of time (" depletion period ") required by the raw, untreated rices from different localities to produce symptoms of *polyneuritis columbarum*. Thus, when this disorder was unaccompanied by concurrent septicæmic states, the raw rice from Rangoon produced nervous symptoms in periods ranging from 25 to 85 days, with an average of 55 days; that from Patna in periods ranging from 36 to 89 days, with an average of 59 days; that from Masulipatam, of the same variety as that used by sufferers from beri-beri, in periods ranging from 47 to 70 days, with an average of 55 days.[2] The test in each case was made with six birds of approximately the same age. The average depletion period in the case of these different varieties of raw rice —the birds being allowed to eat of them as they would—necessary to reduce pigeons to the point of death from polyneuritis thus varied between 55 and 59 days. This figure is just twice as high as that reported by observers in Europe and America. It follows, therefore, that the commercial rices of India which may be in actual use by sufferers from beri-beri are not so completely devoid of vitamin B as the rices used in Europe and America; indicating that complete absence of this vitamin is not necessary for the production of beri-beri, or more properly that this malady can arise in the presence of an avitaminosis which may be extreme, but is not necessarily complete. This observation is in conformity with the finding of Funk and Macallum [3] that larger quantities of vitamins are necessary for stimulating growth than for curing beri-beri.

Influence of Hand-feeding.—Recognizing that the quantity of rice consumed by the birds might have a bearing on the time of onset of symptoms of *polyneuritis columbarum*, experiments were carried out in which a ration of raw rice, amounting to one-fifteenth part of the body-weight of the birds, was introduced daily into their crops by hand-feeding. Pigeons so fed on raw Patna rice died, or were killed at the height of the disease, in an average period of 51 days; those not so fed, and allowed to eat of the rice as they would, in an average period of 59 days. In both cases symptoms of polyneuritis appeared

[1] McCay, D., *Scientific Memoirs of the Govt. of India*, No. 34, 1908, and No. 48, 1911.

[2] Greig, using Bengal and Rangoon rices, found the depletion period of polyneuritis columbarum to be on the average, 51 days, 44 birds having been used (*Scientific Memoirs, Govt. of India*, 1912, No. 49, pp. 61–5).

[3] *Jour Biol. Chem.*, 1916, XXVII. 64.

4 to 7 days prior to the point of death. Pigeons hand-fed on raw Masulipatam rice survived for an average period of 58 days; those allowed to eat of the rice as they wished in an average period of 55 days. With respect, then, to the varieties of raw rice from these two localities—in one of which beri-beri was endemic—hand-feeding made no appreciable difference in the time of appearance of nervous symptoms nor in the length of time the birds survived the dietary. Twelve birds were used in each test, six being controls allowed to eat the test rice as they wished.

Influence of Washing, Soaking, and Boiling the Rice.—The rice was first sifted, then washed in several changes of water, then soaked in fresh water, and finally boiled. This treatment was designed to imitate that followed by the Indians themselves in preparing it for their own consumption. Pigeons fed on rice so treated developed polyneuritis somewhat more rapidly than when the raw uncooked rice was used. Rangoon rice was employed in the test. On the other hand, Greig, using boiled Rangoon rice, found the average depletion period to be 63 days.[1]

Influence of Autoclaving the Rice.—In order effectually to determine the degree of heat required to destroy all vitamins that might be contained in the milled rices used, experiments were conducted with rice autoclaved at a temperature of 130° C. for three-quarters of an hour. The rice was autoclaved in bulk, being placed in cans which fitted the small autoclaves available for my purpose. The temperature of the apparatus was raised to 130° C., and maintained at this point for three-quarters of an hour, when the cans were removed. It was found that the peripheral portions of the mass were more completely penetrated than the central parts. The rice was then spread out on sheets of paper and partially dried before being presented to the birds. A large number of pigeons were fed on rices so autoclaved. In one of my first experiments in which 72 birds were used (36 being controls), raw rice was given to the birds for the first 40 days; since only one bird developed polyneuritis within this period, the rice autoclaved as above was given from the fortieth day onwards. In this experiment the depletion period varied between 30 and 100 days, the average being 67·1 days. In subsequent experiments in which rice so autoclaved was used from the outset, the birds reached the point of death in periods ranging from 27 to 94 days, with an average of 45 days; thirty-two birds having been employed. The effect, therefore, of autoclaving the commercial rices of India at a temperature of 130° C. for three-quarters of an hour is to reduce the period of depletion by approximately one-fourth.

Further experiments were conducted with rice autoclaved in bulk at 130° C. for one hour and a half. This treatment had the effect of reducing the depletion period of polyneuritis columbarum almost to within the limits recorded by observers in other countries, namely 15 to 25 days.[2] It follows, therefore, that, in order to render the commercial rices of India as free from anti-neuritic

[1] Loc. cit.

[2] Vedder, *Beri-beri*, London, 1913; *38th Rep. Med. Res. Com.*, London, 1919.

vitamin as the highly polished rices used in Europe, an exposure to a temperature of 130° C. for one hour and a half in the autoclave is necessary. These observations bring into prominence one very important point—namely, that, given a subminimal supply of vitamin B in association in the dietary with an excess of starch and a deficiency of protein, the time required to produce nervous symptoms is almost directly proportional to the degree of the avitaminosis. The greater the degree of avitaminosis the more rapid the onset of symptoms, the lesser the degree of avitaminosis the slower the onset of symptoms; but whatever be the degree, provided there be an avitaminosis, symptoms will eventually manifest themselves. This is the essential point to realize with regard to deficiency of vitamins; for in the human subject, in whom the avitaminosis may be partial, symptoms of morbidity must eventually supervene. My observations with regard to symptomatology and morbid anatomy were made for the most part in pigeons fed on rice autoclaved at 130° C. for three-quarters of an hour—hereinafter referred to as "autoclaved rice." The depletion period was consequently rather more than twice as long as when highly polished rice is used. This had a decided advantage, since my experiments approximated more closely the conditions in human beings suffering from partial avitaminosis. It afforded me a greater opportunity to observe the slower dissolution of the birds and to study in more detail the symptoms they exhibited prior to the onset of the final nervous stage.

It will be noted also that, in so far as the anti-neuritic vitamin B is concerned, it is resistant to high degrees of heat; consequently it is less susceptible to the effects of ordinary culinary methods than, for instance, vitamin C. The danger of an insufficient supply of vitamin B lies not so much in the risk of its destruction in the process of cooking—except in so far as it may be dissolved out by boiling or destroyed in the presence of alkalis—as in its removal from grains by mechanical means in the processes of manufacture of rice, barley, wheat, and rye for human consumption. These processes are such as render its removal easy; while high milling and the use of sodium bicarbonate in baking is a dangerous combination.[1]

So far, then, these experiments indicate that an exclusive diet of rice—one devoid of vitamins of every class, deficient in protein, in fat, and in salts, while disproportionately rich in starch—gives rise in pigeons to certain symptoms of disease which are dependent in their time of onset on the degree of the avitaminosis. This degree of avitaminosis is the only variable factor in the experiments so far detailed, and variation in this factor entails variation in the time of onset of symptoms.

Effects of adding Butter and Onion to a Diet of Autoclaved Rice.—Using rice as the basis of the dietary, various other experiments were devised with the object of rendering the food rich in one or more essential vitamins, while excluding as far as possible the other or others. Thus pigeons were fed on a diet of autoclaved rice—capable *per se* of producing polyneuritis columbarum in an average of forty-five days—to which fresh butter and chopped onions were added. These addi-

[1] *Jour. Am. Med. Assoc.*, 1916 (April 22), LXVI. 1314.

tions made good the deficiency in vitamins A and C, the deficiency in inorganic salts, and the deficiency in fat; they also slightly increased the protein components of the food owing to the small protein-content of the butter and the onions, nitrogenous substances forming 1·68 per cent. of the latter and 0·95 per cent. of the former. The butter was added to the food mixture to the amount, in different experiments, of $\frac{1}{12}$ ounce to $\frac{1}{6}$ ounce per bird; it was intimately mixed by hand with the other ingredients of the food. The resultant mixture was thus deficient in vitamin B, and disproportionately rich in starch. It was also disproportionately rich in fats, since in nature pigeons would not consume so large an amount of fat. Forty-two pigeons were fed on this dietary, while as controls twenty-four birds were used to whose diet of mixed grains butter and onions were added in the same proportions as in the deficient food mixture. The birds fed on the deficient food at first partook of it greedily; the average daily consumption per bird being as high as 30 to 40 grams. Later, however, they lived mostly on the onion constituent of the food, eating of the rice but sparingly. The result of this experiment was remarkable; the birds lost weight, and developed polyneuritis columbarum in typical form, or profound asthenia, with extraordinary rapidity. The controls remained to all appearances healthy, increasing rapidly in weight for the first half of the experiment, and then showing a tendency to decline in weight (Figs. 1 and 2). The first case of polyneuritis columbarum, among birds consuming the deficient food mixture, occurred on the twenty-first day, the last on the thirty-sixth. In several cases the symptoms were limited to diarrhœa and profound asthenia without any manifest nervous symptoms; the majority, however, exhibited polyneuritis columbarum in typical form. One bird died from other causes, while three presented no evidences of disease, apart from looseness of the bowels, within 50 days, when the experiment ceased. The average period which elapsed before the birds reached the point of death was 29 days as compared with 45 days in pigeons fed on autoclaved rice only. The addition of butter and onions to the basal diet of autoclaved rice had thus the effect of greatly hastening the onset of symptoms and the death of the birds, and of causing them to lose weight more rapidly. It had other special effects on internal organs, and with regard to the incidence of œdema, which will be referred to in succeeding chapters. It will have been noted that neither the butter nor the onion contributed sufficient vitamin B to retard the onset of symptoms of polyneuritis. Further experiments were carried out in order to ascertain which of these foods—the butter or the onions—was responsible for thus increasing the harmful effects of the deficient dietary. Pigeons were fed on autoclaved rice to which butter alone was added in the above proportions; others on autoclaved rice to which onion alone was added. In brief it was found that the butter was the harmful factor, and the conclusion reached was that its noxious action was due to the excess of fats in the deficient food mixture. It was thus learned that a degree of avitaminosis which will produce a definite train of symptoms in the presence of an excess of starch will produce the same, or approximately the same, train of symptoms almost twice as rapidly if there be also an excess of fats in the

dietary. That is to say, an incomplete avitaminosis in the presence of an excessive intake of energy-bearing constituents will produce symptoms as rapidly as a complete avitaminosis when the intake of energy-bearing constituents is not so excessive. Vitamin B is thus correlated in its action with the metabolism of such energy-bearing constituents of food as starches and fats. In short, the greater

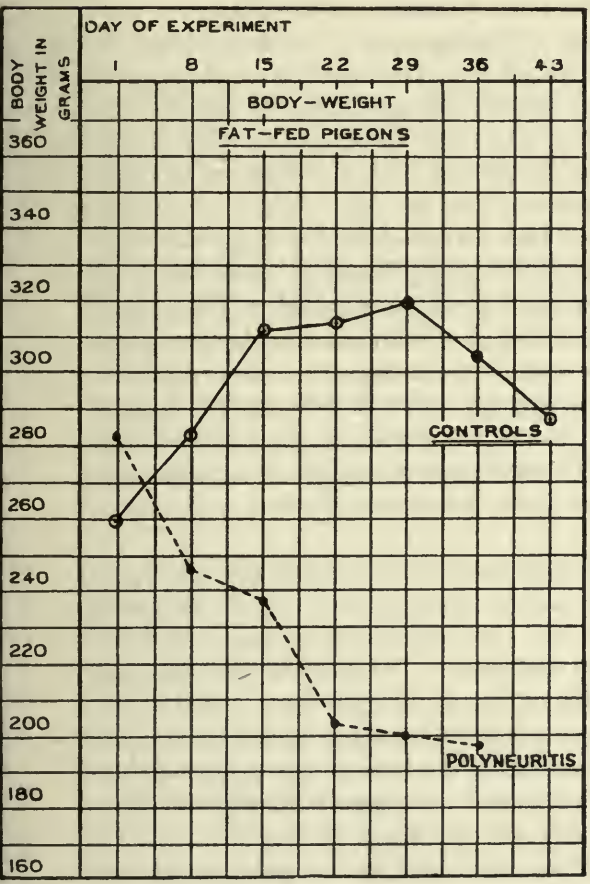

FIG. 1.—Showing weekly average body-weight of twenty-four control pigeons, and of twenty cases of polyneuritis resulting from a diet of autoclaved rice, butter, and onions.

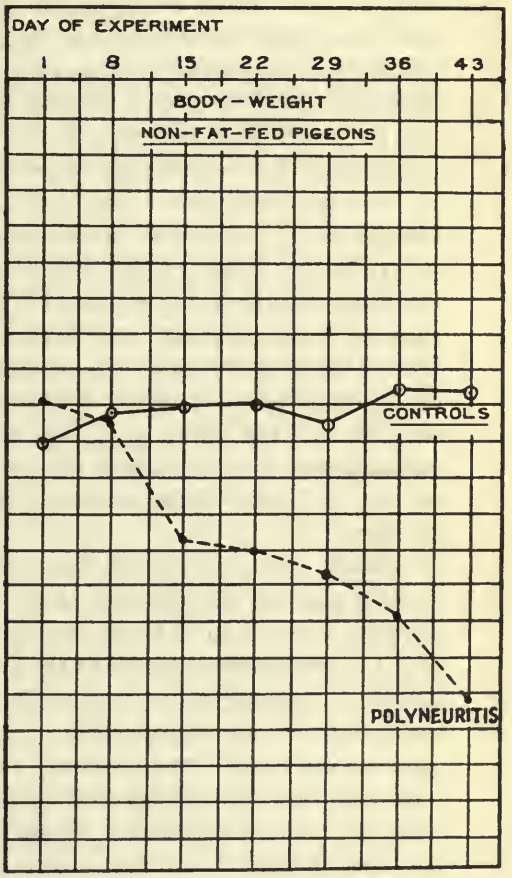

FIG. 2.—Showing weekly average body-weight of twenty-four control pigeons, and of twenty-four cases of polyneuritis resulting from an exclusive diet of autoclaved rice.

the intake of starches and fats, the greater must be the intake of vitamin B. This result as observed in pigeons at first puzzled me greatly, and it was not until I had repeated the experiments with monkeys and obtained an identical result that I was able to place upon them the interpretation here given.

Other Experiments with Pigeons.—Further experiments were carried out with pigeons for definite objects, such as to determine the effect of age or of sex in favouring or delaying the onset of symptoms due to the food deficiencies;

or to ascertain the effects of different varieties of fresh butter and vegetable oils on the production of deficiency œdemas and on the adrenal glands. These will be referred to in detail in succeeding chapters.

Experiments of the nature above recorded would not have been complete or capable of full interpretation without comparison with others in which pigeons were deprived of all food with the exception of water. Six birds thus starved died, or were killed at the point of death, in an average period of twelve days without exhibiting evidences of polyneuritis. The degree of avitaminosis being as complete in starved pigeons as in pigeons fed on autoclaved rice, it would appear that the reserve stores of vitamin B in the case of starved birds are sufficient to protect them from polyneuritis for a period of twelve days, and that the starch component of the food plays a part in the production of the symptoms in birds fed on autoclaved rice. Since it has been shown that the time of onset of nervous symptoms in the latter is dependent on two factors—(1) the degree of the avitaminosis, and (2) the degree of excess of energy-bearing constituents of the food—it seems to me that the starchy component of the food in the case of pigeons fed exclusively on autoclaved rice must play some part in the precipitation of these symptoms. It certainly plays an important part in the production of the symptoms observed during the pre-neuritic stage of polyneuritis columbarum. On the other hand, I have, in exceptional instances, seen polyneuritis columbarum develop within the period of twelve days in pigeons fed exclusively on raw or boiled Rangoon rice. But in these instances infection was always present.

Finally, an experiment was conducted in order to ascertain the effects of feeding pigeons on vitamins alone, or as nearly alone as they can be procured without extraction of foods containing them. Six pigeons were hand-fed daily with rice polishings containing the pericarp and germ. The birds died of inanition in periods ranging from 12 to 28 days, with an average of 22·6 days. This result was, of course, to be expected. It illustrates a point, however, which it is necessary to emphasize; namely that, just as the purified proximate principles of the food—proteins, carbohydrates, fats, and salts—will not support life without vitamins,[1] neither will vitamins support life without proximate principles; the two are complemental in their action. Further, the birds fed on rice polishings died of inanition and did not develop polyneuritis.

EXPERIMENTS WITH GUINEA-PIGS

Guinea-pigs were employed for special purposes, such as to ascertain the effects of absence of the water-soluble anti-scorbutic vitamin C on the adrenal glands, the thyroid gland, the gastro-intestinal tract, and the bladder.

The animals were taken from laboratory stock, isolated in separate cages and fed on crushed oats and autoclaved milk. The oats were of poor quality. The milk was auto-

[1] Hopkins, G., *Analyst*, 1906, XXXI. 395; *Jour. Physiol.*, 1912, XLIV. 425; *Biochem. Jour.*, 1913, VII. 97.

claved at 130° C. for one hour. Experiments were usually continued until the death of the animals; post-mortem examinations were made immediately after death in order to avoid the occurrence of post-mortem changes in the tissues.

In the case of these animals the food had two main defects: it was lacking in vitamin C and deficient in bulk. The results will be referred to under the headings of the special organs concerned.

EXPERIMENTS WITH MONKEYS

The later stages of my investigations were carried out in monkeys, with the double object of controlling the observations already made in pigeons, and in order to determine the effects of food deficiencies on animals more closely related to man.

Wild monkeys (*Macacus sinicus*), to the number of thirty-six, captured in the jungles of Madras were used. The experiments were commenced within a few days of their arrival in my laboratory. The animals were thus not debilitated by previous experimentation or confinement, and came to the laboratory with all the reserves of vitamins that are provided by a perfectly natural life in the wild. With one exception they were in perfect health, very active and difficult to handle. The exception occurred in the case of a young monkey which, seven days after arrival in my laboratory, died of general peritonitis, due, it was thought, to injury during capture. No blood parasites were present in the peripheral blood of these animals.[1] It was subsequently ascertained that a considerable proportion of them harboured *Entamœba histolytica* cysts in their intestines. None, however, had any evidences of dysentery or other gastro-intestinal disorder at the time the experiments commenced. All ate greedily. These animals were, with certain exceptions, confined in separate cages. The exceptions were two young monkeys still with their mothers, but not being suckled by them; they were allowed to remain in the same cage with their mothers. The dimensions of the cages were 24 in. × 15 in. × 14 in. Little movement was, therefore, possible, a circumstance which operated alike in controls and other animals. Minute attention was paid to general hygiene. When necessary the animal room was heated to an appropriate temperature at night, while further protection from cold was afforded by thick curtains drawn at night around the shelves on which their cages were placed. These precautions were necessary, since the animals whose natural habitat was the warm, moist climate of the east coast of India were very susceptible to cold at an altitude of 6,000 feet above sea-level. The precautions taken were successful in preventing the death of any animals from causes attributable to climatic conditions. Their weights ranged from 1,350 grams in young monkeys to 2,760 grams in adults (Table II).

The dietaries employed were the following:

A. A control diet consisting of wheaten bread, 120 grams; milk, 120 c.c.; groundnuts, 10 grams; fresh onion, 5 grams; fresh butter, 2 grams; plantains, 2; water. This dietary was both well-balanced and contained vitamins of all classes. Nine monkeys were fed upon it throughout the course of the experiment. They remained in good health, with the exception of an attack of jaundice in some of them; this was thought to be due to the sudden lack of exercise, as well as to the too generous provision of monkey-nuts, which in the earlier stages of the experiment were not limited to 10 grams. The jaundice was corrected by reducing the diet to milk and bananas for a few days, and adding magnesium sulphate to the drinking-water. After recovery, which occurred in all cases, the diet, as above detailed, was used without recurrence of jaundice or any untoward symptoms whatever. These control animals were mostly adults.

[1] These examinations were made by Col. Donovan, I.M.S.

B. An exclusive diet of 120 grams of autoclaved rice and water. This dietary was deficient in suitable protein, in fat, in salts, and in vitamins of all classes, and was excessively rich in starch. It was found that monkeys in vigorous health could not, or would not, even when hungry, eat more than 120 grams of autoclaved rice daily. This amount was, therefore, fixed as the ration. Ten monkeys were fed to the point of death upon it; they were mostly adolescents or young adults.

C. A diet of autoclaved rice and butter—120 grams of the former and 15 grams of the latter—and water. This dietary was deficient in suitable protein, in vitamin B, in vitamin C, and disproportionately rich in starch and in fat. Four monkeys were fed to the point of death upon it; they were adults.

D. A diet of autoclaved food plus fresh onion: autoclaved wheaten bread, 60 grams; autoclaved rice, 60 grams; autoclaved milk, 120 c.c.; autoclaved ground-nuts, 10 grams; fresh onion, 5 grams; water. This dietary was deficient in vitamin B and in vitamin A. Six monkeys are included in this category: three were adolescents and three were adults.

E. A diet of autoclaved food, plus fresh onion and fresh butter: autoclaved wheaten bread, 60 grams; autoclaved rice, 60 grams; autoclaved milk, 120 c.c.; autoclaved ground-nuts, 10 grams; fresh onion, 5 grams; fresh butter, 15 grams; water. This dietary was deficient in vitamin B. Five monkeys are included in this category; they were adults.

The rice, wheaten bread, milk, and ground-nuts used in these deficient dietaries were autoclaved at 130° C. for one hour and a half. How far this treatment may have altered the foods in other respects than in their content of vitamins I am unable to say.

In Table II the duration of the experiments, the dietaries employed, the sex of the animals, and their initial and final body-weights are shown.

It is seen from this table—(1) that monkeys fed exclusively on autoclaved rice died, or were killed at the point of death, in periods ranging from 19 to 28 days, or in an average period of 23·4 days; (2) that monkeys fed on the same autoclaved rice to which butter was added died, or were killed at the point of death, in periods ranging from 13 to 18 days, or in an average period of 15 days; (3) that monkeys (Nos. 21, 22, 25) fed exclusively on autoclaved food plus a small ration of fresh onion died, or were killed at the point of death, in periods ranging from 43 to 100 days, or in an average period of 65 days; (4) that monkeys partially depleted of reserve vitamin by a dietary of autoclaved rice and butter for 10 days (Nos. 28, 31, 32, 33, and 34), and thereafter fed on autoclaved food plus fresh butter and fresh onion, died, or were killed at the point of death, in periods ranging from 43 to 100 days, or in an average period of 69 days; (5) that control monkeys fed on a well-balanced dietary remained—with the exception already referred to—in good health without much loss of weight except in one case, and in two instances with some increase in weight, throughout the period of the experiment. It appears, therefore, that monkeys of this species cannot sustain life for longer than approximately thirty days on an exclusive diet of autoclaved rice; during this period they do not develop symptoms resembling those of human beri-beri. It appears also that the addition of fresh butter to the dietary of autoclaved rice hastens the death of the animals, thus confirming previous observations in pigeons. The conclusion reached with regard to birds, that, given a certain degree of avitaminosis, the time of onset of symptoms is related to the excessive richness of the food in energy-bearing elements, is

TABLE II

No. of Monkeys.	Sex and Age.	Original Body-weight in Grams.	Final Body-weight in Grams.	Percentage Gain or Loss in weight.	Days under Experiment.	Category and Dietary employed.
	CONTROLS :					
13	Female adult. . .	2,300	2,300	+ 0	33	A — Fresh milk, wheaten bread, onion, plantains, groundnuts, water.
15	Female adult. . .	2,680	3,050	+13	92	
16	Female adult. . .	2,740	2,300	−17	106	
17	Male adolescent . .	1,780	1,900	+ 6	106	
18	Male adult . . .	2,320	2,170	− 7	104	
19	Female adult. . .	2,420	2,200	−10	104	
20	Male adult . . .	2,470	2,420	− 2	101	
24	Male adult . . .	2,170	2,120	− 3	101	
	EXPERIMENTAL ANIMALS :					
1	Male young adult .	2,000	1,500	−25	19	B — Autoclaved rice; water.
2	Female adolescent .	1,350	950	−30	26	
3	Male adolescent . .	1,470	1,040	−30	22	
4	Female adolescent .	1,570	1,170	−26	22	
5	Male young adult .	1,900	1,400	−27	24	
6	Male adolescent . .	1,380	980	−29	19	
7	Female young adult.	1,930	1,450	−25	26	
8	Female adolescent .	1,650	1,320	−20	26	
11	Male young adult .	1,900	1,470	−23	22	
12	Male young adult .	1,780	1,420	−21	28	
27	Male young adult .	1,810	1,250	−31	15	C — Autoclaved rice, fresh butter, and water.
29	Female adult. . .	2,130	1,720	−20	13	
30	Female adult. . .	2,520	1,850	−27	14	
36	Male adult . . .	2,410	1,800	−26	18	
9	Male adult . . .	2,090	1,320	−37	82	D — Autoclaved food, fresh onion, and water.
21	Male adolescent . .	1,280	900	−30	67	
22	Female young adult.	1,850	1,200	−36	67	
25	Female adolescent .	1,190	850	−29	62	
26	Female adult. . .	2,760	1,820	−35	51	
35	Male adolescent . .	1,320	1,050	−21	98	
28	Male adult . . .	2,720	1,700	−38	100	E — Autoclaved food, fresh butter, and onion; water.
31	Male adult . . .	2,250	1,410	−38	71	
32	Female adult. . .	2,400	1,950	−19	51	
33	Male young adult .	2,030	1,590	−22	43	
34	Female adult. . .	2,710	1,900	−30	80	

NOTE.—Three animals (Nos. 9, 25, and 26) included in Category D were fed on autoclaved rice; for the first 28 days of the experiment in the case of No. 9, and for the first 16 days of the experiment in the case of Nos. 25 and 26. Thereafter they were fed on Dietary D. Five animals (Nos. 28, 31, 32, 33, and 34) were fed for the first 10 days of the experiment on autoclaved rice and butter, thereafter on Dietary E.

justified. It appears also, from the results observed in monkeys fed on autoclaved food, that the more perfect balance of the food with respect to proteins and carbohydrates greatly delays the onset of symptoms consequent on avitaminosis. Further, that in these circumstances an excessive richness of fats in the dietary is not so harmful. It is to be noted that, even in animals which survived the autoclaved food dietaries for eighty days or longer, no œdema, obvious on clinical examination, occurred. These experiments emphasize the prime importance of two factors in the causation of morbid states resulting from food deficiencies: (1) want of vitamins, and (2) want of balance of the food with respect to proximate principles—carbohydrates, fats, protein, and salts.

SUMMARY

In Table III are summarized the dietaries employed in the various experiments. The table shows the nature of the deficiencies in each case, the nature of the excesses, where such occur, and the animals employed to determine the effect of the faulty dietaries. The minus sign indicates deficiency; the plus sign excess; and the plus and minus sign together a sufficiency of the several components of the food.

TABLE III

Dietaries.	Proximate Principles.				Vitamins.			Animals used.
	Protein.	Carbohydrate.	Fats.	Salts.	A	B	C	
1. Autoclaved rice .	−	+	−	−	−	−	−	Pigeons and monkeys.
2. Autoclaved rice and butter		+	+	−	±	−	−	Pigeons and monkeys.
3. Autoclaved rice plus butter and onion .		+	+	±	±	−	±	Pigeons.
4. Autoclaved food plus onion	±	±	±	±	−	−	±	Monkeys.
5. Autoclaved food plus onion and butter .	±	±	+	±	±	−	±	Monkeys.
6. Crushed oats and autoclaved milk .	±	±	±	−	±	±	−	Guinea-pigs.

These combinations of food faults will, I think, be found to have their counterparts in the dietaries of human beings. The first three are such as are used by sufferers from alimentary beri-beri; all of them give rise in pigeons to morbid states closely resembling this disease in the human subject. The fourth and fifth were devised with the object of determining the effects on monkeys of want of vitamins A and B; we shall see that these are mainly gastro-intestinal disorders. The sixth is a scorbutic diet, capable of causing in guinea-pigs a scorbutic state similar to that occurring in man. It is true that such extreme degrees of avitaminosis are rarely encountered in the food of Europeans during times of peace. But, bearing in mind that a less extreme deprivation of vitamins, when protracted over longer periods of time, will ultimately produce results similar to those of more extreme deprivation for shorter periods, it becomes apparent that the manifestations of disease produced by these dietaries are comparable in kind, if not in degree, to those which may be found in human beings who subsist on foods of low vitaminic value and imperfect balance for long periods.

Having thus ascertained the more important factors relative to the food itself in determining the production of deficiency disease, we may now proceed to a consideration of certain other factors which also influence the onset of symptoms.

PART II

FACTORS INFLUENCING THE ONSET OF DEFICIENCY DISEASE—SYMPTOMATOLOGY

CHAPTER IV

FACTORS INFLUENCING THE ONSET OF MORBID STATES DUE TO FOOD DEFICIENCY

Instinct and Appetite.—Among animals instinct is a powerful protective agent against deficiency disease ; it is less effective in man. In man there is good reason to believe that one cause of deficiency disease is the limitation in the choice of food imposed by the conditions of our civilization. It has been found that swine reared for the market, when afforded the opportunity, tend to select for themselves those foods in due proportion which are essential to their well-being and the perfection of their reproductive functions. Osborne and Mendel, using purified foods in biscuit form, found that rats, although they might eat the less adequate food presented to them in the biscuit, after a few days showed preference for more adequate food. I have observed the same in all my experimental animals. Indeed, it is remarkable to note how eagerly they continue to search for food grains or other particles likely to make good the deficiencies. Monkeys spend, while their strength is maintained, much time in endeavouring to catch flies which may approach their cages, and when successful, which is but rarely, they eagerly consume them. They may even eat their own excreta. Both pigeons and monkeys whose deficient dietaries contained fresh onions invariably ate this component first. Anyone who watches the monkeys confined in large open-air cages in the Zoological Gardens must have noted with what eagerness they rush to secure a fragment of cabbage leaf or other green food with which one may come provided. Fowls will consume their own feathers or those of their neighbours, although supplied with abundance of deficient food. This habit is one of the most outstanding symptoms of avitaminosis in these birds. I have known them kill one of their number and eat portions of its body, impelled to cannibalism by the instinct which prompts them to make good the food deficiency ; deficiently-fed rats may behave in the same way. This desire for fresh food, so universal in the animal kingdom, must possess some great advantage in the preservation of the race.

Species and Race.—Among animals used for experimental purposes, different species vary greatly in their susceptibility to given food deficiencies. Thus pigeons and fowls are very susceptible to lack of vitamin B ; guinea-pigs to lack of vitamin C ; rats to lack of vitamin A, much less to lack of vitamin C. Vita-

min A does not appear to be so necessary to young puppies [1] nor to young children [1] as it is to the rat. In general the effects of vitamin deprivation manifest themselves more slowly the longer the average life in different species. While, for instance, a monkey weighing 2 to 3 kilograms requires the same absolute amount of orange juice to prevent the onset of scurvy as a guinea-pig weighing 300 to 400 grams, the time of onset is different: three weeks in the guinea-pig, two months in the monkey.[2] In the same species different strains present differing susceptibilities; this is probably best exemplified in the case of man. According to Darling [3] the same deficient diet in a Tropical African negro miner may cause severe symptoms of scurvy, which in a Cape Colony African miner may cause only mild symptoms. Again, a dietary that in some African negroes caused scurvy, in others caused beri-beri. It is recorded also by Brown [4] that in a certain tin-mine in the East Indies the Chinese coolie is stricken with beri-beri, while his European overseer develops sprue, although in no essential condition, even in that of diet, are the circumstances of their daily life materially different. Since this opinion was expressed in 1908, knowledge has so greatly advanced that in all probability it would not now bear searching criticism; nevertheless the same predisposing cause—deficient diet—may give rise in one person to beri-beri, and in another to grave gastro-intestinal disturbance. These examples provide sufficient evidence of the varying susceptibilities of different species and different races of mankind to food defects. In mammals the differences are chiefly those of detail: "Any circumstance which involves absolute failure in the fundamental nutrition of one kind of mammal will most certainly be liable to produce untoward results of some kind in the case of any other mammal. Nutritional phenomena are basal phenomena. They differ in detail, but fundamentally they are the same in all animals." (Hopkins.) [5]

Age.—This is a factor of importance in determining the onset of symptoms due to food deficiencies. A number of young pigeons, whose ages were known to range from 3 to 5 months, were fed on autoclaved rice. They developed polyneuritis columbarum in periods varying from 17 to 33 days, the average depletion period for ten birds being 24 days, as compared with 45 days in adult birds similarly fed. Growing animals are thus much more susceptible than mature to the effects of this dietary. It would seem that they require more vitamins for the acceleration of the chemical processes requisite for their growth. The concentration of vitamin B in the seeds of plants and in the eggs of animals points in the same direction. Mellanby [6] has found that a dietary which will produce rickets in young puppies may not do so in those over five months of age. Drummond,[7] too, finds in the case of rats that the length of time the animal can

[1] Mellanby, *Lancet*, 1920 (April 17), p. 856.
[2] Harden and Zilva, *Biochem. Jour.*, 1920, XIV, No. 2, p. 131.
[3] *Trop. Dis. Bull.*, V, 1915.
[4] Brown, *Sprue*, New York, 1908.
[5] *Brit. Med. Jour.*, 1920 (July 31), p. 147.
[6] Loc. cit.
[7] *Biochem. Jour.*, 1918, XII. 25.

maintain itself on a diet deficient in vitamin B without suffering a serious loss of body-weight is directly proportional to the age at which the restriction is imposed.

Mellanby [1] has noted that the onset of experimental rickets occurs considerably earlier in rapidly-growing than in slow-growing puppies. So that even in animals of like age varying rates of metabolism cause variations in the time of onset of the final morbid result.

Sex.—In one of my earlier experiments, in which 34 pigeons were fed to the point of death, for the first 40 days on raw rice, and thereafter on autoclaved rice, it was found that among 20 males, which developed polyneuritis columbarum, the average period required to bring about a fatal issue was 67·9 days; and among 14 females, 79·8 days. In a second experiment, in which autoclaved rice was used from the outset, the corresponding figures for males were 38 days, and for females 53 days. In females, also, the range was wider, being 27 to 94 days, as compared with 29 to 73 days in males. Male pigeons, therefore, appear to be more susceptible to the effects of this form of food deficiency than are females. As it appeared possible that the difference might be due to males eating more than females, this point was investigated. Of seven pigeons, which were hand-fed on autoclaved rice to the point of death, three were males and four were females; the former died, or were killed at the height of the disease, in an average period of 47 days, the latter in an average period of 44 days. In a second series seven older birds were similarly hand-fed: of these four males died, or were killed at the height of the disease, in an average period of 60 days, three females in an average period of 56 days. Each bird received one-fifteenth part of its body-weight of rice daily. It appears, therefore, that the amount of rice which the birds consume has an influence in determining the slower onset of symptoms in female birds, since hand-feeding tends to equalize their time of onset and the time of death in the two sexes. It is an interesting question whether this is sufficient to explain wholly the sex difference in pigeons, or whether the explanation is related to the different effects of food deficiency on the endocrine organs in the two sexes, especially on those concerned with the metabolism of carbohydrates—the pituitary body, the adrenal glands, the thyroid gland, and the pancreas. Thus, while the pituitary body enlarges on the average in male pigeons fed naturally on autoclaved rice, it does not do so in female pigeons. In these circumstances, also, the average enlargement of the adrenals is greater in females than in males, as is the decrease in weight of the pancreas and thyroids. It may be a coincidence that in four female and three male pigeons which were forcibly fed, these differences were of the reverse order: the adrenals being smaller, and the pituitary body, thyroid, and pancreas larger, in females than in males.

This sex difference is one which occurs also in beri-beri and "war œdema"; in the former males are more frequently affected than females, in the latter the mortality is higher in males. It seems likely that differences in metabolism

[1] Loc. cit.

and in endocrine action of the two sexes, as well as differences in the amount of the deficient food consumed, are the essential factors concerned in this variation in sex incidence.

Individual Idiosyncrasy.—Individuals of the same age, sex, and species exhibit the widest variations in their susceptibility to food deficiencies; this, no doubt, is due in some part to the natural variability of basal metabolism in individual subjects. It has already been pointed out that in experimental rickets an increased metabolic rate hastens the onset of symptoms, as evidenced by the greater rapidity with which rapidly-growing puppies develop this malady. In one of my experiments with pigeons fed on polished rice, pushed to the point of death of every bird, one among 20 adult males developed polyneuritis in 27 days, and another in 93 days. In the same experiment among 15 adult females, one developed the malady in 43 days, three others not until after the lapse of 100 days. In another experiment, the duration of which was 75 days, one bird developed polyneuritis in 24 days, another in 70 days, while a third escaped it altogether. Among young birds of which the ages were known, similar differences, though not so wide, were found. Even when pigeons are fed by hand on autoclaved rice in measured quantity, the factor of individual idiosyncrasy is still much in evidence; one bird taking, it may be, twice as long to develop polyneuritis columbarum as another. It is a well-known clinical fact that children who are growing with abnormal rapidity are more susceptible to scurvy than those whose growth is slower. It appears, therefore, that the quantities of vitamins necessary for the harmonious regulation of the metabolic processes vary with the individual and his rate of metabolism. This fact explains many of the anomalies in the incidence of deficiency disease with which clinicians are familiar, and indicates that an amount of vitamin which may not be subminimal for one individual may be subminimal for another. It will be shown, when dealing with the morbid anatomical changes induced by food deficiencies, that, just as individuals vary in their susceptibility, so do different organs of the body, and the same organs in different individuals. Thus idiosyncrasy, whether of individual subjects or of individual organs, is an important factor in determining the onset and the manifestations of deficiency disease.

Segregation : Excessive Physical Exertion : Overwork.—It is difficult to apportion to each of the factors which come into operation among congregated birds its due share in lessening the beneficial influence which segregation exercises in delaying the onset of symptoms in pigeons. These factors include, in addition to greater exposure to infective agencies, excessive physical exertion and the excitements incidental to sexual stimulation. In one experiment carried out during the early spring months, when the sexes would ordinarily have been mating, the last two factors came into operation among birds congregated in large cages. Fighting was constant during the earlier days of the experiment, and continued well into it—until, with increasing feebleness, sexual impulses disappeared. In these cages the birds had not the calm existence of their segregated neighbours; their metabolic resources were thus not conserved to the same

degree. It may be for this reason that in one experiment, where I had an opportunity to observe 48 congregated birds at the same time as 24 segregated birds, the latter took considerably longer to develop polyneuritis; all 72 birds having received the same rice and the experiments running concurrently. The segregated birds took on the average 80 days to acquire the disease and 85 in which to die of it; the congregated birds 61 days to acquire it and 65 to die of it. Analysing the results further, it was found that the average depletion period in segregated males was 69 days, in congregated males 59 days; the corresponding figures for females being 91 days and 65 days. It is evident, therefore, that congregation favours the onset of symptoms. This influence was not due, in the experiment just related, to less perfect hygiene nor to any greater prevalence of infections among congregated birds, but was, in all probability, related to the greater physical fatigue, since the most obvious difference between segregated and congregated birds was the calm life of the one class, and the harassed life of the other. The demand for vitamins appears to be greater the greater the physical work; a conclusion which is justified as much by clinical experience as by experimental results. Thus the onset of human beri-beri is often rendered acute, or that of hunger œdema sudden, by excessive physical exertion. Further, the incidence of a deficiency disease, such as beri-beri or pellagra, has been shown to be highest among those whose work is hardest. Sprawson,[1] writing of beri-beri in Chinese labourers in Mesopotamia, and comparing its incidence in boiler-makers, fitters, riveters, hammermen, turners, carpenters, and tinsmiths, relates that " the boiler-makers have the highest incidence, a fact I also found in investigating the incidence of the disease in Amara. The boiler-makers probably have the hardest work of any of the above."

On the other hand, the want of exercise, a factor operating among segregated pigeons fed on autoclaved rice, does not hasten the onset of symptoms, as appears to be the case with puppies in experimentally-produced rickets (Mellanby). Moderate exercise is no doubt beneficial, whereas excessive physical exertion is harmful.

Cold: Warmth: Rest: Fear: Mental Depression.—Although the influence of these factors has not come within my own experimental experiences, their importance in favouring in the case of cold, and in disfavouring in the case of warmth, the onset of scurvy,[2] malnutritional œdemas, and pellagra is emphasized by writers on these subjects. These factors operate, no doubt, by exhausting the available calories, as when the badly-fed persons are subjected to cold and damp; or by conserving them, as when such persons are subjected to rest and warmth. Excessive physical exertion acts in this regard in the same way as cold. There is, however, reason to believe that the effects of cold, warmth, and rest are connected with their influence on the endocrine regulators of metabolism—the adrenal glands especially.[3] This influence will be referred

[1] Sprawson, *Quart. Jour. Med.*, 1920, XIII, No. 52, p. 352.
[2] Willcox, *Proc. Roy. Soc. Med.*, Sect. Therapeut. and Pharmacol., Jan. 1920.
[3] Cramer, *VI Scientific Rep. Imp. Cancer Res. Fund*, London, 1919, p. 5.

to when the endocrine organs and malnutritional œdema are considered. Other factors which hasten the onset of symptoms, and probably act also through their influence on the endocrine glands, are panic, fear, and mental depression. Willcox [1] has drawn attention to these contributory causes as having been prominent in hastening the onset of deficiency disease in the course of the Mesopotamian campaign.

Lack of Balance of the Food.—The importance of this factor is illustrated by the examples given in the preceding chapter, wherein it was shown that more perfect balance of the food with respect to proteins, carbohydrates, and fats delayed markedly the onset of symptoms, whereas disproportionate richness of the food in carbohydrates and fats hastened it. It was first shown by Funk [2] that, when no food was metabolized, beri-beri symptoms did not appear, whereas an increased intake of foods, especially when these were mainly carbohydrates, hastened the onset of polyneuritic symptoms. This observation has since been confirmed by other investigators, notably by Braddon and Cooper.[3] My own results in this connexion have already been narrated. Dutcher,[4] in substantiating the original work of Funk and of Braddon and Cooper, was inclined to believe that overloading the oxidative mechanism with any energy-producing food will usually hasten the onset of symptoms, a view which is supported by my observations on animals fed on autoclaved rice and butter. Mellanby,[5] in his investigations in connexion with rickets, has also emphasized the important relations between vitamins and the energy-bearing portions of the food. He found that a food disproportionately rich in carbohydrates increases the tendency to rickets in puppies, whereas a well-balanced food retards it. He remarks, with regard to the beneficial influence of protein, that "increasing the protein alone in the absence of 'anti-rachitic' vitamin does not make a food safe," and considers that the protein aids the vitamin, so that less of the latter will suffice to keep growth normal. Similarly, Pitz [6] found that improvement of the protein and calcium content of the diet will protect guinea-pigs from scurvy for a number of weeks, and will greatly prolong the life of the animals, even though the physical character of the diet has not been improved. Lewis,[7] also, recorded that a lower content of anti-scorbutic principle may be sufficient to protect against scurvy if the diet be adequate in its other essential dietary constituents. Similar results might be multiplied from the literature; but these, conforming as they do to my own experimental experiences, will suffice to emphasize the great importance of proper food balance in delaying the onset of symptoms of deficiency disease. Indeed, if the food be balanced with

[1] Loc. cit.

[2] *Jour. Physiol.*, 1913–14, XLVII; *Proc. Physiol. Soc.* (Dec. 13); *Zeit. f. Physiol. Chem.*, 1914, LXXXIX. 373.

[3] *Jour. Hyg.*, 1914, XIV. 331.

[4] *Proc. Nat. Acad. Sci.*, 1920, VI. 10.

[5] *Lancet*, 1920 (April 17), p. 856; 1920 (March 13), p. 604.

[6] *Jour. Biol. Chem.*, 1918, XXXVI, No. 2, p. 439.

[7] *Jour. Biol. Chem.*, 1919, XL, No. 1, p. 91.

due regard to the biological value of the proteins, carbohydrates, fats, and salts, it is hardly conceivable that deficiency disease, with the possible exception of scurvy, could arise outside the laboratory. In practice, however, it will usually be found that the vitamin-content of the food is reduced in proportion to its lack of balance: the two factors are intimately correlated. Funk,[1] Funk and Schönborn,[2] Braddon and Cooper[3] associate vitamin B with carbohydrate metabolism, and especially with starch metabolism, and it will have been noted that my own observations point in the same direction. Funk and Schönborn,[2] and more recently Funk,[4] report hyperglycæmia with reduction in the hepatic glycogen as a consequence of avitaminosis. Vitamin diminished the hyperglycæmia and increased the liver glycogen. There is still some controversy with regard to the part played by the starch component of a polished rice dietary in producing the nervous symptoms of polyneuritis columbarum and of human beri-beri.[5] The evidence I have to present from my own experiments is fully recorded in the preceding and succeeding chapters. Readers will be able to form their own estimate as to whether, as maintained by some,[5] the starch component of the food introduces a positive toxic element in association with the negative element of deficiency of vitamin in the production of the nervous symptoms. It is, however, to be noted that monkeys fed on autoclaved food, in which there was no excess of starch, develop symptoms of nervous disorder with degeneration of nerve fibres (Fig. 13) similar to the syndrome in the human subject known as " dry beri-beri." Further, rats, when fed on synthetic dietaries, " have been observed to show symptoms of muscular incoordination due to involvement of the nervous system,"[6] and their " immediate recovery is effected by administering the missing factor, provided the condition of the animal is not extreme."[6] Polyneuritic symptoms have also been produced in cats by an exclusive diet of lean beef that was autoclaved in alkaline reaction at 120° for three hours (Voegtlin and Lake.)[7] An excess of starch is thus not necessary to the production of the nervous symptoms. Finally, there is the remarkable effect of vitamin extracts in relieving the acute nervous symptoms of polyneuritis columbarum with such dramatic suddenness as to indicate, as indeed does histological study of the nervous tissues, that extensive degenerative changes have not taken place in the nervous system, but rather that the curable nervous symptoms are the result of disordered cell metabolism, which the provision of the vitamin almost immediately adjusts. There is no doubt that the starch component of the food hastens the onset of symptoms both of the pre-neuritic and the neuritic stage; that it does so by overloading the oxidative mechanism in the presence of endocrine insufficiency seems probable; but that it con-

[1] *Jour. Physiol.*, 1913, XLVII.; *Proc. Physiol. Soc.* (Dec. 13).
[2] *Jour. Physiol.*, 1914, XLVIII. 328.
[3] *Jour. Hyg.*, 1914, XIV. 331.
[4] *Jour. Physiol.*, 1920, LIII. 247.
[5] *Brit. Med. Jour.*, 1920 (July 31), p. 147.
[6] 38*th Rep. Med. Res. Com.*, 1919.
[7] *Jour. Pharm. and Exp. Therap.*, 1918, XI, 167.

tributes a toxic factor which causes the nervous symptoms is in my opinion unproven.

Previous Food Conditions.—This factor is of importance both in relation to the onset and incidence of deficiency disease in human beings and in animal experiments. Before an experiment is undertaken, it is necessary to know whether or not the animals to be subjected to it have been receiving a well-balanced food of sufficient vitamin-value. If not, their reaction to the deficiency will vary in accordance with the completeness or incompleteness of the supply of the vitamin in question previous to the initiation of the experiment. Animals living under natural conditions store vitamins as emergency supplies; consequently they will react later to food deprivations than those confined in cages and sometimes indifferently fed on stale foods. The importance of this factor

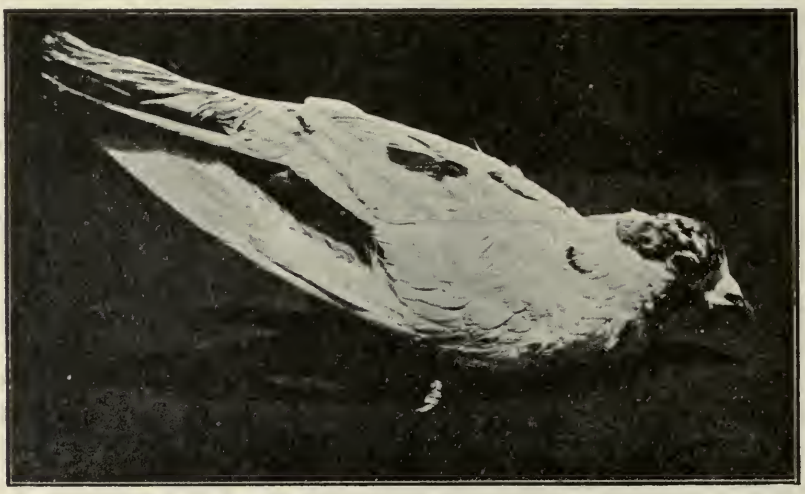

FIG. 3.—Infective polyneuritis columbarum, resulting from the subcutaneous injection of living culture of *Bacillus suipestifer*.

may be illustrated by scurvy in the human subject. Among Indian troops, for instance, whose supply of anti-scorbutics prior to their arrival in Mesopotamia was very scanty, scurvy developed rapidly when, at this war front, the supply was scantier still. British troops, on the other hand, reached Mesopotamia well fortified with anti-scorbutics, and in them the latent period of scurvy was much longer (Willcox).[1] Sprawson[2] has made similar observations with regard to beri-beri among troops and coolies in Mesopotamia. The dietaries habitually used by many people provide but a small margin of safety with respect to vitamins. When, therefore, some further deprivation occurs, or such factors as cold, damp, hard work, over-exertion, or infection come into operation, symptoms due to avitaminosis may manifest themselves.

Infection.—This important factor operates in one of two ways: it may

[1] Loc. cit. [2] Loc. cit.

precipitate the onset of symptoms due to food deficiency, or it may impart new clinical features to the food deficiency syndrome. My experimental experiences have provided two instructive examples of the connexion which exists between food deficiency and the invasion of the body by pathogenic organisms.

The first relates to pigeons: While conducting experiments with these birds, in the year 1914, I found that *Bacillus suipestifer* was complicating the results attributable to food deficiency alone. After much labour—repetition of experiments, isolation of the organism, determination of its pathogenicity for healthy pigeons, and immunization of birds by means of attenuated cultures—I succeeded in separating the symptomatic effects attributable to the organism *per se* from those attributable to the deficient food alone—in this case raw Rangoon rice. It was found that the organism itself was capable, on subcutaneous inoculation, of producing paralysis of the limbs in well-fed pigeons (Fig. 3), fowls (Fig. 4), and rabbits, and that the clinical picture so produced simulated closely that due to alimentary polyneuritis columbarum. When pigeons fed on raw Rangoon rice were congregated together, the organism spread to every one of them, causing polyneuritis and death more rapidly than did the deficient food alone in isolated birds. The control birds, on the other hand, similarly confined in one large cage and equally exposed to infection, almost completely escaped its effects—only one out of twenty-four dying in consequence of it. While, therefore, the deficient food greatly favoured the spread of the organism, good food hindered its spread as effectually as did segregation or immunization.

FIG. 4.—Infective polyneuritis gallinarum, resulting from the subcutaneous injection of living culture of *Bacillus suipestifer*.

The second experience relates to monkeys: It was found, among those fed on deficient food, that dysentery was very common, and was sometimes associated with the presence in the stools of enormous numbers of vegetative forms of *Entamœba histolytica*. The control and well-fed animals living in the same room and exposed to the same risks of infection did not develop dysentery, although microscopical search in their stools revealed the presence of *E. histolytica* cysts or of blastocysts (degenerated forms of *E. histolytica* cysts) in a number of them.

In both these examples the presence of the pathogenic organism was fortuitous: in the one case there was present an organism, itself capable of causing polyneuritis, which, acting on a community debilitated by deficient food, gave rise to an epidemic of polyneuritis. In the other case a pathogenic agent superimposed its own peculiar effects upon the symptoms due to food deficiency. The

experiences indicate also that, in the presence of food deficiency, pathogenic organisms, which may be comparatively harmless when the subject is properly nourished, are very likely to take on rank growth in those debilitated by deficient food. This finding is of the highest practical significance. Ample confirmation of it is provided by the work of other investigators. Thus Drummond [1] comments on the fact that slight vitaminic deficiencies produce a great tendency in experimental animals to increase the incidence of intercurrent diseases of all sorts. It may be noted, as probably an illustration of the same point, that, according to Lemoine,[2] during the German occupation of Lille, tuberculosis became very prevalent, in consequence, as he concluded, of malnutrition, so that in 1917 an actual epidemic of glandular tuberculosis occurred. This diminished resistance to infection is apparently related to an insufficient supply of vitamin A,[3] although no doubt other vitamins are concerned in it also. Another striking example of the lowered resistance to toxic agents produced by avitaminosis is that of the diminished tolerance of the subjects of " war œdema " to drugs.

Overcrowding and Imperfect Hygiene.—Intimately related to infection in determining the onset or affecting the character of symptoms initiated by food deficiency are imperfect hygiene, overcrowding, and deficient oxygen-supply. These in themselves diminish the functional capacity of the cells, impair their protective resources against infecting agents and multiply these agents. As my experiments proceeded, I found it more and more difficult to exclude pathogenic micro-organisms from my animal rooms. Indeed, it was only by confining each animal in a separate cage that the purity of the results could be secured. But the purity of laboratory experimentation is rarely repeated in nature. It is, indeed, under conditions of congregation and imperfect hygiene that experiments in the laboratory would imitate most closely those in nature. Their results are then of greater practical significance provided the right interpretation can be attached to the various contributing factors; a matter of increasing difficulty with the increase in number of the factors involved. Beri-beri, for instance, arises in deficiently-fed communities subjected to attack by innumerable bacterial and parasitic agencies. It would be shutting one's eyes to obvious facts to exclude the influence of such agents in contributing to the production of this malady, and indeed of deficiency diseases in general. Recognition of the importance of infections does not in the least detract from the vast importance of the food deficiency as an etiological factor in the causation of deficiency disease, but rather enhances it, since the part played by perfect food in enabling the body to resist the ravages of bacterial and other pathogenic organisms is the more clearly emphasized. I have shown in this chapter, in connexion with organisms of high virulence, that perfect food affords protection as adequately as does segregation or immunization. It is to my mind by recognizing the part played by each of these agencies—food faults on the one hand and infection on the other—that

[1] Drummond, *Brit. Med. Jour.*, 1920 (July 31), p. 160.
[2] Lemoine, G., *Bull. Soc. Méd. des Hôpitaux de Paris*, 1919 (Jan. 31), XLIII, No. 4, p. 56.
[3] 38*th Rep. Med. Res. Com.*, 1919.

the mechanism of deficiency-disease production can be best understood. It is not necessary to assume the presence of a specific infection as a cause either of beri-beri, rickets, or scurvy, although in my own experiments I have encountered organisms capable of producing both polyneuritis and hæmorrhagic lesions in the tissues. Any infection or debilitating agency which further reduces the efficiency of the cells, and especially the efficiency of the endocrine regulators of metabolism, may, in my view, be a determining factor in the production of any form of deficiency disease so far known to us—be it goitre due to want of iodine, chlorosis due to want of iron, beri-beri due to want of vitamin B, keratomalacia due to want of vitamin A, scurvy due to want of vitamin C, or pellagra due to want of protein of good biological value.

SUMMARY

The data afforded in this chapter make manifest to how great an extent the factors of race, age, sex, previous food conditions, individual idiosyncrasy, variability of basal metabolism in individual subjects, rate of metabolism, imperfect balance of the food, fatigue, cold, damp, panic, fear, mental depression, overcrowding, imperfect hygiene and, most important of all, infection, may influence the onset or modify the course and character of a malady due primarily to dietetic defects. It is to be emphasized that these factors all involve metabolic variations in individual subjects, impose additional burdens on the metabolic resources of the body, or depress the functional capacity of the endocrine regulators of metabolism. Especially important is it to realize that persons receiving too little vitamins are living in a state of potential morbidity which may be converted into one of actual disease by a variety of factors that further exhaust metabolism. It is necessary, also, to realize that a degree of avitaminosis which may produce ill-effects in one individual may not do so in another, although the length of exposure may be in both instances the same. Indeed, it may be said that no two individuals will, with respect to symptoms and time of their onset, exhibit precisely the same response, although, speaking generally, animals of the same species, age, and sex require approximately the same amount of vitamins for the activation or energizing of the chemical reactions requisite for their growth and metabolism.

CHAPTER V

SYMPTOMS OF DEFICIENCY DISEASE IN PIGEONS

THE symptoms of deficiency disease as observed in pigeons and in monkeys have now to be considered. In this chapter those in pigeons will be dealt with; in the succeeding chapter those in monkeys.

I. THE EFFECTS OF INANITION

These were studied in six pigeons—two males and four females—deprived of all food with the exception of water; this was introduced into the crop twice daily by means of a syringe. The birds exhibited a gradually increasing weakness which culminated in death in an average period of twelve days. They presented no evidence of polyneuritis. They lost weight rapidly. The initial and final body-weights, together with the total loss of weight in each bird, are shown in Table IV.

TABLE IV

No. of Pigeon.	Sex.	Initial Weight in Grams.	Final Weight in Grams.	Total Loss of Weight in Grams.	Days till Death.
122	Female	265	150	115	12
123	Female	265	150	115	12
124	Female	240	140	100	13
125	Male	280	160	120	11
126	Male	280	170	110	11
127	Female	270	185	85	14

The average daily loss of body-weight was about 9 grams. Males died more quickly than females, and their daily average loss of weight was greater: 10·4 grams as compared with 8·3 grams. Since the greater susceptibility exhibited by males to food deficiency is observed also as a result of inanition, it would seem that the variation in sex incidence of deficiency disease is not to be explained wholly by the larger food consumption by males, but rather by differences in metabolism in the two sexes. Apart from progressive asthenia and adynamia, the most notable symptoms presented by these birds were a progressive fall in body-temperature and a progressive slowing of the respirations. Thus in one case (No. 124) the initial temperature was 108° F. in the cloaca. In a week it had dropped to 105°, in twelve days to 104°, falling rapidly to 99·4° F. prior to the

death of the bird. In another (No. 127) the respirations dropped from 78 per minute on the first day of the experiment to 48 on the tenth and 36 on the twelfth. The fall in body-temperature and in respiratory rate occurs both in pigeons subjected to inanition and in those fed on autoclaved rice—always provided that concurrent septicæmic states are absent—although the manner of the fall differs somewhat in the two cases.

II. THE EFFECTS OF A DIETARY OF AUTOCLAVED RICE

The clinical evidences of disease due to this dietary are the result of five factors operating in conjunction—avitaminosis, excess of starch, deficiency of protein, of fats, and of salts—with the occasional co-operation of a sixth—infection. The symptoms are divisible into two stages:

(*a*) Those preceding the final polyneuritic stage, and
(*b*) The polyneuritic stage itself.

Hitherto attention has been paid principally to the polyneuritic stage, and too little to the manifestations of morbidity which precede it; the latter are at least of equal importance to the former, and their applicability to the human subject is more general. For it is these earlier evidences of disease that are most likely to be found in persons subjected to partial degrees of avitaminosis.

Loss of Appetite.—For the first few days the birds eat the rice freely; later they spend much time in searching among the autoclaved grains for some that are more to their taste. Finally they eat but little or not at all. Even when the rice is introduced artificially into the crop a portion of it may be rejected.

Diarrhœa.—This symptom is one of the earliest, as it is one of the most frequent, manifestations of deficiency disease in pigeons. Its occurrence is evidence of the distaste, on the part of the gastro-intestinal tract, for the deficient food presented to it. The excess of starch in the dietary interferes with the assimilation of protein, and the diarrhœa further increases the deficiency owing to the rapid transit of the food through the tract. The discharges are often very fluid, and may be emerald green in colour. *Bacillus pyocyaneus* has been isolated from such discharges in a few cases. Microscopical examination showed the frequent presence of tapeworms' eggs. The mass of fæces was made up of a serous discharge containing an enormous number of bacteria, the eggs of parasites and undigested or partially digested starch. Microbic fermentation of the ill-digested starch results in an excessive production of mineral and organic acids, which on absorption may presumably lead to a condition of acidosis. It has been noted that in cases treated with vitaminic extracts the diarrhœa has ceased with a rapidity equalled only by that with which the acute nervous symptoms disappear. In applying these results to the human subject, it is to be remembered that the character and severity of the diarrhœa will depend upon the character of the bacterial flora which happens to be present at the time the patient is being subjected to the avitaminosis.

Fall in the Respiratory Rate.—The average respiratory rate in apparently

healthy pigeons at an altitude of 6,000 feet was found, as a result of 129 observations, to be about 80 per minute. In consequence of the deficient food the respirations become progressively deeper and slower (Fig. 5). In exceptional cases the respiratory rate may fall as low as 18 per minute at the height of the polyneuritic stage of the disease. Birds frequently exhibit respiratory movements suggestive of " air-hunger." More rarely the abdominal movements are indicative of disordered diaphragmatic action; this feature is only observed at the height of the polyneuritic stage, and is due probably to functional derangement of the phrenic nerve. The slowing of the respiratory rate is no doubt the result of progressive asthenia; the deepening of the respirations and the evidences of " air-hunger " are suggestive of acid irritation of the respiratory centre. Birds subjected to prolonged inanition, which is known to give rise to acidosis, although they exhibit these respiratory phenomena, do not do so in such marked degree as those fed on autoclaved rice. The slowing and deepening of the respirations, observed by all investigators, has been attributed to paralysis of the respiratory muscles. But while certain of the respiratory phenomena observed at the height of this malady may be due to this cause, it seems hardly likely that the steady decline of the respiratory rate from the very outset of the experiment is to be accounted for in this way.

Fall in Body-temperature.—Another cardinal effect of food deficiency of the order under consideration is fall in body-temperature. Like the fall in respiratory rate, it begins within the first fortnight of the experiment. The average body-temperature of apparently healthy pigeons, when taken in the cloaca, is 107·4° F., as estimated by 129 observations made in the forenoon. In exceptional cases the temperature in the cloaca at the height of polyneuritis columbarum may be as low as 99° or 98° F., or even 96° F. just prior to death (Fig. 6). It has been observed, in cases of polyneuritis resulting from an exclusive diet of autoclaved rice, that, if the temperature be higher than 104° F. at the height of the disease, concurrent septicæmic infections are almost invariably present. Dutcher [1] also has observed this fall in body-temperature. He records the interesting fact that in polyneuritic birds a drop in catalase-content of the tissues occurs, being 56 per cent. below normal; indicating that " oxidative processes are depressed when the organism is not receiving the normal amount of vitamin."

Progressive Loss of Body-weight.—This is due to loss of body fat, to muscular wasting, to thinning of the bones, and to atrophic changes in the organs and tissues of the body. The loss commences during the first week of the experiment in birds fed on autoclaved rice, butter, and onions (Fig. 1); during the second week in those fed on autoclaved rice only (Fig. 2). In the former the progressive loss is more rapid, and the total loss greater. The average total loss of weight within a period of forty-three days in birds fed exclusively on autoclaved rice was 86 grams, in those fed on the same rice to which butter and onions were added the average total loss was 94 grams. Considerable variations in the loss of weight occur in different individuals.

[1] *Jour. Biol. Chem.*, 1918, XXXVI. 63

In connexion with these observations regarding fall of body-temperature and loss of body-weight, some interesting calorimetric observations, recently published by Novaro,[1] relating to pigeons subjected to inanition and to dietaries of polished rice may be considered. He finds that in pigeons fed on *polished rice* the weight, body-temperature, and amount of heat given off show no notable alteration during the first week of the experiment. After this period the amount of heat given off begins to diminish, the quantity of food taken is smaller, and

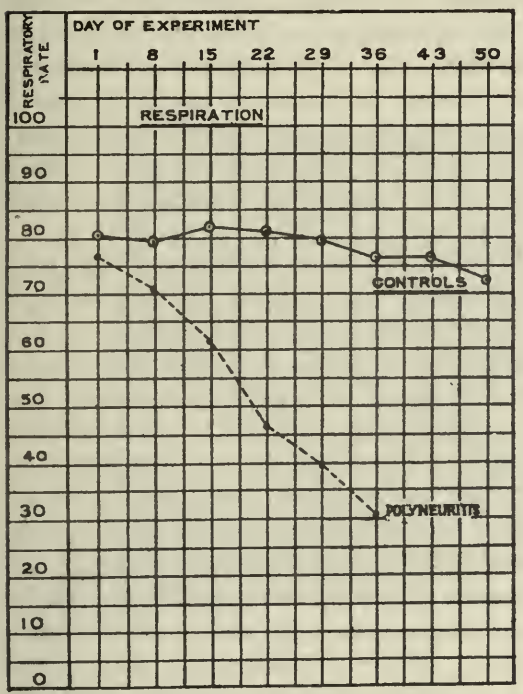

FIG. 5.—Showing weekly average respiratory-rate in twenty-four control pigeons, and in twenty cases of polyneuritis resulting from a diet of autoclaved rice, butter, and onions.

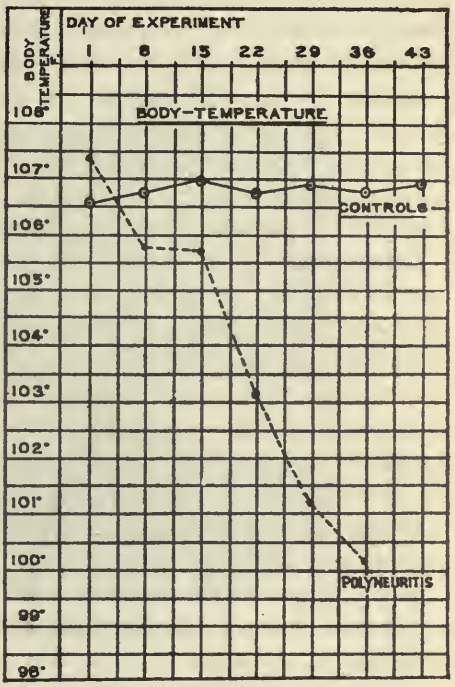

FIG. 6.—Showing weekly average body-temperature in twenty-four control pigeons, and in twenty cases of polyneuritis resulting from a diet of autoclaved rice, butter, and onions.

the body-weight decreases. The temperature remains practically unchanged for a little while longer, and for another considerable period it is only one or two degrees Centigrade lower than the average normal temperature. In the last few days of the experiment, however, there is generally a drop in temperature which may amount to as much as six degrees. Three or four days after the temperature has begun to fall, the amount of heat given off averages only 40 to 50 per cent. of the normal amount. The loss in body-weight is greater when the animals take less food, but the loss is comparatively greater in those fed on polished rice than in those subjected to starvation. In the latter the diminution in body-weight is in

[1] Novaro, P., *Pathologica*, 1920, XII. 87.

direct relation to the amount of heat given off and to the length of the starvation period. It is notable also that, after the first 7 to 13 days, the temperature is lower, and the amount of heat given off is smaller, in birds fed on polished rice than in those that are starved. In the later periods of the experiments the amount of heat given off is constantly small in birds fed on polished rice, whereas it increases in the corresponding period of starvation. The remarkable lowering of the temperature without a corresponding increase of the heat given off in birds deprived of vitamins indicates, according to Novaro, that the mechanism of heat-production is affected by the deficiency of vitamins. Provision of these substances to birds previously deprived of them causes an increase in the amount of heat given off and in the body-temperature. The body-weight, however, may continue to diminish unless the animals receive an adequate supply of food. These results are of great interest in connexion with my discovery of the changes in the adrenal glands which result from inanition and deficiency of vitamin; according to Cramer,[1] these organs form part of a humoral or autocoid mechanism for the chemical heat-regulation of the body.

Anæmia.—The clinical evidences of anæmia are not easy to detect in pigeons, but a fall of the red blood count can be observed; in apparently healthy birds it varies within wide limits, namely: from 2,720,000 to 4,752,000 per c.mm. No doubt the varying degrees of halteridium infection found in Indian pigeons are in some measure responsible for the variation. In deficiently-fed pigeons the range of variation is on a lower scale, running from 1,232,000 to 3,452,000 per c.mm., the estimations being made at the height of the disease. The average of 15 estimations in control birds was 3,599,733 per c.mm., as compared with 2,763,500 per c.mm. in 10 diseased birds. No marked diminution or alteration in the proportion of the white cells was definitely established in pigeons. In "war œdema," with which "wet" cases of polyneuritis columbarum may be compared, a moderate oligocythæmia is present—3 to 5 millions—and moderate leucopenia, while the colour index is normal (Masse and Zondek).[2] The sugar-content of the blood is said to be low in "war œdema" (Jensen),[3] while in pigeons fed on a vitamin-free diet hyperglycæmia occurs (Funk).[4]

Progressive Asthenia.—For the first ten days or so, often for much longer, pigeons fed on the deficient dietaries retain their active habits. Later a gradually increasing weakness assails them. Then they no longer perch, but sit, with ruffled feathers, huddled upon the floor of their cages, showing little inclination to bestir themselves. When taken out and thrown into the air, they fly feebly or fall fluttering to the ground. To these evidences of increasing weakness others referable to changes in the central nervous system are often suddenly added, and the final or neuritic stage of the disorder is reached. We meet thus with three types of polyneuritis columbarum: the first in which inco-ordination and cere-

[1] *Jour. Physiol.*, 1915; *Proc. Physiol. Soc.* (July 15), p. *xxxiii*.
[2] Masse and Zondek, *Das Hunger-Ödem*, Leipzig, 1920.
[3] *München. Med. Wochschr.*, 1918, LXV. 925.
[4] *Jour. Physiol.*, 1920, LIII. 247.

bellar symptoms predominate, the second in which polyneuritis exists alone, the third in which profound asthenia masks any nervous symptoms that may be present. Of these the first is the most common; the last the least common. "Fulminating" types occur, but in my experience usually in association with concurrent septicæmias.

Nervous Symptoms.—The nervous symptoms exhibited by pigeons are—weakness of the legs, tendency to stumble, inability to surmount small obstacles placed in their way, pareses of the legs or wings or both, paralysis, astasia, incoordination, cerebellar symptoms, and convulsive seizures. To these may be added varying grades of loss of sensation to touch, to pain, and to heat, impairment of deglutition, and in some cases impairment of vision. It is to these symptoms

FIG. 7.—Polyneuritis columbarum; opisthotonos.

that the term "polyneuritis columbarum" is applied; it corresponds with beri-beri in man. A typical example of this form of deficiency disease as seen in the pigeon is shown in Fig. 7. The bird has complete astasia, the legs are paralysed, the toes turned in, the head is retracted in a position of extreme opisthotonos; the reverse picture of emprosthotonos may occur (Fig. 8). Every few moments, or at longer intervals, it is afflicted with convulsive seizures in which it turns "cart-wheels" backwards, it may be for a distance of several yards; or it may pursue its beak round and round in a circle, its tottering limbs acting as the pivot on which it rotates. These evidences of cerebellar disorder have been observed in birds only; they do not occur in human beri-beri. They are to be regarded as due to functional changes in cell-groups within the sphere of influence of the cerebellum and consequent on malnutrition. On clinical grounds alone the term "polyneuritis" as applied to these cases is inapt. The nervous symptoms are not due to a peripheral neuritis, but to disordered function of the main body of nerve-cells, with death of comparatively few—rarely exceeding 15 per cent. The

functional impairment can be cured by the administration of vitaminic extracts which restore normal physiological action, but leave untouched the disorder due to death of neurons. Functional impairment of neurons is thus an important manifestation of the food deficiency under consideration, whilst destruction of neurons is much less common.

Onset and Course of Polyneuritis Columbarum.—The onset of the nervous symptoms may be gradual or sudden : frequently the latter, usually the former. Sudden death is not unusual ; it may occur during a convulsive seizure, more frequently it is associated with hydropericardium. The duration of the malady is from 2 to 5 days as a rule, but in exceptional cases I have seen it persist for 12,

Fig. 8.—Polyneuritis columbarum : emprosthotonos.

15, and 21 days. It is usual for birds to show evidences of polyneuritis first, and after a day or two to have superadded symptoms referable to the cerebellum.[1]

Dropsy.—This symptom is rarely recognized clinically. Œdema is frequently encountered at autopsy : hydropericardium being particularly common in pigeons fed on Indian rices.

Summary.—The symptomatic effects, then, of a dietary wholly devoid of vitamins, deficient in suitable protein, fats, and salts, and excessively rich in starch are : loss of appetite, diarrhœa, anæmia, loss of weight, low temperature, slow respiration, a general depression of bodily health, marked tendency to hydropericardium or other evidence of œdema, and symptoms referable to malnutrition of the nervous system.

[1] For more detailed description of polyneuritis columbarum the reader is referred to the author's original papers (*Pathogenesis of Deficiency Disease*, No. 1 ; *Ind. Jour. Med. Res.*, Jany. 1919) or to Vedder's *Beri-beri*, 1913.

III.—THE EFFECTS OF A DIETARY OF AUTOCLAVED RICE, BUTTER, AND ONIONS

The clinical evidences of disease due to this dietary are the result of three factors operating in conjunction—deficiency of vitamin B, excess of starch, and excess of fats—with the occasional co-operation of a fourth—infection. They are in general similar to those resulting from an exclusive diet of autoclaved rice. Certain important differences are, however, to be noted: (1) The birds die sooner, lose weight more rapidly and develop symptoms more quickly; (2) the body-temperature and respirations begin to fall within the first week of the experiment (Figs. 5 and 6); (3) cases of an asthenic type are more common and cases of the cerebellar type less common; (4) convulsive seizures are not so frequent; (5) the diarrhœic motions may contain much fatty acid; and (6) œdema, as evidenced in post-mortem examinations, is much less common. As contrasted, then, with an exclusive diet of autoclaved rice, the addition of fresh butter and fresh onions to this diet is followed by certain notable results: (1) these additions do not prevent polyneuritis, which is due to the absence of vitamin B; (2) they protect to a great extent against œdema, which is due to the absence from autoclaved rice of some substance other than vitamin B; and (3) they kill the birds more quickly, due probably to the incomplete combustion of fats and to the more excessive production of toxic substances harmful to the organism.

Summary.—The symptomatic effects of a dietary devoid of vitamin B and excessively rich in fats and starch are thus: loss of appetite, tendency to diarrhœa of a fatty character, anæmia, rapid loss of weight, low temperature, slow respiration, rapid deterioration of bodily health, toxæmia, and symptoms referable to malnutrition of the nervous system.

CHAPTER VI

SYMPTOMS OF DEFICIENCY DISEASE IN MONKEYS

MONKEYS fed on the deficient dietaries to which reference has been made in Chapter III presented in general the same clinical features as pigeons: loss of appetite, gastro-intestinal disturbances, progressive loss of weight, progressive anæmia and asthenia, and, in those surviving long enough, symptoms due to malnutrition of the nervous system. These are to be regarded as the cardinal effects of the food deficiencies. The essential differences in the effects produced by the four dietaries were the greater or lesser degree of rapidity with which symptoms manifested themselves, and the greater or lesser delay in the inevitable issue—death. In animals the basis of whose food was autoclaved rice symptoms appeared early, and death resulted rapidly; in those receiving autoclaved food they appeared later and death was longer delayed.

Loss of Appetite.—Distaste for the deficient food is the first symptom to appear. In animals fed on autoclaved rice loss of appetite was complete in about ten days to a fortnight, after which death resulted in a comparatively short time; the fatal issue was hastened by an insufficient intake of food and by the severe diarrhœa. Loss of appetite made its appearance later in animals fed on autoclaved food. The appetite may become depraved; some of the animals have actually been observed to eat their own fæces. Distaste and loathing of food, loss of appetite, and it may be, also, depraved appetite, are thus cardinal symptoms of deficiency disease, and their significance is great. They are due in part to the monotony of the food, but in the main to insufficient supply of vitamins, and of vitamin B in particular. Thus Osborne and Mendel [1] have found that if animals, fed on purified dietaries free from this vitamin, are given yeast separately, it increases their appetite for the deficient food, no doubt in consequence of its high content of vitamin B. The well-known effect of yeast in improving the appetite in human beings is probably due to the same cause. Drummond [2] provides further evidence in regard to the action of vitamin B in this connexion. He finds that the addition of this vitamin to a synthetic diet causes a greatly increased intake of food, and consequently increased rate of growth. It would seem that the improved appetite is due to the improvement in the growth processes [3] and general condition of the animal consequent on

[1] *Jour. Biol. Chem.*, 1917, XXXI. 149, and 1918, XXXV. 19.
[2] *Biochem. Jour.*, 1918, XII. 41.
[3] Hopkins, *Jour. Physiol.*, 1912, XLIV. 425.

the provision of this vitamin; an improvement which results in the production of gastric and other digestive juices, and in acceleration of the chemical reactions requisite for growth. The animals are impelled to eat more in order that the cells stimulated to growth by the vitamin may be provided with energy-bearing and building materials, and with a suitable medium in which to perform their tasks. Vitamins are thus indirect stimulants of appetite; they induce the desire for food, and are, therefore, indirect stimulants of digestive juices. It seems to me that " loss of appetite " is one of the most fundamental of the signs of vitaminic deprivation. It is a protective sign: the first danger signal of impending disaster. It should at once excite suspicion as to the quality of the food in any patient who may exhibit it; for food deficiency is to be found in the most unlikely subjects, and in cases of the most diverse symptomatology. Thus the distaste for boiled milk exhibited so often by sufferers from enteric fever may indicate the necessity for supplementing the milk diet with vitamins. It is certain that invalid dietaries are frequently dangerously deficient in these indispensable substances. Persons receiving too little of them are often " finicky " eaters, nibbling at their food. I suspect also that the depraved appetite of some children has a like origin.

Vomiting.—This symptom was observed in four animals fed on autoclaved rice and in one fed on autoclaved food. It did not persist long. The animals receiving autoclaved rice and exhibiting it refused all food and died rapidly. In the case of the animal fed on autoclaved food and onion, in which vomiting was present, marked congestion of the stomach was found at autopsy, the mucous membrane of the pyloric half of the viscus being especially congested and ecchymotic. Clinicians are familiar with the resentment of the stomach to one-sided and monotonous dietaries, especially in the case of infants. This clinical fact may find its explanation in the observations here recorded. The changes in the adrenal glands are of importance in connexion with this symptom, since failure of their inhibitory action on the stomach may be concerned in its production.

Diarrhœa.—The most important, as well as one of the most constant, symptoms of food deficiency in monkeys is diarrhœa either with or without mucus and blood in the stools. It is also one of the earliest, as well as one of the most constant, symptoms of food deficiency in the human subject as is abundantly evident from the literature of such deficiency diseases as " war œdema " and " pellagra." But its true significance is rarely recognized in writings on these subjects, since authors have not fully realized that the same fundamental cause which produces the war œdema or the pellagra is responsible also for the diarrhœa or dysentery, namely food deficiency. Attempts are thus constantly made to account for the intestinal flux by one etiological factor—infection—and for the more obvious deficiency disease syndromes by another. Indeed, the gastro-intestinal disorder has been regarded by some as *predisposing* to, or causative of, these syndromes, by others as a *complicating* factor. In a sense both are right, for the diarrhœa increases the deficiency by hurrying the food rapidly through the tract, and

no doubt impedes recovery, especially when pathogenic organisms become firmly implanted upon, and in, the debilitated gastro-intestinal mucosa. But, as the experience now to be recorded proves beyond doubt, the food deficiency is the primary cause of the diarrhœa or dysentery as much as of the deficiency disease syndrome. And of greater importance still, it proves that a well-balanced food containing a sufficiency of vitamins will prevent the diarrhœa or dysentery as certainly as it will prevent the more obvious deficiency disease syndrome. With the knowledge provided by these observations in monkeys, "the colitis with mucus and blood" so frequently noted [1] as "the most common and troublesome complication of 'war œdema'" assumes a new significance, as does the observation that "diarrhœa of this type rarely occurred among well-fed prisoners, although they were exposed to infection." [1]

Of the 25 monkeys fed on the deficient dietaries, 21 suffered either from diarrhœa or from dysentery, while the controls remained free from both throughout the whole course of the experiment, although confined in the same animal room, cared for by the same attendant, and subjected to the same sources of infection. The far-reaching importance of this observation cannot be over-estimated. The *only* difference between animals which suffered from diarrhœa or dysentery and the controls which did not was in food. In animals receiving the autoclaved rice dietaries, diarrhœa made its appearance between the fourteenth and the twenty-fifth day of the experiment. In those fed on autoclaved food it appeared, as a rule, later. The symptom persisted either as a frank diarrhœa or merged into true dysentery. In animals fed on autoclaved food it exhibited a tendency to disappear, and to reappear at a later date, either as a diarrhœa or as a dysentery. The diarrhœic motions were small numerous, and pale in colour. Microscopical examination showed the stool to consist of (1) epithelial cells in various stages of disintegration; (2) enormous numbers of bacteria; and—in iodine-stained specimens from cases fed on autoclaved rice—(3) a small amount of undigested starch. *Amœbæ coli* were sometimes present. In animals receiving butter in addition to the autoclaved rice, another feature was added to the microscopical character of the stools: large amounts of fatty acids were present. In such cases the stools were paler than usual, and in two instances distinctly frothy, resembling those of sprue, the resemblance being carried further by their high fatty acid content.

Dysentery.—Out of twelve cases of diarrhœa occurring in monkeys fed on autoclaved rice, the symptom was preliminary to dysentery in four. After the lapse of a day or two during which diarrhœa occurred, the motions became mucoid and streaked with blood, later they consisted of pieces of tough blood-stained mucus intermingled with traces of pale yellow-white fæcal matter, but more often consisting solely of mucus and blood. In two cases among animals fed on autoclaved rice dysentery made its appearance without any preliminary diarrhœa. In animals fed on autoclaved food, dysentery without preliminary diarrhœa occurred in five cases, diarrhœa alone in four; in these the

[1] Park, *Jour. Am. Med. Assoc.*, 1918 (June 15). LXX. 24, 1826.

symptoms usually persisted longer than in animals fed on autoclaved rice, the latter dying within 4 to 7 days of their first appearance.

In the diagnosis of these cases I had to limit myself to investigation of the microscopical characters of the stools. Bacteriological examinations could not, unfortunately, be undertaken. I am, therefore, unable to say how far bacilli of the dysenteric group may have been responsible for, or participated in, the production of the dysenteric symptoms. There were present in the stools enormous numbers of cellular elements of the most diverse forms and sizes. These elements included, in addition to amœbæ in some cases: (1) desquamated epithelial cells in various stages of disintegration, appearing singly or in connected groups of a dozen or more; (2) red blood-corpuscles always in considerable numbers; (3) leucocytes and pus cells in large numbers; (4) single, double, and more rarely four-nucleated round cells; and (5) large mononuclear cells ranging in size up to 25 μ or even more; the majority of these cellular elements showed degenerative changes. In arriving at a diagnosis as to the " amœbic " character of the dysentery, no case was so classed unless amœbæ with included red blood-corpuscles were present, or unless definite *Entamœba histolytica* cysts were associated with the amœbæ in the stools. On this basis four cases among animals fed on autoclaved rice were classed as " amœbic " ; two cases among animals fed on autoclaved food. Search was made among the controls for amœbæ-carriers, and although one examination only was made—which is rarely sufficient to exclude them—*E. histolytica* cysts were found in one case, blastocysts (degenerative forms of *E. histolytica*) [1] in two, and *E. coli* in three others. It follows, therefore, that some among the control animals were carriers of pathogenic amœbæ. It is possible that flies may have conveyed *E. histolytica* cysts or dysenteric bacilli from infected to non-infected animals in the same room, but whether or not this occurred it is obvious that a well-balanced dietary secured the immunity of the controls. In the case of certain animals fed on autoclaved rice, the effect of substituting an adequate dietary for the deficient food was observed. It was noted, in the few cases in which such substitution was made, that diarrhœa and dysentery disappeared rapidly. I am informed by Dr. Drummond that, among rats fed on synthetic foods deficient in vitamins, blood-stained diarrhœa is often noted.

Loss of Body-weight.—As the animals were wild and difficult to handle, they were weighed only at the beginning and end of the various experiments. Their weights are shown in Table V (p. 60).

From Table V it is seen that the controls maintained a fairly constant level of weight throughout an average period of 93·5 days; individuals, however, showed varying moderate losses or gains in weight (Table II, p. 33), the most notable being No. 16, which lost considerably. The relatively slight average loss of weight in the controls as a whole is attributable to the fact that sudden confinement of wild animals cannot fail to influence them unfavourably. The

[1] Flu, *Mededeelingen van den Burgerl ijken Geneeskundigen Dienst in Nederlandesch-Indie*, Deel, 1918, VI. 113-16 and 164.

TABLE V

Category and Number of Animals in Each.	Average Weight before Experiment, in Grams.	Average Weight after Experiment, in Grams.	Average Loss of Weight per Kilogram of Original Body-weight in Grams.	Average Days under Experiment.	Average Daily Loss of Weight in Grams per Kilogram of Original Body-weight.
(*a*) Controls, 8 . . .	2,360	2,307	22	93·5	0·23
(*b*) Autoclaved rice, 10 .	1,693	1,270	249	23·4	10·6
(*c*) Autoclaved rice and butter, 4. . .	2,217	1,655	253	15	16·8
(*d*) Autoclaved food and onion, 6 . . .	1,748	1,190	320	71·1	4·5
(*e*) Autoclaved food, butter and onion, 5 .	2,442	1,710	294	65	4·5

comparatively high level of health maintained by the controls is sufficient evidence of the appropriateness of their food-supply.

It will be noted that, in all four categories of deficiently-fed animals, the loss of weight ranged between 25 and 32 per cent., the most rapid loss occurring in animals fed on autoclaved rice and butter. The table emphasizes the harmful influence exercised by the addition of the butter to a dietary excessively rich in starch and deficient in proteins and accessory food factors. It emphasizes also the important part played by an adequate supply of suitable protein in prolonging the life of the animals.

Respiratory Rate, Body-temperature, and Heart's Action.—Owing to the difficulty of handling the animals, it was found impracticable to make extended observations with regard to respiration, temperature, and heart's action. Such as were made towards the end of the experiment indicated that the temperature was lower than normal, and the heart's action weaker than in health.

Anæmia.—This symptom made its appearance rapidly in animals fed on autoclaved rice, more slowly in those fed on autoclaved food. The pallor, often intense and suggestive of pernicious anæmia, of the deficiently-fed animals was in marked contrast to the lack of it in controls fed on an adequate dietary. No blood estimations could be undertaken; the pallor was indeed sufficient evidence in itself of a severe anæmia.

Asthenia.—This symptom was gradual in its onset in monkeys fed on autoclaved food, rapid in its onset in those fed on autoclaved rice. Towards the end of the experiments the degree of asthenia and muscular weakness among animals in all categories was profound.

Weakness of the limbs.—This symptom was, as a rule, well marked during the later stages of the experiments in all animals. I was unable to satisfy myself in every case that this weakness was due to nerve change rather than to muscular wasting. Examination of the peripheral nerves after treatment by Marchi's method revealed, however, degenerative change in a high proportion of the animals: in three out of fourteen fed on autoclaved rice; in six out of eleven fed on autoclaved food. The presence or absence of these

changes appeared to depend to a great extent on the longevity of the animal. No doubt the weakness of the limbs was due in some measure to nerve lesions. Monkeys exhibiting leg symptoms were observed to limp, one leg being kept flexed and held away from the ground, giving the impression of pain in the limb. It was noted also, in more than one instance, that the right leg would be so held one day, the left leg another. Towards the end of the experiment, when they were made to move about the laboratory, it was often noticed that one leg tended to give way under the monkey's weight. This observation applied to both the upper and the lower limbs, so that animals so affected, when moving on all fours, often toppled over on their sides, and regained the erect position laboriously; such was the case in the animal shown in Fig. 9. Sometimes the lower limbs assumed a spread-eagle appearance, and could only be drawn under the body with difficulty. As a rule, animals fed on autoclaved rice or on autoclaved rice with butter died before any noteworthy symptoms, other than intense weakness, were observable in their limbs. The proportion of these cases exhibiting degenerative changes in the peripheral nerves was small in comparison with that in animals fed on autoclaved food.

FIG. 9.—Monkey No. 26, fed for sixteen days on autoclaved rice, and subsequently on autoclaved food (bread, milk, ground-nuts, and rice) with fresh onion. Photograph taken on the fiftieth day of experiment. Note wrist-drop. Femoral nerves showed moderate degree of degeneration.

Wrist-drop.—An appearance suggestive of wrist-drop (Fig. 9) was sometimes noted in animals fed on autoclaved food. The hands of healthy monkeys are often held in the dependent position shown in the figure; but while in health this position appeared to be one of choice, in the diseased animals it was often one of necessity. An animal, seated as in the figure, might be observed to interest itself in the capture of body fleas, all movements to that end being carried out with the wrist in the wrist-drop position. In this pursuit it seemed to be unaware that the tips of the first finger and thumb were not touching each other, and to be greatly surprised when the object of its search was not found between them.

Headache.—This appeared to be a fairly constant symptom, if one is justified in assuming its presence by the attitudes taken up by the animals: they were often observed to support the head in the hand as though it ached. Those fed on autoclaved food almost always presented, in the later stages of the experiment, a dazed, apathetic, and woebegone expression.

Gangrene of the Tail was met with in a number of cases.

Diminished Sensibility was undoubtedly present in the majority of animals towards the end of the experiments. It was often noted, as regards the tail, that

FIG. 10.—Fibres of the femoral nerve showing typical Wallerian degeneration. From a monkey fed on autoclaved food and onion. × 250.

the animal seemed to be quite unaware of the fact that one had placed one's foot upon it. I have often tapped the tail sharply with a ruler from the tip to the root, without the animal appearing to be aware of my action.

It is obvious, then, that the majority of animals which survived the deficient food for any length of time—especially those in the autoclaved food categories—exhibited a pronounced depression of functional capacity on the part of the nervous system. Histological study of the nerves removed at autopsy showed that death of a number of its neurons had occurred (Fig. 10).

Disorders of the Skin.—Disordered function of the skin was evidenced chiefly by the changes which occur in the hair. It becomes coarse and staring

(Fig. 9) and falls out easily. The skin is often rough and scaly, showing branny desquamation, and in some cases a scaly eczematous condition was present. A bleeding eczema of the parts surrounding the anus was observed in two monkeys.

Summary.—The clinical evidences of disease resulting in monkeys from deficient foods are the following: Distaste and loathing of the food, loss of appetite, depraved appetite, vomiting, diarrhœa, dysentery, anæmia, loss of weight, low body-temperature, cardio-vascular depression, asthenia, loss of health of the skin, and finally symptoms referable to malnutrition of the nervous system.

It is notable that dropsy did not occur in any of the monkeys. While, therefore, a morbid state comparable to that known as " dry beri-beri " was produced in monkeys fed on autoclaved food, the state known as " wet beri-beri " was not reproduced.

It will have been noted, by those familiar with the clinical picture of pellagra, that the gastro-intestinal disturbances, the unhealthy skin, and the evidences of malnutrition of the nervous system observed in monkeys fed upon autoclaved food are features which are also present in this malady.

CHAPTER VII

SUMMARY OF SYMPTOMATOLOGY

I. SYMPTOMS ASSOCIATED WITH LACK OF VITAMIN C

GUINEA-PIGS fed on a scorbutic diet of crushed oats and autoclaved milk develop in the course of a few weeks a condition of ill-health which closely simulates scurvy in man: swelling and tenderness of joints, and a spongy, hæmorrhagic, and painful condition of the gums appear; the teeth become loose, eating is painful or impossible; and finally death ensues after a period which is longer or shorter according to the degree of deprivation of the specific vitamin C, and to the degree of ill-balance of the food in other respects. Hæmorrhages may occur from the bladder or bowel, in the neighbourhood of joints, and may, indeed, be found anywhere. Swelling of the ribs occurs, and fractures at the junction of the bone with the cartilage may be present. Such features may also be found at the junction of shaft and epiphysis of long bones in which rarification is the rule.

The optimum conditions for the development of this malady in the human subject are provided when in a rapidly-growing child the food is deficient in vitamin C, ill-balanced with respect to other essential ingredients, and the gastro-intestinal tract is in a state of ill-health. I have not had an opportunity to go into the question of the pre-scorbutic manifestations of this form of food deficiency in the same detail as in the case of the pre-neuritic manifestations of disease associated with lack of vitamin B, but in the succeeding chapters evidence will be found indicating that hæmorrhagic lesions of the adrenal glands, the intestinal walls, and the bladder, all of which may be productive of pre-scorbutic symptoms, may occur before the classical evidences of scurvy manifest themselves.

II. SYMPTOMS ASSOCIATED WITH LACK OF VITAMIN-A

As in food deficiencies of other orders, the optimum conditions for the development of morbid states are provided (1) by deficiency of the specific vitamin; (2) by lack of balance of the food; (3) by factors which impose additional burdens on the metabolic resources of the body; and, possibly, (4) by the co-operation of pathogenic micro-organisms. The results associated with lack of this vitamin may be summed up as follows:

(1) Failure of the processes of growth[1]; (2) a greatly reduced resistance to

[1] *38th Rep. Med. Res. Com.*, London, 1919.

infectious agencies; (3) failure in the development of bone, cartilage, and teeth, and in calcium metabolism; (4) tendency to œdema; (5) failure of nutrition of the cornea. The morbid states in the genesis of which deficiency of this vitamin is believed to be concerned are the following: keratomalacia,[1] rickets,[2] deficient calcification of the teeth,[3] osteomalacia,[4] malnutrition œdemas, and phosphatic urinary calculi.[5] Although it is not unequivocally proved that lack of this vitamin is the sole cause of any of these, it may be accepted that it has often to do with their causation.

III. SYMPTOMS ASSOCIATED WITH LACK OF VITAMIN B

A consideration of the data afforded in the two preceding chapters indicates that the symptoms resulting from faulty foods deficient in vitamin B are essentially the same in monkeys and pigeons. It may be anticipated, therefore, that they will be essentially the same in the human subject. It has been shown that these symptoms occur in a fairly definite order; the first to appear are those referable to the digestive and endocrine systems, the last those referable to the nervous system. The earlier manifestations are the more important since they are the signs by which it may be recognized that our ship is running on the rocks. These signs are clear; although not all of them are always present in the same animal nor in equal degree in all animals. They include: (1) distaste for food, loss of appetite or depraved appetite; (2) gastro-intestinal derangements, indigestion, colitis, and intestinal fluxes; (3) loss of weight, weakness, and lack of vigour; (4) headache, anæmia, tendency to œdema, and unhealthy skin; (5) subnormal temperature and cardio-vascular depression. Finally, the clinical picture may be completed by the later appearance of symptoms due to malnutriti onof the nervous system.

These, then, are the main symptoms of deficiency disease as observed in animals. They do not include the subjective sensations of the animals themselves. In human beings, under like conditions of faulty feeding, such symptoms as flatulence, pain in the abdomen due to gaseous distension of the hollow viscera, headache, giddiness, weakness, breathlessness, palpitation, coldness, pains in various parts of the body, will be added. We must expect to hear complaints of such subjective sensations as these among the deficiently fed, having regard to the morbid changes in the various organs and tissues of the body which result in consequence of deficient and ill-balanced food.

CONCLUSION

Recollecting that all these evidences of deficiency disease are influenced in their onset by the variety of factors to which reference has been made in

[1] 38*th Rep. Med. Res. Com.*, London, 1919.
[2] Mellanby, *Jour. Physiol. Proc.*, 1918, LII. xi.
[3] Mellanby, May, *Lancet*, London, 1918 (Dec. 7), p. 767.
[4] *Brit. Med. Jour.*, 1920 (April 3), p. 477.
[5] *Jour. Am. Med. Assoc.*, 1917 (July 7), LXXIX. 32.

Chapter IV; that their onset is invariably delayed by a lesser degree of avitaminosis and more perfect balance of the food, or hastened by a greater degree of avitaminosis and more imperfect balance of the food; that deficiency of one vitamin is often combined with deficiency of another, with excess of one proximate principle or with deficit of a second, it becomes evident that such permutations and combinations of factors intrinsic to the food and of factors extrinsic to it may occur as will include within their orbit a vast amount of ill-health among human beings at the present day.

PART III

PATHOGENESIS OF DEFICIENCY DISEASE

CHAPTER VIII

MORBID ANATOMY

We come now to a consideration of the morbid anatomical changes found to result from food deficiency.

I. THE EFFECTS OF INANITION IN PIGEONS

The morbid anatomical changes resulting from inanition were studied in six pigeons. The following account taken from my post-mortem notes is representative of the appearances observed in four of them. In two others, killed on the thirteenth day of the experiment, generalized atrophy was the only noteworthy feature.

Pigeon No. 125.—Bird died on the eleventh day of the experiment, having lost 80 grams in weight. Wasting was very pronounced. *Skin:* darkish in colour, owing to complete loss of subcutaneous fat. No petechiæ. *Pericardium:* two large drops of amber-coloured fluid pipetted off from the sac. *Heart:* ventricles atrophic; auricles greatly dilated, like a cap on top of the small atrophic ventricles, filled with dark clot. Auricle walls very thin, quite transparent in parts. Well-marked band of œdema at the auriculo-ventricular junction. *Lungs:* no naked-eye change. *Liver:* small, light chestnut colour, no hyperæmia. *Spleen:* very small, slate-grey in colour. *Pancreas:* great atrophy, dead-white in colour for the most part, few ecchymoses, splenic end bile-stained. *Stomach:* much reduced in size; contents *nil*, lining very dark green, suggesting *B. pyocyaneus* infection (culture negative). *Œsophagus:* thin, no congestion. *Intestines:* very thin, almost transparent in parts; upper 2 inches show ecchymoses on mucous surface. Lower part of bowel greatly bile-stained. No intestinal parasites. *Testicles:* small. *Adrenals:* larger than normal, colour yellowish, no hyperæmia, not so yellow-ochre-coloured as in health. *Kidneys:* slightly smaller than normal, some congestion of lower pole of left kidney. Few drops of fluid in the abdominal cavity. *Thyroids:* pale, very small. *Parathyroids:* not examined. *Thymus:* greatly atrophied, existing only as a thin thread of tissue on either side. *Brain:* very anæmic; very soft. *Pituitary:* appears to be of usual size; very pale in colour. Heart's blood and organs sterile.

While this description applies in general to four cases of the six, each differed in some respect from the others. In No. 122, three drops of fluid were pipetted off from the pericardial sac. Some œdema of the lungs was present, as well as slight œdema of the groins. In Nos. 123 and 124, no fluid was present in the pericardium, although in both there was well-marked œdema at the auriculo-ventricular junction of the heart. In No. 122, no ecchymoses were present in the pancreas, but small pin-point necrotic-like areas were seen.

Apart from the generalized atrophy, the most marked features in these birds were (1) the enlargement of the adrenals; (2) the band of œdema replacing

the band of fat at the auriculo-ventricular junction of the heart; and (3) the pronounced changes in the pancreas.

While the effects of starvation in producing generalized atrophy of the body tissues, fall of the respiratory quotient, acidosis, and even degenerative changes in tissue cells—as, for example, in those of the liver and nervous system—are well known, it has seemed to me essential to establish, by weighing the organs, a mathematical basis for comparison with conditions in which the food was qualitatively deficient. The number of birds employed is small, but is sufficient for the purpose in view.

In Table VI the weights of these organs are given. In Table VII they are contrasted, per kilogram of body-weight, with those of controls and of birds fed solely on milled rice.

TABLE VI

SHOWING WEIGHTS OF ORGANS OF "INANITION PIGEONS"

No. of pigeon	122	123	124	127	125	126	
Sex	Female	Female	Female	Female	Male	Male	
Weight before experiment	265	265	240	270	280	280	grams.
Weight after experiment	150	150	140	185	160	170	,,
Weight of thymus	60	105	52	62	26	15	milligrams.
Weight of thyroids	15	18	16	20	11	15	,,
Weight of liver	3·9	4·41	2·855	3·891	4·15	4·5	grams.
Weight of spleen	150	42	63	120	52	110	milligrams.
Weight of stomach	3·72	4·305	4·335	4·84	4·345	3·435	grams.
Weight of kidneys	1·28	1·335	0·93	1·022	1·131	1·09	,,
Weight of adrenals	31	40	28	28	28	45	milligrams.
Weight of testicles or ovary	35	88	62	85	460	580	,,
Weight of pancreas	395	578	388	535	382	380	,,
Weight of heart	1·585	1·785	1·405	2·07	1·57	1·345	grams.
Weight of lungs	2·372	2·74	2·195	2·95	2·023	1·66	,,
Weight of brain	1·815	1·762	1·965	1·92	1·954	1·92	,,
Weight of pituitary	4	3	3	5	5	5	milligrams.

The organs of birds dying of inanition fall into two categories when contrasted as regards weight with those of healthy birds:

1. Those which increase in weight: the adrenal glands and the brain.

2. Those which decrease in weight: the thymus, the testicles, the spleen, the ovary, the pancreas, the heart, the thyroids, the liver, the stomach, the kidneys, and the pituitary body. The degree of atrophy is approximately in the order in which the organs are named. To these must be added the intestines, which were, however, not weighed.

It would seem that in pigeons the more urgent needs of the adrenal glands, the brain, the pituitary body, the thyroid gland, the kidneys, and the heart for proteins, fats, glycogen, vitamins, and salts are supplied for a time at the expense of organs less essential to the life of the individual: notably at the expense of the thymus, the reproductive organs, and the spleen.

These observations afford an interesting contrast to those presently to be recorded in the case of pigeons fed on milled rice dietaries (Fig. 11). It will be

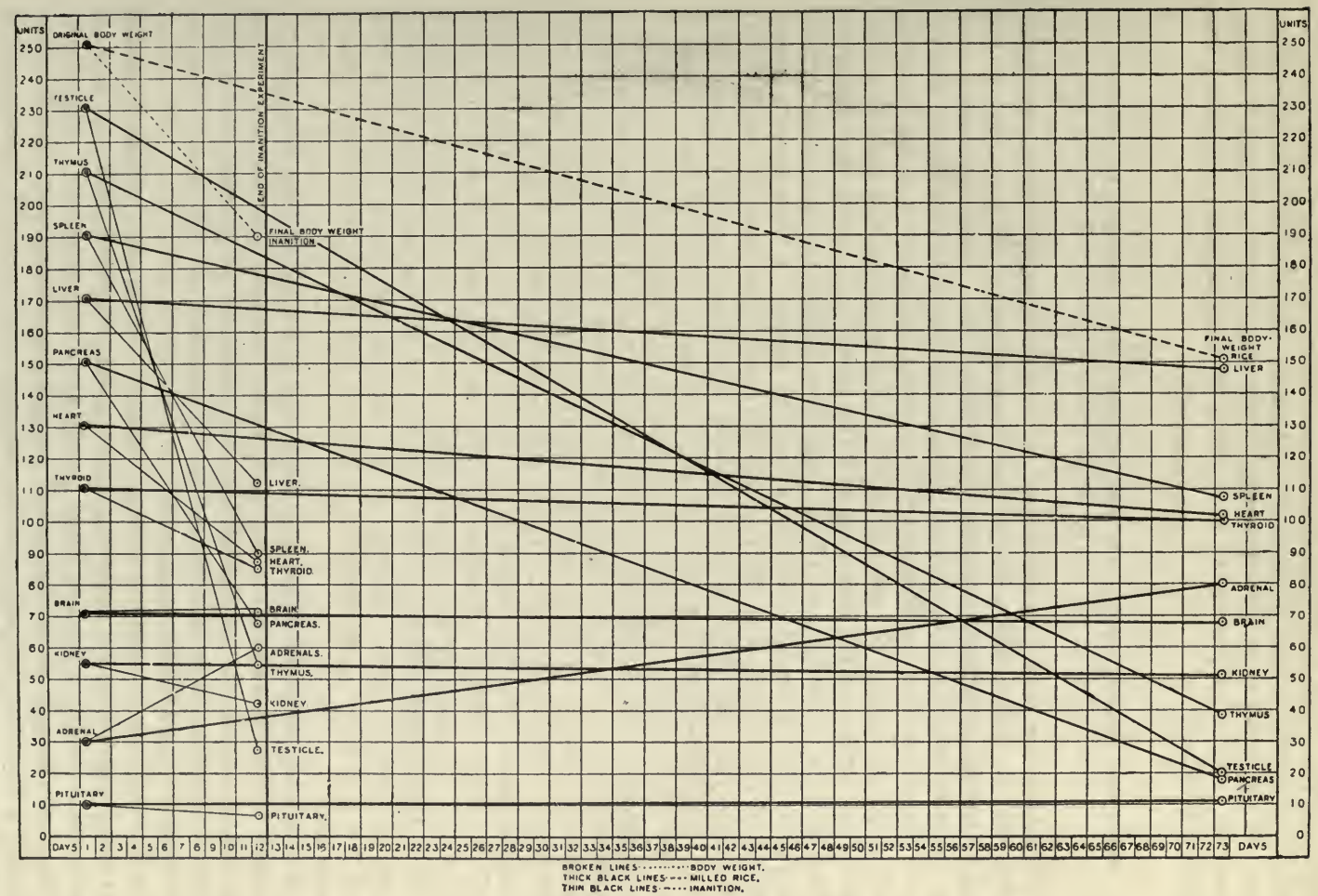

FIG. 11.—Showing degree of atrophy or hypertrophy of individual organs with respect to length of subjection to deficient food in (*a*) inanition and (*b*) milled rice dietaries.

observed that, while the atrophy and hypertrophy are alike in kind, they are greater in degree in birds subjected to inanition. In the one case inanition is acute, in the other it is more prolonged. Inanition is thus shown to be an important cause contributing to the genesis of morbid states resulting from a sole diet of milled rice.

II. THE EFFECTS OF AN EXCLUSIVE DIET OF MILLED RICE IN PIGEONS

At autopsy the great general wasting was very striking. The skin was slightly darker than in control birds, due to the disappearance of all subcutaneous fat: no petechiæ or cutaneous ecchymoses—although the surface and deep veins were often engorged—were observed. The neck was thin, the breast muscles greatly wasted so that the sternum projected like the keel of a racing yacht. In a very small percentage of cases slight subcutaneous œdema was present, especially in the regions of the abdomen and the groins. The flesh was usually of normal tint, and presented, apart from the great wasting, no macroscopical appearance appreciably different from that of healthy birds. In some cases a curious mottling of the muscles was observed, darker and lighter areas alternating with each other. In others the muscles were of a uniform darkish red hue much darker than that observed in control birds; still more rarely the tint of the flesh was very dark, approaching that characteristic of septicæmic cases. The fact that septicæmic states imparted to the skin and muscles different appearances from those in which the tissues were shown to be sterile is of considerable practical importance. One can tell almost at a glance which birds have sterile organs and which have died of septicæmia. It has not been observed that the muscles were invariably damp. Indeed, œdema of the muscles was rare, but in those cases in which it was present it was a marked feature; in one it was so marked as to necessitate the use of swabs to clear the field of operation of the fluid exuding from the tissues. Hydro-pericardium or other evidences of œdema were present in about 45 per cent. of all cases. Œdema at the auriculo-ventricular junction of the heart was common. The bones were thinned, and the bone-marrow reduced in amount.

Here it may be pointed out that, while the general pathological features of cases of polyneuritis columbarum are likely to be the same in all countries where experiments on pigeons are carried out, they need not be identical. The chief causes of variation in morbid anatomical appearances are differences in degree of avitaminosis and infectious agencies.

In Table VII are shown the average weights of the internal organs of thirty-five control pigeons, and of thirty-four pigeons which developed morbid states in consequence of a diet consisting solely of milled and autoclaved rice. The weighing was done immediately on removal of the organs from the body. The autopsy, except in a few cases, was performed immediately after death. Attention to this point is of great importance, especially when the tissues are to be subjected to

histological study, and when dealing with such organs as the adrenals, whose epinephrine-content is so liable to rapid oxidation and decomposition after death. In all sixty-nine cases the heart's blood and internal organs were sterile.

TABLE VII

SHOWING WEIGHTS OF ORGANS OF CONTROL PIGEONS, OF THOSE FED ON RICE, AND OF PIGEONS SUBJECTED TO INANITION: WEIGHTS CALCULATED IN TERMS OF ORIGINAL BODY-WEIGHT OF BIRDS; ALL WEIGHTS IN MILLIGRAMS.

Organs.	Controls.		Rice.		Inanition.	
	Average Weight.	Weight per Kilogram.	Average Weight.	Weight per Kilogram.	Average Weight.	Weight per Kilogram.
	MALES		MALES		MALES	
Thyroids	24·7	84·7	22·5	76	—	—
Liver	6,168	21,136	5,178	17,540	—	—
Spleen	339·2	1,162	87·2	295	—	—
Heart	3,084	10,568	2,250	7,621	—	—
Kidneys	1,594	5,464	1,563	5,298	—	—
Adrenals	29·2	100·3	42	139·5	—	—
Thymus	678	2,324	14	47	—	—
Testicles	1,355	4,643	119	401·5	520	1,857
Pancreas	949·7	3,254	615	2,082	—	—
Brain	2,010	6,910	1,986	6,843	—	—
Pituitary	5·3	18·3	5·8	19·6	—	—
Stomach	5,716	—	3,514	—	—	—
	FEMALES		FEMALES		BOTH SEXES	
Thyroids	22·6	85·5	21·2	75·8	15·8	59
Liver	5,405	20,371	5,556	19,793	3,961	14,900
Spleen	284	1,071	71	252	89·5	336·6
Heart	2,713	10,228	2,139	7,621	1,626	6,119
Kidneys	1,480	5,578	1,543	5,500	1,164	4,379
Adrenals	24	90	41·9	149	33·3	125·4
Thymus	318	1,201	—	—	53·3	209
Ovary	253	953	85·7	305	67·5	260
Pancreas	898	3,383	562	2,004	443	1,666
Brain	1,861	7,015	1,862	6,635	1,889	7,107
Pituitary	5·9	22·1	6·3	22·4	4·1	15·6
Stomach	5.716	—	3,514	—	4,163	—

From a study of Table VII and the chart (Fig. 12) which illustrates it, it will be seen that the organs fall into two classes: 1. Those which increase in weight—the adrenals and, in males, the pituitary body.

2. Those which diminish in weight—the thymus, the testicles, the spleen, the ovary, the pancreas, the heart, the liver, the thyroids, the kidneys, the brain; the degree of atrophy being in the order in which the organs are named. To these must be added the intestines, the œsophagus, the stomach, and the bones.

Marked variations occur in different individuals in the degree of atrophy or of enlargement of any particular organ.

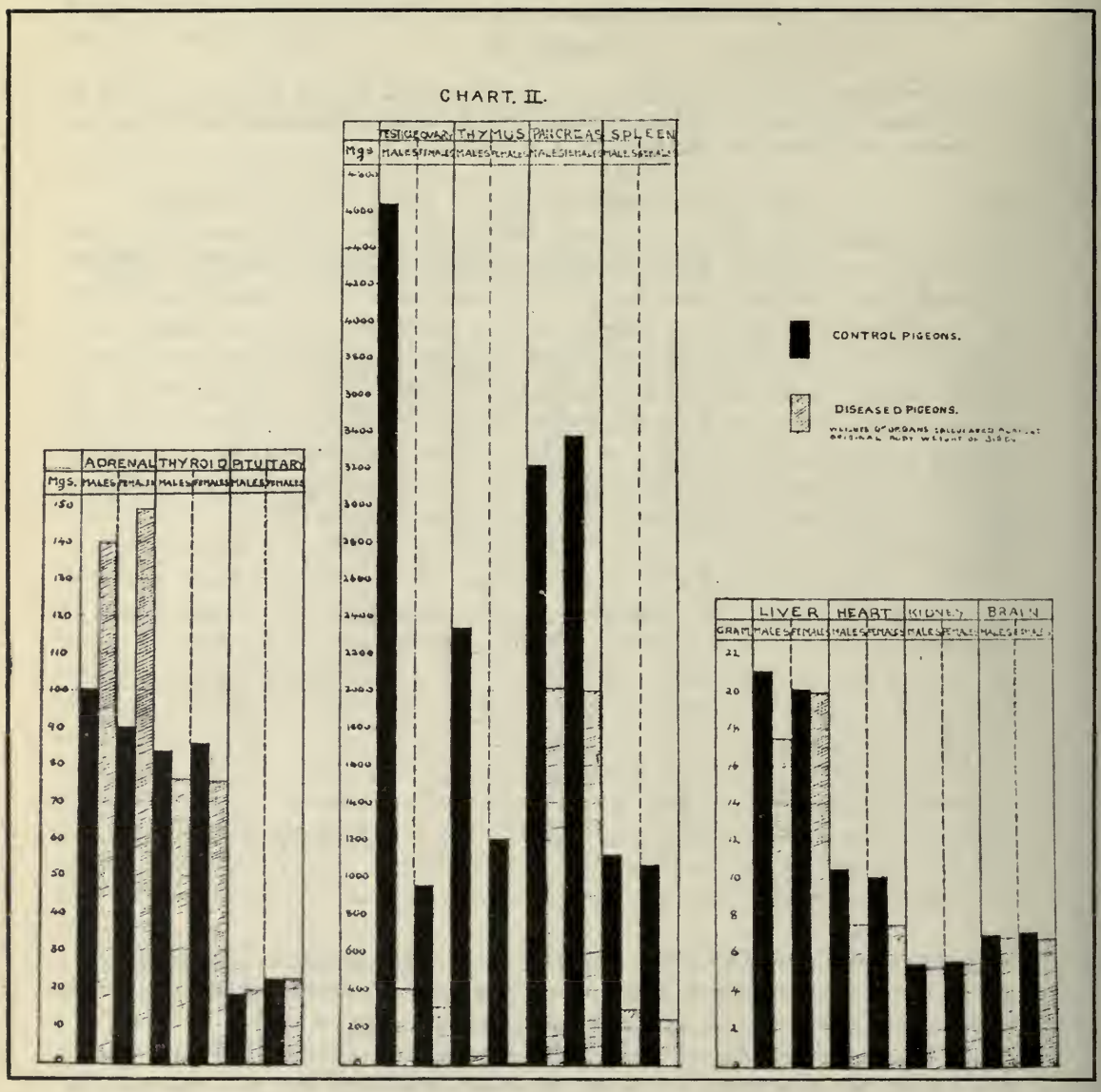

FIG. 12.—Showing weights of organs per kilogram of body-weight in control pigeons and in pigeons fed on milled rice; weights of the latter calculated against *original* body-weight of the diseased birds. Black columns, controls; shaded columns, polyneuritis columbarum.

III. THE EFFECTS OF A DIET OF AUTOCLAVED RICE PLUS BUTTER AND ONIONS IN PIGEONS

Since butter and onions are not normal constituents of the food of pigeons, it was necessary to control the observations under this heading by adding both of these to the natural food of healthy pigeons. The effects of this addition are shown in Table VIII.

TABLE VIII

SHOWING THE AVERAGE WEIGHT OF ORGANS PER KILOGRAM OF ORIGINAL BODY-WEIGHT IN (1) 24 PIGEONS FED ON MIXED GRAINS, BUTTER, AND ONIONS; (2) 20 PIGEONS FED ON AUTOCLAVED RICE, BUTTER, AND ONION; (3) 35 PIGEONS FED ON MIXED GRAINS ONLY; (4) 31 PIGEONS FED EXCLUSIVELY ON AUTOCLAVED RICE; AND (5) 6 PIGEONS FED EXCLUSIVELY ON RICE POLISHINGS.

Organs.	Grams or Milligrams.	Controls *with* Butter and Onions.	Polyneuritis Autoclaved Rice *with* Butter and Onions	Controls *without* Butter and Onions.	Polyneuritis: Autoclaved Rice *without* Butter and Onions.	Rice Polishings.
Thyroids	milligrams.	88·3	69·7	85·1	75·9	85
Liver	grams.	26·107	19·388	20·703	18·666	14·9
Spleen	,,	1·480	0·225	1·116	0·273	0·25
Heart	,,	11·033	7·148	10·398	7·621	6·05
Kidneys	,,	5·728	5·471	5·521	5·399	5·45
Adrenals	milligrams.	69·7	161	95·1	144·2	147·5
Thymus	grams.	1·752	Trace only	1·762	0·023	Trace only
Testicles	,,	4·853	0·279	4·643	0·401	0·61
Ovary	,,	1·215	0·356	0·953	0·305	0·23
Pancreas	,,	3·806	2·084	3·318	2·043	1·81
Brain	,,	6·262	7·212	6·962	6·739	7·23
Pituitary	milligrams.	17·3	18·5	20·2	21	20·2
Stomach	grams.	20·345	16·819	—	—	17·6
Lungs	,,	8·808	9·782	—	—	—
Average weight of birds	,,	308	276	280	288	257

A reference to columns 1 and 3 of Table VIII, and to the chart which illustrates it (Fig. 13), reveals the fact that the addition of butter and onions to the dietary of healthy pigeons causes marked differences in the weights of their organs as compared with those of birds fed on the more natural dietary of mixed grains. These differences may be regarded as departures from normal, and in some sense as evidences of morbidity. It will be observed that the organs of overfed birds group themselves into three classes:

(1) Those showing no appreciable difference in weight: the thymus.
(2) Those showing a difference in weight in the direction of increase; the spleen, the ovary, the liver, the pancreas, the heart, the testicles, the thyroid, the kidneys; the degree of increase being in the order in which the organs are named.
(3) Those showing a difference in weight in the direction of decrease: the adrenals, the brain, and the pituitary.

Subsequent experimentation has shown that these differences are in the main due to the addition of butter to the dietary of mixed grains, rather than to the addition of onions. This being so, it may be concluded that the over-

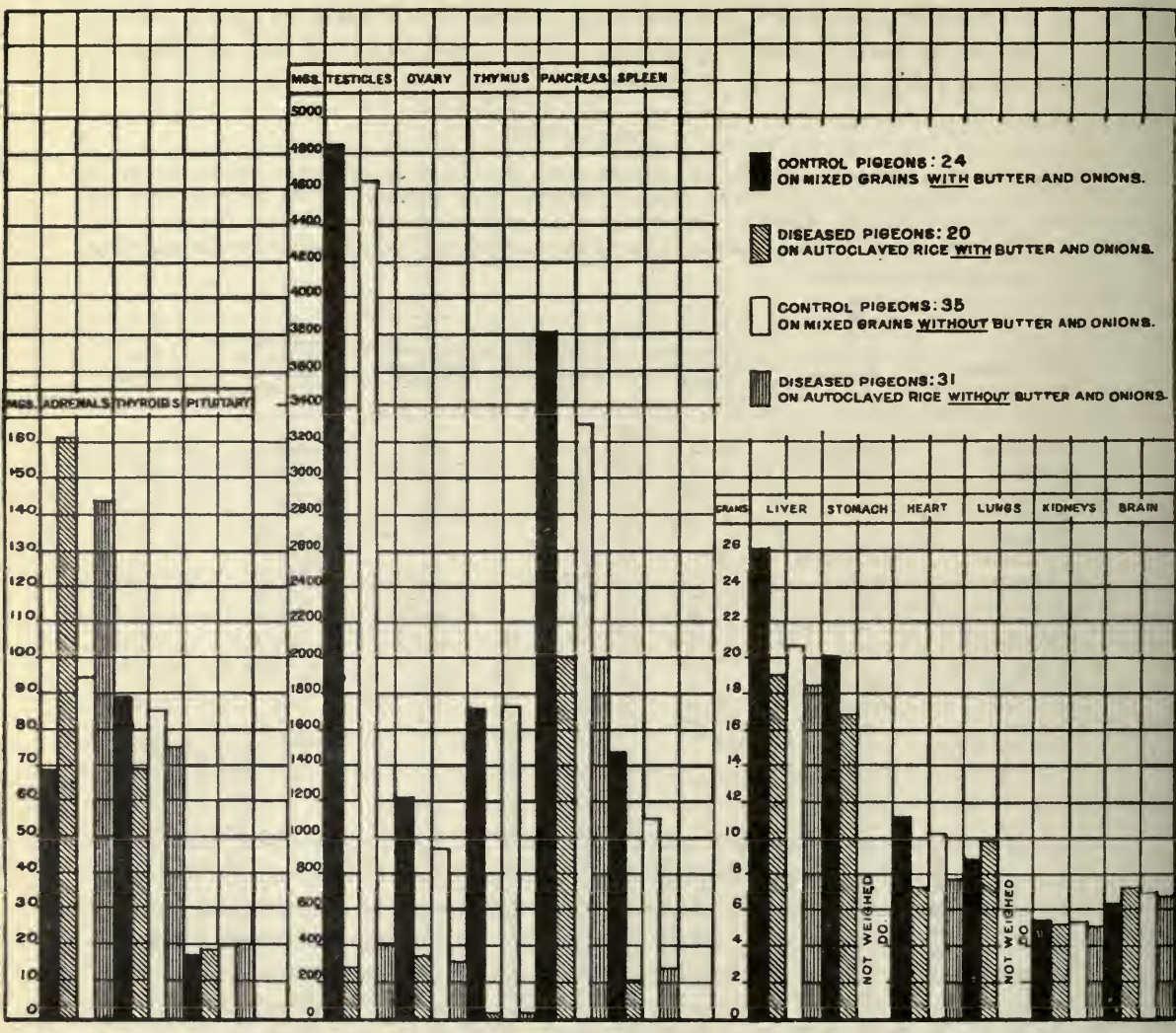

FIG. 13.—Showing average weight of organs per kilogram of body-weight in two series of control pigeons, and in two series of cases of polyneuritis columbarum. The chart illustrates the effect of an excess of fat in the dietary of healthy pigeons, as well as the effects of (*a*) a dietary deficient in all three classes of accessory food factors, and (*b*) a dietary deficient in the " B " factor alone.

loading of the body with fats leads to changes in the digestive and endocrine systems and in the heart which, it may be presumed, will ultimately cause a relative impairment of their functional capacity. The metabolic fire is thereby overstoked, requiring a greater draught to keep it burning briskly. In this

connexion the tendency to depression of the respiratory rate in the fat-fed control pigeons (Fig. 5) is not without significance. A further point suggested by the simile has reference to the thyroid gland. Although the average weight of this organ was not notably in excess of that found in birds fed only on mixed grains, it was noted that, in four instances out of twenty-four, the thyroid glands were well above the normal size; the weights being 129, 114, 137, and 300 milligrams per kilogram of body-weight as compared with the average weight of 85 milligrams. Subsequent experimentation on a large scale has confirmed this effect of overfeeding on the thyroid gland. By this means I have been able to produce in pigeons, within a period of 250 days, changes in this organ indistinguishable histologically from those found in Graves' disease.[1]

The most notable results in this experiment are the smaller size of both adrenals and pituitary, and the tendency to an increase in the size of the thyroid as a result of the addition of the unnatural food, butter, to the normal food of healthy pigeons. The adrenal glands, the pituitary body, and the brain are in these circumstances the only organs which diminish in weight. *Per contra*, under conditions of vitaminic deprivation these are the only organs which tend to increase in weight; they are thus very sensitive to food influences, and such influences affect their weights in like manner.

Reverting now to the morbid anatomical changes observed in the organs of pigeons fed on autoclaved rice, fresh butter, and onions—that is to say, on a food deficient in vitamin B and disproportionately rich in starch and fat—it is found that the general appearances were similar to those of birds fed exclusively on autoclaved rice. Evidences of œdema were, however, much less common. Table VIII gives the average weights of the organs per kilogram of original body-weight as compared with fat-fed controls, and with controls receiving no fat. The contrast is represented graphically in Fig. 13. It will be observed that the organs of the deficiently-fed birds group themselves into two classes:

1. Those which increase in weight: the adrenal glands, the pituitary body, the brain, and the lungs.
2. Those which decrease in weight: the thymus, the testicles, the spleen, the ovary, the pancreas, the heart, the liver, the thyroid, the stomach, and the kidneys; the degree of atrophy being in the order in which the organs are named. To these must be added the intestines, which undergo pronounced atrophy.

Marked variations occur in different individuals in the degree of atrophy or hypertrophy of any particular organ.

In general these results are similar to those noted in pigeons fed exclusively on autoclaved rice. They differ, however, in the following respects: the heart, the thyroids, the spleen, the testicles, and the pituitary body are smaller; the liver, the adrenals, the ovary, and the brain are larger. Some of these differ-

[1] *Ind. Jour. Med. Res.*, 1920, VII, No. 3, pp. 633–47.

ences may be due to variations in the ages of the birds employed in the two experiments; others, especially when they are found also in the case of monkeys, are to be attributed to the excess of fat in the deficient food.

It is thus seen that, when the food of pigeons is deficient in vitamins and excessively rich in energy-bearing elements, profound changes take place in the internal organs. Inanition brought about by deprivation of vitamin B plays a prominent part in their production, since they occur alike in pigeons deprived of all food and vitamins, in those deprived of all vitamins, and in those deprived of vitamin B only.

IV. THE EFFECTS OF AN EXCLUSIVE DIET OF RICE POLISHINGS IN PIGEONS

This diet, while containing an abundance of vitamin B, was very deficient in protein and in energy-bearing constituents. The birds fed upon it did not develop polyneuritis. They presented at autopsy great emaciation but no œdema. The weights of their organs are shown in Table VIII; they group themselves into three classes:

1. Those which are not appreciably altered in weight: the thyroid glands and the pituitary body.
2. Those which increase in weight: the adrenal glands and the brain.
3. Those which decrease in weight; the thymus, the ovary, the testicles, the spleen, the pancreas, the heart, the liver, the stomach, and the kidneys.

Marked variations occur, in different individuals, in the degree of atrophy or of hypertrophy of any particular organ. These results are in general similar to those noted in other categories, although differing in certain respects. In practice it is unlikely that human beings would ever make use of rice polishings as the sole source of food. The effects of such a diet do not, therefore, come within the range of practical medicine. They emphasize, however, that vitamins are but links in the chain of materials requisite for perfect nutrition, and that the state of inanition which is brought about by their absence results also from the absence of proximate principles, although vitamins be abundantly present.

Summary of Results in Pigeons.—The changes in the organs in all four categories of deficiently-fed pigeons are due to inanition, whether this be the result of deprivation of all food, of deprivation of all vitamins, of deprivation of vitamin B only, or of deprivation of calories, vitamin B being provided in abundance.

V. THE EFFECTS OF DEFICIENT FOOD IN MONKEYS

On coming to autopsy these animals were greatly emaciated, subcutaneous and abdominal fat being totally absent. No subcutaneous evidences of œdema were present; effusion into serous sacs was encountered in only one case, and

then it was but slight. Œdema at the auriculo-ventricular junction of the heart did not occur.

1. **Hæmic Infections**, as demonstrable by aerobic methods of culture, were present in five out of fourteen animals fed on autoclaved rice dietaries, and in one out of eleven fed on autoclaved food dietaries. The heart's blood of the controls was sterile. The organisms found were mainly of two kinds: small cocci and coliform bacilli; no attempt was made to differentiate them. It appears that hæmic infections occur less readily when the deficient food is well-balanced than when it is ill-balanced.

2. **Weights of Organs.**—The weights of the organs, in grams per kilogram of original body-weight, in controls and in deficiently-fed animals are shown in Table IX.

TABLE IX

Organs.	Controls.	Autoclaved Rice.	Autoclaved Rice and Butter.	Autoclaved Food and Onion.	Autoclaved Food, Butter, and Onion.
Adrenals	0·190	0·352	0·293	0·258	0·266
Thyroid	0·083	0·081	0·073	0·069	0·070
Pituitary	0 014	0·015	0·015	0·016	0·0118
Testicles	0·257	0·216	0·218	0·208	0·254
Thymus	0·54	Traces only	Traces only	Traces only	Traces only
Submaxillary glands	1·01	0·80	0·70	0·82	0·78
Pancreas	1·36	1·14	0·95	1·22	1·07
Spleen	1·5	1·3	1·1	1·2	0·9
Liver	29·8	26·4	27·8	22·2	25·3
Heart	4·47	3·53	3·44	3·03	3·8
Kidneys	5·03	5·16	5·3	4·6	4·8
Brain	28 8	41·5	32·4	37·0	29·8
Lungs	6·03	5·5	4·9	5·1	5·2

Note.—Original body-weight was taken as the basis for these calculations, since it appears to afford a fairer criterion of the degree of departure from health. When calculated against the final body-weight of the animals, the results are, of course, much more marked.

From a study of Table IX and the figures (Figs. 14, 15, 16, and 17) which illustrate it, it will be seen that the organs group themselves into three classes:

1. Those which increase in weight in all four categories: the adrenals, the brain.
2. Those which decrease in weight in all four categories: the thymus, the heart, the submaxillary glands, the pancreas, the spleen, the liver, the lungs, the thyroid, and the testicles.
3. Those which show an increase in weight in some categories, and a decrease in others: the pituitary body and the kidneys.

Marked variations occur, in different individuals, in the degree of atrophy or of hypertrophy of any particular organ.

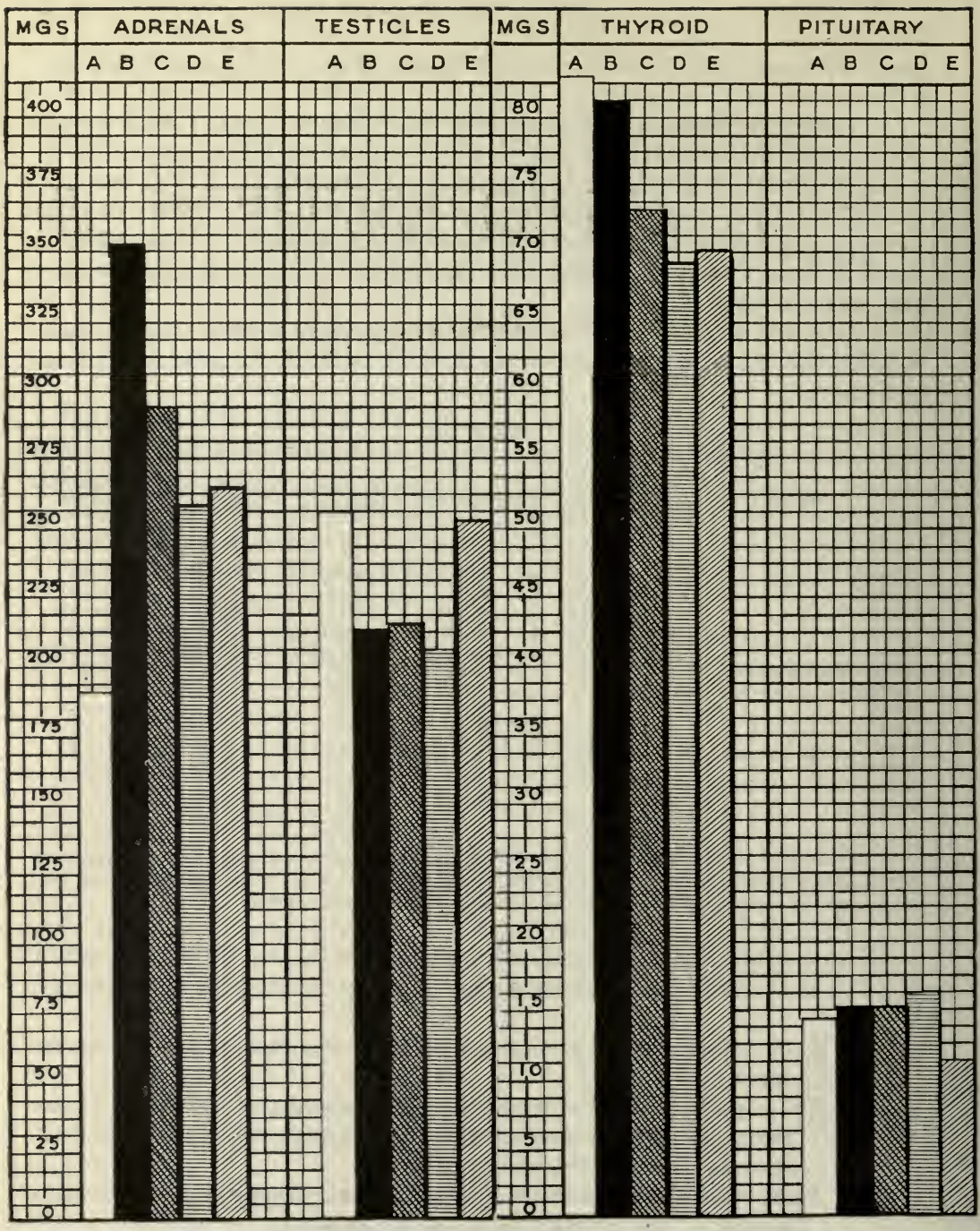

FIG. 14.—Showing the average weights of the adrenal glands, the testicles, the thyroid gland, and the pituitary body per kilogram of *original* body-weight in monkeys fed on deficient dietaries:—Column A: Controls; Column B: Autoclaved rice; Column C: Autoclaved rice and butter; Column D: Autoclaved food and onion; Column E: Autoclaved food, onion, and butter. Note the enlargement of the adrenal glands in all four categories, and that of the pituitary in categories B, C, and D; also the atrophy of the testicles in categories B, C, and D, and their freedom from atrophy in category E.

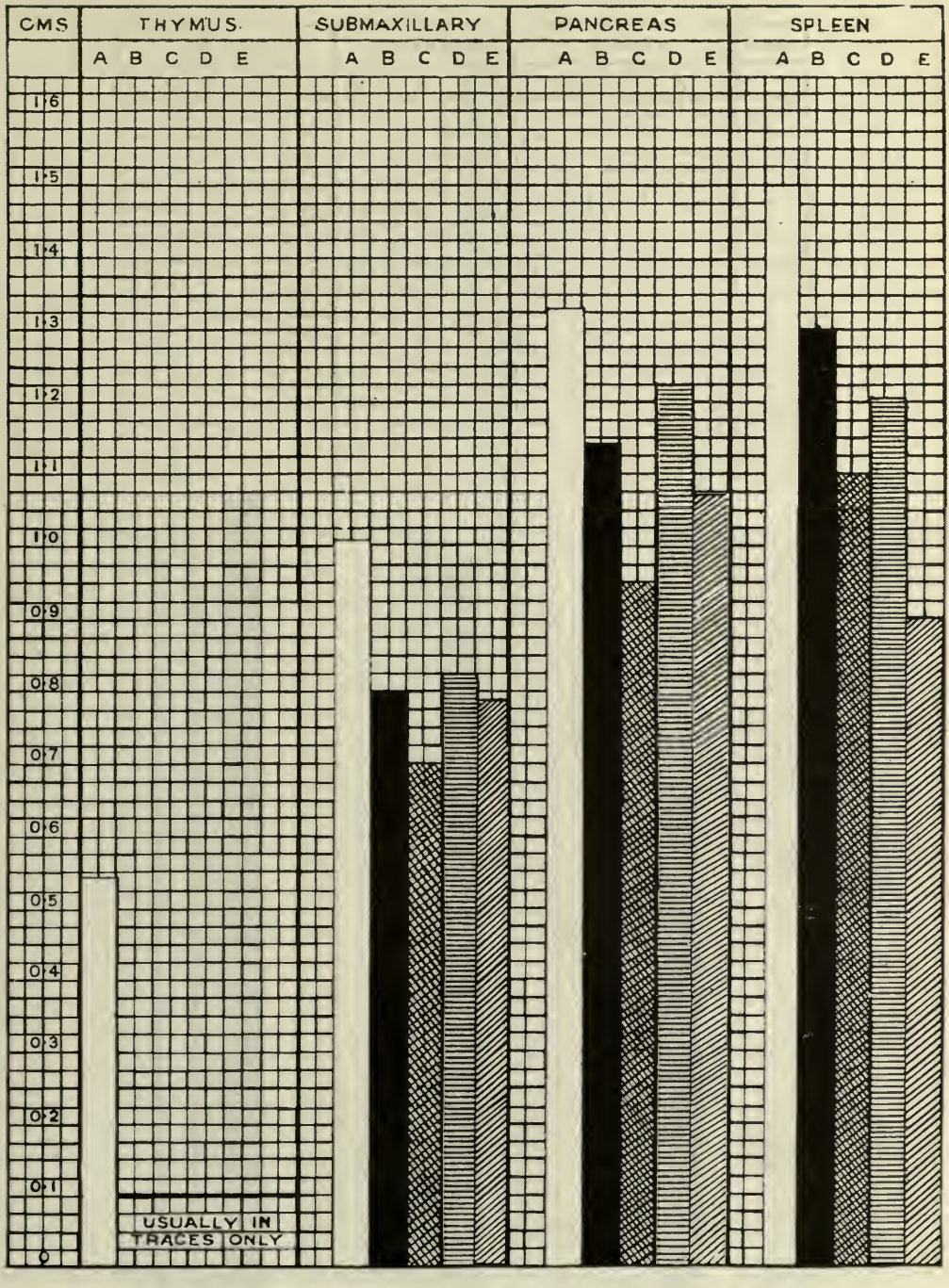

FIG. 15.—Showing the average weights of the thymus, the submaxillary gland, the pancreas, and the spleen per kilogram of *original* body-weight in monkeys fed on deficient dietaries:—Column A: Controls; Column B: Autoclaved rice; Column C: Autoclaved rice and butter; Column D: Autoclaved food and onion; Column E: Autoclaved food, butter, and onion. In all categories the thymus existed, as a rule, in traces only. Note the greater atrophy of the pancreas, the submaxillary gland, and the spleen in butter-fed animals.

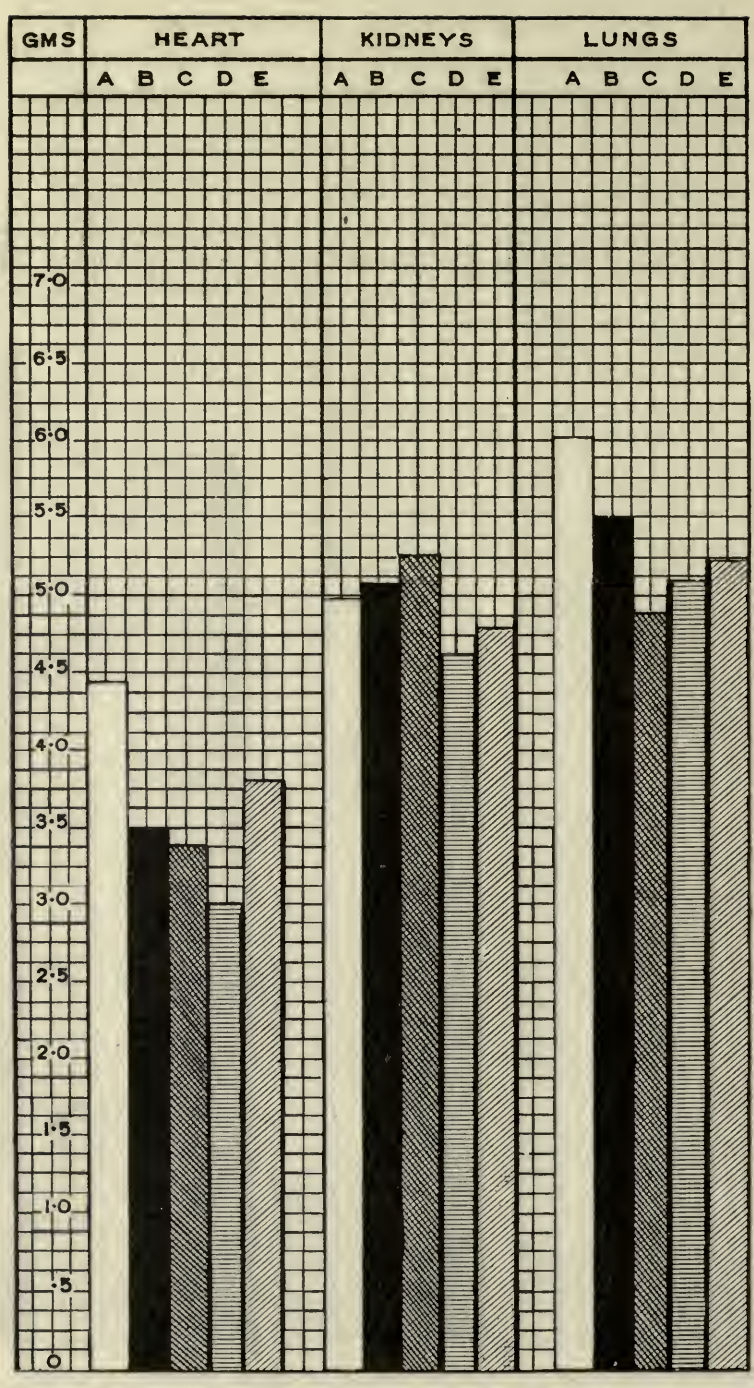

FIG. 16.—Showing the average weights of the heart, kidneys, and lungs per kilogram of *original* body-weight in monkeys fed on deficient dietaries:—Column A: Controls; Column B: Autoclaved rice; Column C: Autoclaved rice and butter; Column D: Autoclaved food and onion; Column E: Autoclaved food, butter, and onion.

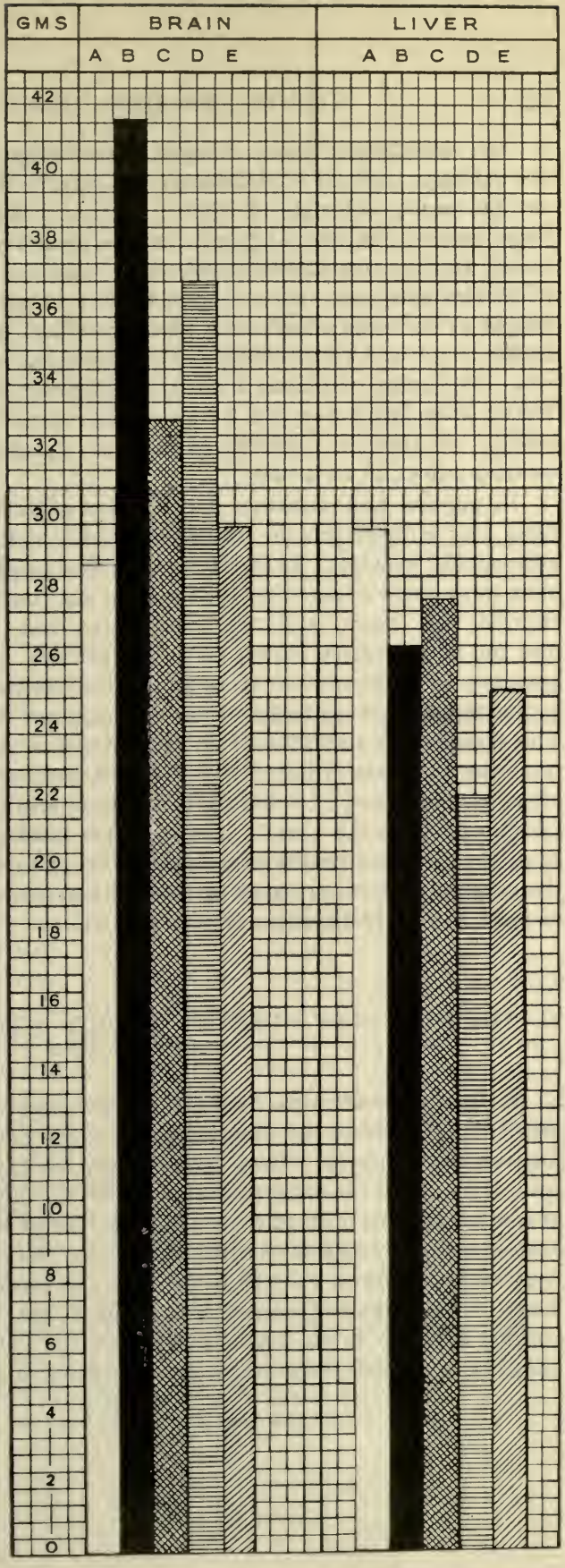

FIG. 17.—Showing the average weights of the brain and liver per kilogram of *original* body-weight in monkeys fed on deficient dietaries :—Column A : Controls ; Column B : Autoclaved rice ; Column C : Autoclaved rice and butter ; Column D: Autoclaved food and onion ; Column E : Autoclaved food, butter, and onion. Note the greater weight of the brain in all four categories. Allowance has to be made for the fact that the animals were all adolescents in Category B, while half of them were adolescents in Category D. Even with the correction for age the increased weight of the brain is a notable feature.

The similarity of these changes in the weight of the organs of deficiently-fed monkeys to those of deficiently-fed pigeons is very striking. In kind they are the same, although in degree they may differ. There is the same enlargement of the adrenal glands and the pituitary body, and the same atrophy of the thymus, the pancreas, the heart, and the thyroid gland. The atrophy of the testicles and spleen is much more intense in birds. The increase in weight of the brain observed in monkeys whose dietary was excessively rich in butter was found also in pigeons which received butter in addition to autoclaved rice. The lungs presented a material difference in the two species: in pigeons fed on autoclaved rice and butter, an increase in the weight of the lungs was noted; whereas in monkeys in all four categories, these organs showed a marked reduction in weight.

In pigeons and monkeys, the addition of butter to a diet deficient in vitamins and suitable protein, while excessively rich in starch, gives rise to some remarkable results. In both species the weight of the brain was greater than in animals whose deficient food did not contain butter, while that of the thyroid, the heart, and the spleen was less. In monkeys the pancreas and the submaxillary glands also weighed less. It would seem that, in the presence of deficiency of vitamin B, fats are incompletely oxidized and yield products which are harmful to the organism and to certain organs in particular. This observation may provide an explanation of the clinical fact that in children receiving an excess of butter with a boiled, pasteurized, or dried milk dietary the effect of the excess of butter is bad. Everhard and Felker [1] maintain that an excess of fats in the foods " always makes trouble." It renders the urine acid to methyl red, and results in bodily distress of various kinds. They suggest that the high fat percentage keeps the protein and carbodydrates so low as to produce anæmia and other disorders of malnutrition.

VI. THE EFFECTS OF A DIET OF CRUSHED OATS AND AUTOCLAVED MILK IN GUINEA-PIGS

As these animals were used for special purposes only, the data which they afford with regard to the weights of organs are not so complete as in the case of pigeons and monkeys. They concern only the thyroid, the adrenal glands, the spleen, the heart, the liver, the kidneys, and the lungs. The average body-weight of control animals prior to the commencement of the experiment was 521 grams, that of animals which received the scorbutic diet 532 grams. The final average body-weight showed a slight increase in the former, a marked decrease in the latter. In animals deprived of vitamin C the average loss within a period varying from 19 to 29 days was 152 grams. The weights of the organs per kilogram of original body-weight are contrasted in Table X.

[1] *Ohio State Med. Jour.*, 1919 (Aug.), XV, No. 8, p. 498.

TABLE X

Organs.	Controls.		Experimental Animals.	
	Average Weight in Grams.	Average Weight per Kilogram of Body-weight in Grams.	Average Weight in Grams.	Average Weight per Kilogram of Original Body-weight in Grams.
Thyroid	0·051	0·095	0·116	0·218
Liver	20·023	37·566	14·126	26·652
Spleen	0·640	1·200	0·300	0·566
Kidneys	5·543	10·400	4·901	9·247
Adrenals	0·450	0·846	1·009	1·903
Heart	2·290	4·302	1·800	3·396
Lungs	5·473	10·270	6·186	11·671

It is thus seen that the adrenals, the thyroid, and the lungs increase in weight, while the spleen, the liver, the heart, and the kidneys decrease in weight. Hæmorrhagic infiltration of the viscera was frequent.

CONCLUSION

The data afforded by this gravimetric method of study are of great importance, for although neither the increase nor the decrease in weight of an organ is *per se* conclusive evidence of its increased or decreased functional capacity, yet notable departures from normal weight, when taken in conjunction with histological changes, afford important indications of disordered function. These data demonstrate that not all organs of the body are affected in the same way by malnutrition, whether this be due to deprivation of calories or to the state of inanition resulting from foods deficient in vitamins and ill-balanced in other respects. The most remarkable result is the enlargement of the adrenal glands in all forms of food deficiency; one which is probably of much significance is the enlargement in males of the pituitary body. We also learn that, while in general certain organs enlarge and other organs atrophy, the degree of enlargement or of atrophy varies within wide limits in different individuals. This is of much importance; for while in one animal an organ, such as the pancreas, may be markedly atrophic, and certainly depreciated in functional capacity, in another it may be but little affected. We learn, further, that the organs least essential to the life of the individual are those which suffer most, and that nature does its best to protect the more important structures. We have seen, too, that while butter may be beneficial in one regard, as in its tendency to protect against œdema, it may be injurious in another when added to a dietary deficient in vitamin B and ill-balanced in other respects. Finally, the data indicate the important part played by vitamins in general, and by proper balance of the food, in relation to the functional perfection of every organ and tissue of the body. It may be again emphasized that, indispensable as are vitamins in a properly constituted diet, the proximate principles of the food are equally so.

CHAPTER IX

THE GASTRO-INTESTINAL TRACT

We come now to consider in more detail the special effects of food deficiency on various organs of the body; and since the digestive system is the first to be concerned with such deficiency, and the first to exhibit symptoms of disorder in consequence of it, this system will be considered first. Its disorder has a fundamental bearing on the pathogenesis and symptomatology of deficiency disease in general.

I. EFFECTS OF AN EXCLUSIVE DIETARY OF AUTOCLAVED RICE IN PIGEONS

The pathological changes in the gastro-intestinal tract were studied macroscopically in 152 cases of polyneuritis columbarum resulting from this dietary, and microscopically in twenty-four of them.

Macroscopical Appearances.—*The œsophagus* was thinned and often congested; *the crop* was usually empty and also much thinned. *The stomach* was atrophied and averaged 3·5 grams in weight as compared with 5·7 grams in health. Its vessels were often congested, and its contents consisted usually of an emerald green fluid, which on culture occasionally yielded *Bacillus pyocyaneus.* One of the results of this dietary is, therefore, to permit of the growth in the stomach of organisms which are foreign to it. The abdominal viscera were wholly devoid of fat. *The intestines* were atrophic and congested; all cases presented atrophy in a greater or lesser degree, while approximately 70 per cent. exhibited congestion appreciable by the naked eye. The upper portion of the intestines in healthy pigeons, especially that part embracing the pancreas, is thick and muscular. It is this portion which suffers most in consequence of the deficient food. *The atrophy* was of all grades of severity in different birds; sometimes it was comparatively slight, at others it had progressed to a point at which the intestinal walls were so thin as to be transparent. As a rule the atrophy was more marked the longer the bird had been under the influence of the faulty food. *The congestion* was commonly confined to the upper part of the alimentary tract; less often it involved its whole extent. The branches of the mesenteric vessels surrounding the bowel were often greatly engorged, and extravasations of blood were occasionally seen under its serous covering.

On splitting open the bowel, the upper three to six inches were often found to be distended with tapeworms, more rarely with round-worms—the latter usually dead, the former almost invariably alive. Round-worms were occasionally found in the œsophagus. Diseased birds did not show these helminths with greater frequency than healthy birds; nor do the parasites appear to have favoured the onset of symptoms.

On examining the surface of the bowel with the hand-lens, varying degrees of atrophy and erosion of the mucous membrane were encountered. These were not

always uniformly distributed over the whole surface of the bowel ; some areas exhibited them in greater degree than others. Ecchymoses were common over the mucous surface ; in the more severe cases pin-point hæmorrhages into the bowel lumen had occurred. I have repeatedly cultured the duodenal contents often aerobically, occasionally anaerobically, injecting subcutaneously the organisms so obtained into healthy pigeons ; but while such inoculations usually killed the birds and produced changes in the internal organs (especially the thyroid, thymus, adrenals, and testicles) of great interest, I have not found that they gave rise to symptoms of polyneuritis.

Histo-pathology.—Apart from some degree of atrophy of all coats of the bowel, which was universal in birds dying in consequence of this dietary, no marked histological changes, with the exception of slight congestion, were found in approximately 30 per cent. of cases. In the remainder the histo-pathological appearances were very striking, although they varied widely in degree in different birds.

The pathological changes comprised the following :

(1) Congestion and hæmorrhage.
(2) Atrophy of the myenteron.
(3) Degenerative changes in the myenteric plexus of Auerbach.
(4) Atrophic and inflammatory changes in the mucous membrane.
(5) Atrophy of lymphoid structures.
(6) Fibrosis.
(7) Changes favouring systemic infection from the diseased bowel.

Congestion and Hæmorrhage.—In its mildest form, this change consisted in engorgement of the subperitoneal vessels, and in distension of the small vessels ramifying between the muscularis mucosæ and the base of the crypts of Lieberkuhn, or the glandular structures corresponding to these in birds (Figs. 18 and 19). The process of congestion was not usually limited to distension of vessels in these areas, but may have extended to those of the villi. The next stage in the congestive process was the occurrence of actual hæmorrhages around the bases of the crypts (Fig. 19). In some cases an almost continuous layer of hæmorrhage surrounded the bowel at this point (Fig. 21). Such remnants of villi as remained were often seen to be much engorged or to contain effusions of blood ; this appearance was frequently very pronounced in the lower bowel (Fig. 23). Free corpuscles were occasionally found in the lumen of the bowel or exuding from its congested and frayed mucous membrane.

A further, or simultaneous, stage in the process was the spread of these hæmorrhagic areas from the submucous coat into the myenteron ; these sometimes involved only the circular layer of muscle fibres (Fig. 21), at others they penetrated to the longitudinal layer. It was not unusual to see large tracts of the circular layer of muscle broken up by extensive hæmorrhages into its substance ; these caused separation and rupture of the muscle fibres. The ruptured fibres presented ragged edges enclosing the collection of effused blood or, as in Fig. 20, the hæmorrhages were more diffuse, the corpuscles being scattered throughout the whole thickness of the myenteron and penetrating to the serous coat.

Added to these appearances was the engorgement—often intense—of the vessels running under the serous coat and ramifying in the muscular layers. Oblique and longitudinal sections of these vessels may at first sight present the appearance of hæmorrhagic effusions. Rupture of the vessel walls was, however, rare. Fig. 24 shows an uninterrupted stream of blood-corpuscles extending from an engorged and atrophic villus—the epithelial covering of which is incomplete—

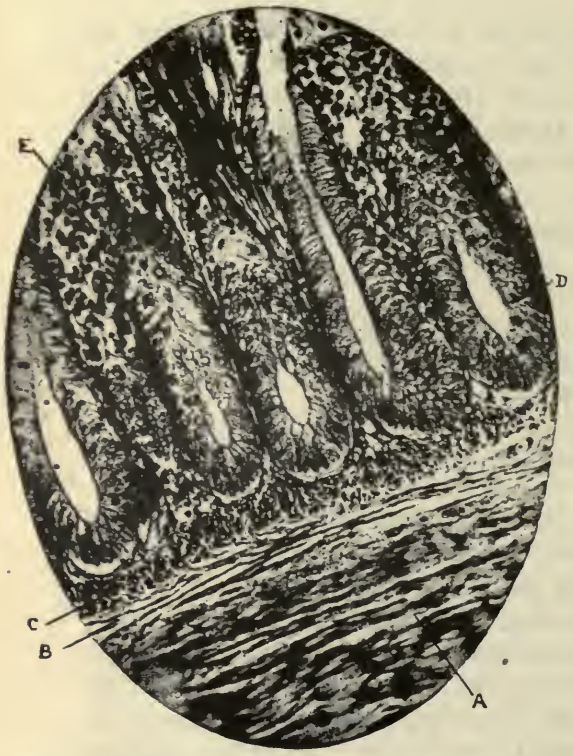

FIG. 18.—Section of upper part of intestine from healthy pigeon, × 105. A, circular layer of myenteron; B, submucous coat; C, muscularis mucosæ; D, glands or crypts of Lieberkuhn; E, lymphoid tissue.

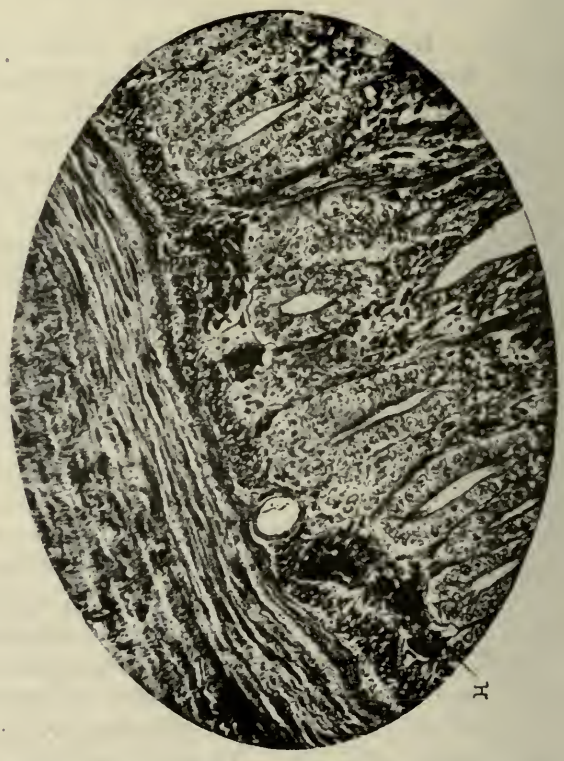

FIG. 19.—Section of upper part of intestine from pigeon dying in consequence of an autoclaved rice dietary, × 105. Taken at same level of bowel as in Fig. 18. Note: hæmorrhages (H) between muscularis mucosæ and crypts; diminished amount of lymphoid tissue; smaller scale of glandular elements. Details as in Fig. 18.

directly into the large subperitoneal vessels. Œdematous infiltration of the coats of the bowel was occasionally encountered.

Congestion of, and hæmorrhages into, the coats of the bowel—and especially into the coats of the upper bowel—sometimes leading to actual breaches in their continuity, are, therefore, amongst the results of this dietary. It may be assumed that resolution of such hæmorrhages would lead to the deposition of fibrous tissue in the myenteron and serous coat.

Atrophy of the Myenteron.—The average thickness of the circular layer

of the muscular coat, at a point 1 to 2 inches from the stomach, is about 0·3 mm. It is not of the same thickness at every point of the bowel's circumference, but gradually merges from a thickness of about 0·35 mm. to one of about 0·25 mm.

In pigeons fed on the deficient diet the degree of atrophy of the circular

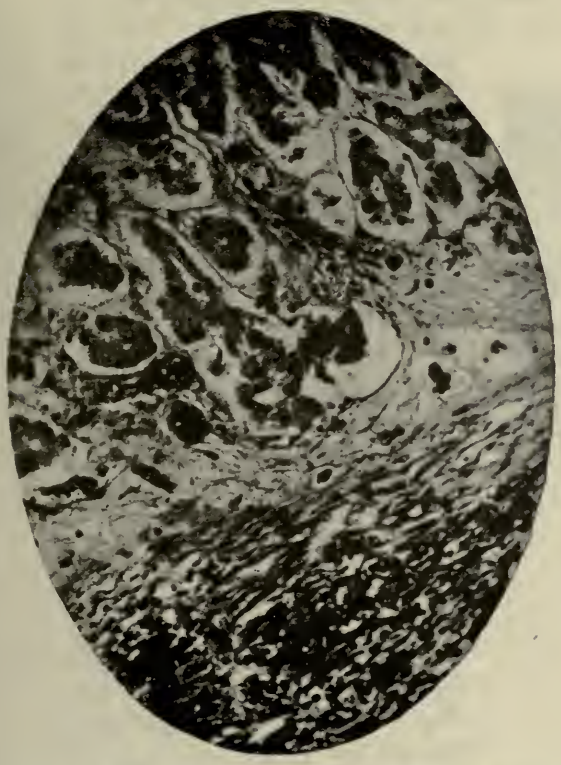

FIG 20.—Section of upper part of intestine from pigeon dying in consequence of an autoclaved rice dietary, × 105. Taken from same level of bowel as in Figs. 18 and 19. Note: diffuse hæmorrhagic infiltration of myenteron; disappearance of muscularis mucosæ; atrophy of secretory elements; separation of glandular cells from their basement membrane: diffuse fibroblastic infiltration of mucous membrane; disappearance of lymphoid structure; fragmentation of muscle fibres of myenteron. Compare with Fig. 18.

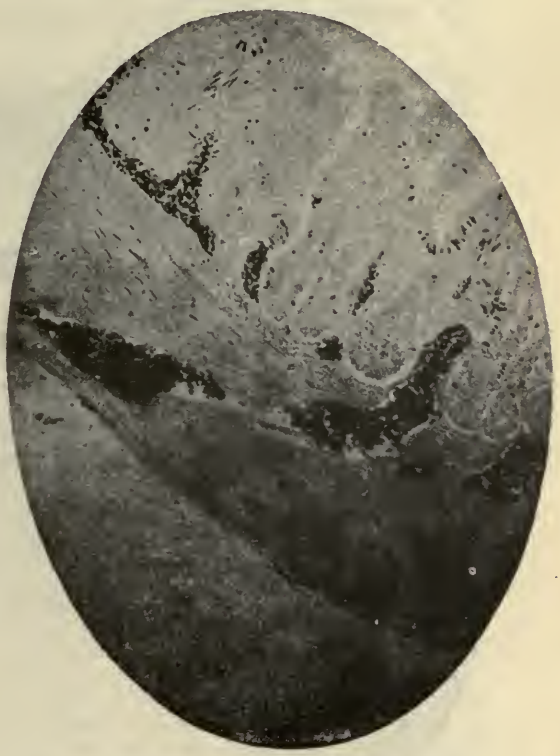

FIG. 21.—Section of upper part of intestine from pigeon dying in consequence of an autoclaved rice dietary, × 85. From same level as in Figs. 18, 19, 20, and 24. Note: hæmorrhages at bases of crypts and extensive hæmorrhage into the muscular coat.

muscular layer varied considerably. It was usually thinnest in birds which survived longest, or in which infection of the bowel walls had occurred; it was atrophied, as a rule, to the extent of one-half to one-quarter its normal thickness in health; its efficiency was thus proportionately reduced. Added to the atrophy, and accentuating the functional depression resulting from it, were frequent hæmorrhages, the rupture and separation of muscle fibres, and, less commonly, segmentation and fragmentation of these fibres (Fig. 20). The extent to which

the motor function of the bowel may be impaired by the deficient dietary will be realized from these statements.

Degenerative Changes in the Myenteric Plexus of Auerbach.—Careful scrutiny is necessary in order to detect, in healthy birds, the ganglionic swellings of this plexus, as they lie between the circular and longitudinal layers of the myenteron. They are compact bodies of oval form, varying considerably in size, the variations being, of course, dependent on their point of section. They fit snugly between the layers of muscle, and give rise to little or no bulging in the contour of these layers.

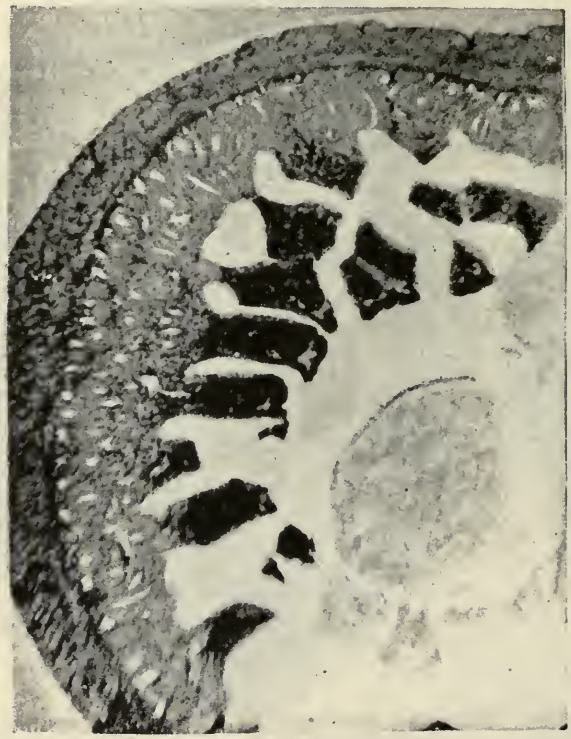

FIG. 22.—Section of lower bowel of healthy pigeon from last V-shaped loop of intestine. Magnification: × 75. Note: healthy mucous membrane; normal appearance of villi, muscular and serous coats.

In hæmatoxylin-stained sections of the intestine these ganglia were much more obvious and caught the eye at once. Their readier recognition may have been due in part to the atrophy and recession of the circular and longitudinal muscle fibres, which rendered them more prominent. Their greater prominence was, however, often the result of swelling, due probably to œdematous infiltration. In size they varied within wide limits, dependent in some measure on their point of section. In general, they were double or treble the size of healthy ganglia. The swollen ganglia frequently caused bulgings of the longitudinal muscular layer towards the serous covering of the bowel or of the circular layer towards its lumen, or both (Fig. 25). The cytoplasm of the ganglionic cells appeared shrunken, their nuclei more excentric than normal, and the nucleoli almost invariably fragmented, the last appearance being the most constant. Occasionally, whole cells or groups of cells appear to have disappeared, leaving in the ganglion lacunæ empty of cellular structure.

There can, I think, be little doubt that the plexus myentericus is involved in a degenerative process in consequence of this dietary. This being so, it may be concluded that the nervous control of the bowel will become impaired in proportion to the degree of degenerative change.

Atrophic and Inflammatory Changes in the Mucous Membrane.—These consisted in (*a*) atrophy and partial or complete disappearance of the villi; (*b*) frequent congestion of such villi as remain; (*c*) atrophy of the glandular cells of the crypts of Lieberkuhn, and separation of these from their basement membrane; (*d*) partial or complete disappearance of the lymphoid cells lying between and around the crypts; (*e*) thinning, or actual disappearance in places, of the muscularis mucosæ; (*f*) a relatively greater proportion of reticular cells, and the scattered deposition of fibroblasts; (*g*) an increased proportion of leucocytes in the atrophic mucous membrane; and, more rarely, (*h*) bacterial invasion with intense inflammatory and necrotic changes in the mucous membrane and underlying coats of the bowel.

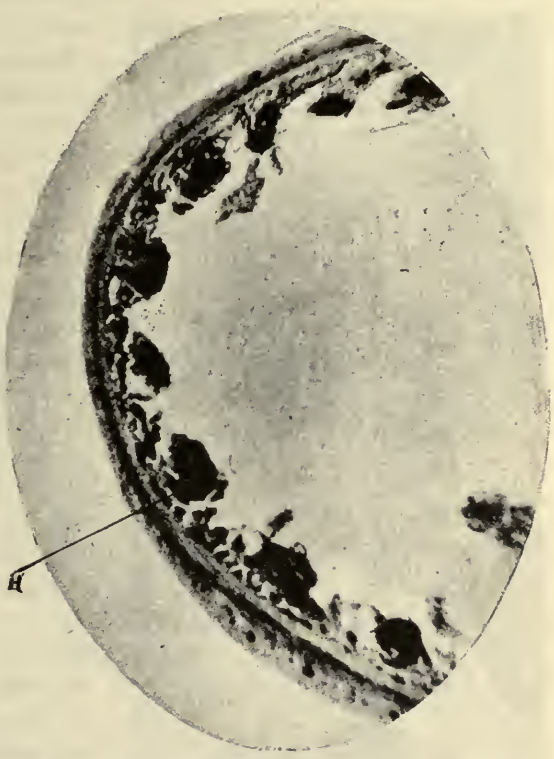

FIG. 23.—Section of lower bowel of pigeon dying in consequence of an autoclaved rice dietary: taken from last V-shaped loop of intestine. Same magnification as in Fig. 22. Note: great thinning of myenteron, thickening of serous coat; atrophy and necrosis of mucous membrane and villi. The dark areas in the remnants of the villi are due to intense hæmorrhagic infiltration (H). In this case, bacteria were found by special staining methods, permeating the mucous membrane and invading the muscular and, in smaller numbers, the serous coats. Bacteria were also found in the vessels of the submucosa. A coccus was grown from the heart's blood at autopsy. Compare with Fig. 22.

These appearances are well shown in Figs. 18 to 25, and call for little further description. They were, as a rule, most marked in birds which survived the dietary for the longest time, or in which infections of the bowel wall were present. They rarely occurred to the same degree at every area of the bowel's circumference. Sections of even the most severely affected intestines often showed some areas in which these changes were much less marked than in others.

Atrophy of Lymphoid Structures.—In the healthy pigeon the lymphoid cells fill in the spaces between the crypts, and present a continuous layer of varying thickness (Fig. 18) between the bowel lumen and the muscularis mucosæ. In diseased birds this protective layer was atrophied in greater or lesser degree. In some areas it was completely wanting, and the muscularis mucosæ also had frequently disappeared (compare Figs. 18 and 20).

Fibrosis.—The evidences of fibrosis were scanty in so far as the mucous membrane itself is concerned. The loss of lymphoid cells and the atrophy of the secretory elements brought into greater prominence the fibrous reticulum. Areas, however, were encountered in which there was a deposition of scattered fibroblasts. Some long-standing cases presented areas of fibrotic infiltration in the muscular coats; but this being a reparative process, it is likely to be encountered only rarely in birds not permitted to recover. It may be expected that, where such recovery is brought about, the resolution of the hæmorrhagic effusions will give rise to fibrotic deposits in the muscular and serous coats of the intestine.

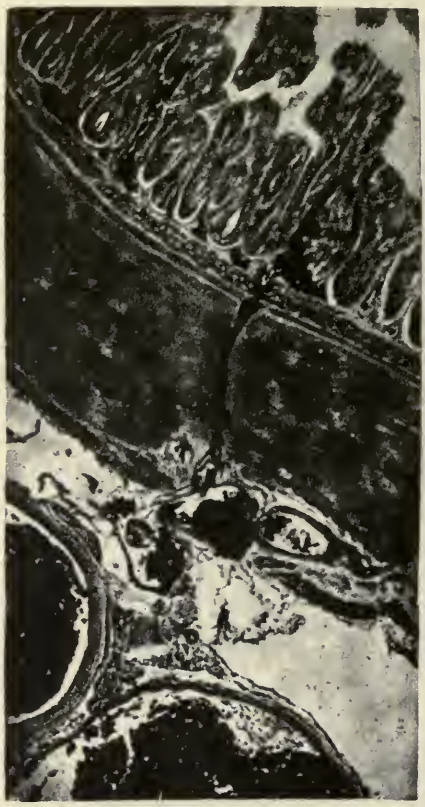

FIG. 24.—Section of upper part of intestine from pigeon dying in consequence of an autoclaved rice dietary, × 65. From same level of bowel as in Figs. 18, 19, 20, and 21. Note: hæmorrhages between muscularis mucosæ and bases of crypts; atrophic glandular elements; eroded villus with blood-track therefrom to distended subperitoneal vessel, constituting a direct passage for intestinal organisms to the blood-stream.

Infection from the Diseased Bowel.—Systemic infection is rendered more easy in the presence of these pathological processes owing (1) to impaired production of digestive juices; (2) to continued congestion of the mucous membrane and consequent malnutrition of its secretory cells; (3) to loss of the protective layer of lymphoid cells; (4) to increased leucocytic invasion of the mucous membrane, and to increased leucocytic traffic in micro-organisms between the bowel mucous membrane and the blood-stream; (5) to the greater facilities which the debilitated mucous membrane provides for the growth of bacteria on its surface and in its substance; (6) to the imperfect digestion of food in the upper alimentary tract, which affords a favourable medium for the growth of micro-organisms; and, although more rarely, (7) to actual breaches of continuity in the walls of the bowel itself. Occasional specimens have shown a direct continuity of blood-corpuscles from an eroded villus to the blood-vessels running external to the serous coat (Fig. 24).

Cases were encountered with comparative frequency in which the atrophic and congestive processes had superadded to them the effects of intense bacterial invasion of the bowel walls. In such cases bacteria of various types were to be found in large numbers throughout the necrotic mucous membrane, and lying

also in the submucous, muscular, and subserous coats.[1] By special staining methods bacteria (chiefly cocci) have been detected in the vessels of the submucosa, and bacteria-laden leucocytes were common objects in the microscopic field. In these circumstances, bacterial organisms were enabled to pass directly into the blood-stream from the infected bowel walls. In four such cases I cultured from the heart's blood at autopsy, by aerobic methods, a small coccus in two, a coliform organism in a third, and a bipolar organism in a fourth. Infection of the blood from the bowel is therefore no uncommon consequence of this deficient dietary.

The mucous membrane may be so destroyed, and the changes in the bowel so pronounced, as to render recovery impossible. I have occasionally been surprised to find that, while in one case the administration of vitamin extracts, or of whole grains of *mung dal* (a species of small pea), will cure polyneuritis columbarum with surprising rapidity, another, to all clinical appearances identical with it, will succumb. Amongst the reasons for this are the varying degrees of pathological change and of bacterial invasion of the bowel walls, as well as systemic infection therefrom. The difficulty in curing some cases of pellagra by a suitable dietary is no doubt to be explained in this way. It is evident also that the ingestion of specific pathogenic organisms (such as *B. dysentericus*, *B. typhosus*, *E. histolytica*, etc.), in the presence of dietaries presenting similar faults to that of the present one, is likely to be followed by their implantation on the debilitated bowel mucous membrane.

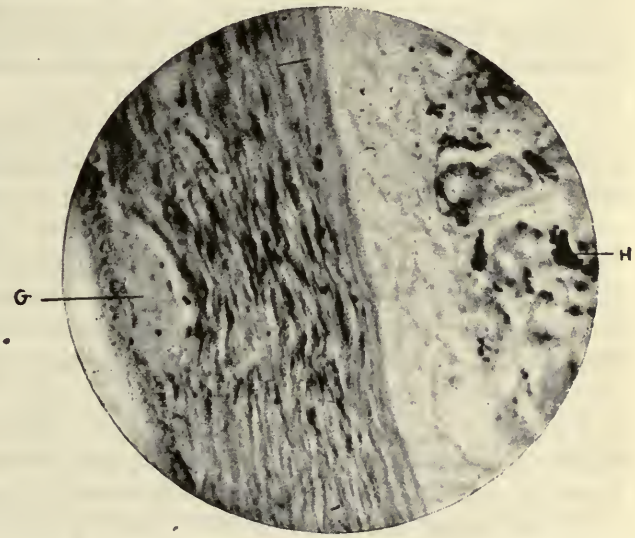

FIG. 25.—Section of upper part of intestine from pigeon dying in consequence of an autoclaved rice dietary, × 105. Note: degenerated and swollen ganglion of myenteric plexus (G), changes in the muscular coat (compare Fig. 18), disappearance of the muscularis mucosæ, diffuse hæmorrhagic infiltration (H) of the atrophic and degenerated mucous membrane.

In connexion with these lesions in the upper alimentary tract of pigeons fed exclusively on autoclaved milled rice, it will be remembered that Hamilton Wright was so impressed with the constancy of pathological changes in this situation in human beri-beri that he attributed this malady to a specific gastro-duodenitis. As is now well known, the pathological changes he described are

[1] I am indebted to Lieut.-Colonel Cornwall, I.M.S., for confirmation of this observation by his independent histological examination of the tissues.

not the cause of beri-beri ; they are, however, important consequences of deficient and ill-balanced food. The fact that Hamilton Wright found a bacillus of constant morphological character in this situation is important. Although the organism is not the specific cause of beri-beri, its presence demonstrates that the wall of the upper intestine may become infected in the human subject in consequence of such a dietary.

II. EFFECTS OF A DIETARY OF AUTOCLAVED RICE, BUTTER, AND ONIONS IN PIGEONS

The pathological changes in the gastro-intestinal tract were studied macroscopically in forty-two cases of polyneuritis columbarum resulting from this dietary, and microscopically in twelve of them.

It was noted that naked-eye evidences of congestion, hæmorrhage, and other pathological processes were less frequently encountered in pigeons fed on this diet ; naked-eye evidences of congestion were slight or *nil* in 50 per cent. of cases.

The atrophy of the bowel, although often considerable, was usually less marked than in cases dying in consequence of an exclusive diet of autoclaved rice. Histologically, one did not, as a rule, encounter the same degree of congestion ; actual hæmorrhages were more rarely met with, while the degree of atrophy of the myenteron and of the elements of the mucous membrane, although usually considerable, were often comparatively slight. Two cases, however, were encountered amongst twelve histologically examined where bacterial infection of the bowel walls had assisted in bringing about changes as pronounced as those so commonly seen in the case of birds fed exclusively on autoclaved rice.

Fresh butter and onions, when added to a dietary of autoclaved rice, thus provide some at least of those factors on which the functional perfection of the alimentary tract is dependent.

III. EFFECTS OF A DIETARY OF AUTOCLAVED RICE AND BUTTER IN PIGEONS

The effects of this dietary were studied macroscopically in eighteen cases, and microscopically in six.

The description given of the effects of an exclusive dietary of rice applies to these cases. The butter used afforded the birds no protection in so far as the intestines were concerned.

With the reservation that the number of birds in this category is small in comparison with those in the two previous categories, one is led to suspect that, since butter did not protect, it was the addition of fresh onions to the basal diet of autoclaved rice that afforded the birds in the second category the measure of protection against congestive and hæmorrhagic processes which they undoubtedly enjoyed.

In order to provide further evidence on this point, the appearances presented by the intestines of guinea-pigs fed on dietaries (*a*) of crushed oats and autoclaved milk, and (*b*) of autoclaved rice, were studied.

IV. EFFECTS OF A DIET OF CRUSHED OATS AND AUTOCLAVED MILK IN GUINEA-PIGS

The macroscopical appearances found in the gastro-intestinal tract were studied in nine cases; the microscopical in five.

Macroscopical Appearances.—The most notable feature present was intense congestion of *the duodenum.* This part of the bowel, for a variable distance from the pylorus, was in four out of nine cases so congested as almost to present the appearances seen in strangulated bowel. The congested area was sharply demarcated by the pylorus, and extended down the bowel for a distance of from 1 to 2 inches. In two other cases the congestion of the duodenum was of a patchy character. In the three remaining cases moderate congestion of the whole bowel was present in two, while no appreciable congestion was present in the third.

In contradistinction to the appearances presented by the upper intestine of pigeons, where the bowel is often greatly thinned, the duodenum of guinea-pigs was usually swollen and turgid, the tumefaction being due largely to hæmorrhagic infiltration of all coats of the bowel. On opening it and examining the mucous surface with the hand-lens, ecchymoses were frequently to be seen, while areas resembling punched-out ulcers, whose base extended almost to the peritoneal coat, were occasionally encountered. At these areas the bowel walls were almost transparent. The intestines are thin in healthy guinea-pigs. Apart from the duodenum, the bowel walls in animals dying in consequence of the deficient dietary were, generally speaking, thinner than in health.

In three cases of the nine referred to, punched-out necrotic ulcers were found in *the stomach.* In one as many as fifteen were counted—the base of the ulcer extending down to the peritoneal coat, and the mucous membrane being studded with the brownish debris of hæmorrhages into the interior of the organ. Thus localized, destructive changes in the mucous and underlying coats of the stomach and duodenum occasionally result in guinea-pigs fed on a dietary of crushed oats and autoclaved milk. This finding is of peculiar interest in connexion with the adrenal insufficiency produced by lack of vitamin C.

These changes were present in the gastro-intestinal tract of guinea-pigs dying in consequence of this dietary, which exhibited none of the characteristic naked-eye appearances of scurvy. In a clinical sense, then, they may be regarded as pre-scorbutic.

Histo-pathology.—The microscopical appearances seen in sections of the duodenum comprised:

(1) Turgidity, with diffuse hæmorrhagic infiltration of all coats of the bowel.
(2) Degenerative changes in the myenteron.
(3) Degenerative changes in the myenteric plexus.
(4) Atrophic and necrotic changes in the cellular elements of the mucous membrane.

These lesions resemble closely those described in the case of pigeons fed on an exclusive dietary of autoclaved rice. In general the same description applies to both. In the case of guinea-pigs, the more diffuse hæmorrhagic infiltration of the mucous membrane may impart to it a degree of turgidity which is not seen in pigeons. As judged by gross histological study, the degenerative process involved the ganglia of the myenteric plexus in a manner similar to that described in pigeons. In some cases, more especially in the vicinity of extensive hæmorrhagic infiltration

of the myenteron, the normal histological structure of the ganglia was much altered. In these circumstances ganglia were encountered which were infiltrated with blood, and in which no single cell contained a normal nucleus. In guinea-pigs, the myenteric plexus was much more prominent than in health. In hæmatoxylin-stained sections the ganglia appeared swollen, the nerve cells ill-defined, the nuclei degenerated, and the nucleolus fragmented. Not all cells, however, are so affected in either species, some exhibiting nuclei of apparently normal structure. Without definitely asserting that the degenerative changes in the myenteric plexus are more pronounced in guinea-pigs than in pigeons, they certainly appear to be no less, There can be little doubt that neural lesions, which may impair the nervous control of the bowel, resulted in consequence of the dietary of crushed oats and autoclaved milk used in this experiment; further histological study by special methods is necessary to determine their precise nature.

FIG. 26.—Section of mucous membrane of upper bowel of healthy guinea-pig showing the normal appearance of the glands and villi. × 105.

The myenteron also was often, although not always, greatly disorganized in consequence of diffuse hæmorrhagic infiltration of its substance; in such circumstances separation of muscular fibres, with their segmentation and fragmentation, were common appearances (Fig. 27). The degenerative and necrotic changes in the mucous membrane were as pronounced in guinea-pigs as in pigeons, and of similar character (Figs. 26 and 27). The same comments as to the facilities which these pathological processes afford for infection of the bowel walls and for systemic infection therefrom apply with equal force to both species.

The histological changes in the lower bowel were of like character to those found in the upper bowel, but more moderate in degree.

V. EFFECTS OF AN AUTOCLAVED RICE DIETARY IN GUINEA-PIGS

For the purpose of this study, four guinea-pigs were employed. They were fed on an exclusive diet of autoclaved rice until death occurred, which event took place within forty-six days of the initiation of the experiment. No histological studies were made.

My *post-mortem* notes with regard to the intestinal tract in these animals read as follows:

"*No.* 1.—The duodenum shows intense congestion, the first 1½ inches look almost gangrenous, so intense is the congestive process; there is a well-marked ulcer at one point, its base extending to the peritoneal coat, so that only the serous covering appears to intervene between the bowel lumen and the abdominal cavity. Both small and large bowel are congested, while they appear thinner than in health.

"*No.* 2.—Perhaps the most interesting pathological appearance is that presented by the duodenum. This part of the bowel is much congested, its vessels being greatly engorged; two hæmorrhagic areas of extensive proportions almost surround the bowel circumference. On opening the duodenum, congestion of the mucous membrane was seen to be pronounced and numerous ecchymoses were scattered over its surface; the viscus was transparent at one part, the peritoneal coat alone appearing to intervene at this area between the bowel lumen and the abdominal cavity.

"*No.* 3.—The duodenum is much congested and turgid, and its mucous membrane is studded with capillary hæmorrhages. The rest of the bowel is excessively thin.

"*No.* 4.—Apart from a moderate degree of generalized congestion of the bowels, and abnormal tenuity, no noteworthy macroscopical characters were recorded."

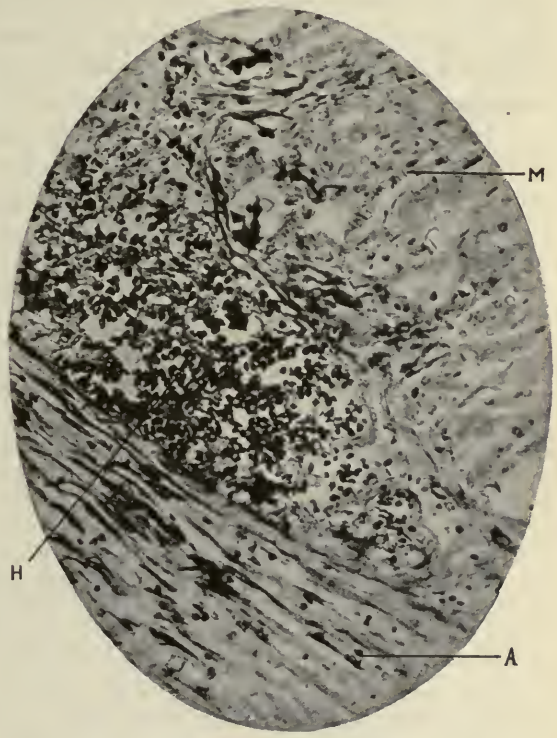

FIG. 27.—Section of upper bowel of guinea-pig (No. 3) which died as a result of a crushed oats and autoclaved milk dietary, × 105. Note: degenerative changes in mucous membrane (M); extensive hæmorrhagic infiltration (H); diffuse hæmorrhagic infiltration with segmentation and fragmentation of muscle fibres of myenteron (A). Compare with Fig. 26.

It appears, then, that congestive, hæmorrhagic, atrophic, and necrotic changes in the bowel walls, usually most pronounced in the upper intestine, are common consequences in guinea-pigs of dietaries deficient in accessory food factors. It will have been noted that, in both pigeons and in guinea-pigs, the pathological processes are similar in character as well as in distribution. The relatively less frequent presence of congestive lesions in pigeons whose dietary was deficient in vitamin B only; the fact that pigeons deprived of both vitamins B and C suffered from pathological lesions of the bowel as pronounced as did those deprived of all three classes of accessory food factors; the fact that these lesions were equally well marked

in guinea-pigs subjected to complete vitamin starvation and in guinea-pigs deprived only of vitamin C indicate that the congestive and hæmorrhagic lesions in the intestines of both species are largely, if not mainly, due to the absence of fresh green foods from the dietary. Control guinea-pigs fed on crushed oats, autoclaved milk, and an abundance of fresh vegetables were wholly protected from gastro-intestinal lesions. It appears, therefore, that the functional perfection of the gastro-intestinal tract is dependent in considerable measure on the adequate provision of vitamins and salts found in fresh vegetable foods; a fact which provides an explanation of the beneficial action of orange juice on the digestive and assimilative processes in bottle-fed infants.

Before leaving this subject, I would again point out that the intestinal lesions I have described in guinea-pigs were present in the majority of my cases before clinical evidences of scurvy were apparent. I suggest, therefore, that the symptoms of scurvy, as described in textbooks, are the grosser evidences of a disordered state of metabolism, the minor or pre-scorbutic manifestations of which are probably frequently overlooked, especially in children.

CHAPTER X

THE GASTRO-INTESTINAL TRACT (*continued*)

THE pathological changes in the gastro-intestinal tract of monkeys fed on deficient foods may now be examined.

VI. THE EFFECTS OF AUTOCLAVED RICE-DIETARIES IN MONKEYS

On opening the abdomen, which may be protuberant and tympanitic, the abdominal wall was found to be greatly thinned and completely devoid of fat. The inguinal glands were often enlarged. **The omentum** existed as a thin transparent membrane from which all traces of fat had disappeared. In healthy monkeys this structure, when removed from its attachments, weighed 50 to 56 grams, while in animals dying in consequence of the deficient dietary (or killed when at the point of death) it weighed but 3 to 4 grams; the loss of weight being due mainly to the loss of omental fat. The protection afforded to the intestines by the omentum was thus much reduced, and no doubt greatly enhanced their susceptibility to cold. **The mesentery** also was excessively thinned; its vessels were rarely engorged. **The mesenteric glands**, especially those of the colonic mesentery, were invariably much enlarged. In healthy animals these structures can be distinguished by the naked eye as small, oval, pink bodies lying at the attachment of the mesentery with the bowel; their size in health rarely exceeded that of a canary-seed, except internal and posterior to the cæcum, where they were sometimes as large as a hemp-seed or even a small pea. In monkeys dying in consequence of the deficient dietary the mesenteric glands ranged in size from that of a hemp-seed to that of a haricot-bean. Especially in the vicinity of the cæcum they were found to be very prominent. Posterior and internal to this part of the viscus a large mass of greatly enlarged and often discoloured glands was invariably found. In colour they varied from a pale pink to a dull grey or a dark slate-grey; in some cases they were of a grey-black tinge. There is no more prominent morbid anatomical feature in these cases than the great enlargement, and the frequent discoloration, of the colonic mesenteric glands; it is an indication of the intense degree of toxic absorption (with which may be included bacterial migration) which takes place from the diseased bowel in these cases. In only one case were the enlarged mesenteric glands examined by cultural methods: a coliform organism, in association with a small coccus, was obtained by aerobic methods of culture.

The **stomach** was invariably greatly dilated and its walls much thinned (Figs. 28 and 29). It but rarely showed external evidences of congestion.

The **small intestine** was always greatly thinned, either throughout its whole

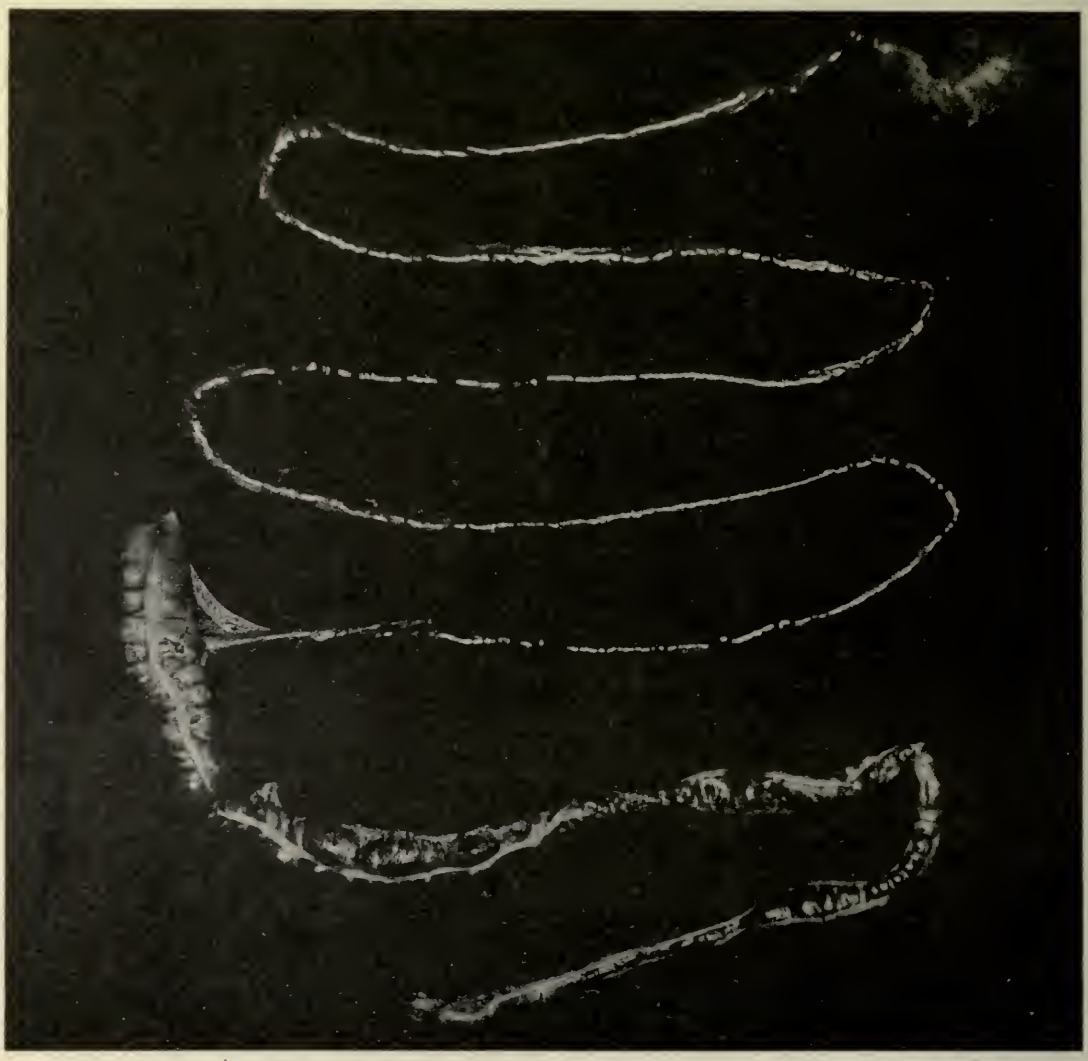

FIG. 28.—Photograph of the gastro-intestinal tract of a healthy control monkey. Animal killed twelve hours after last meal. Note normal size of empty stomach, uniform calibre of small bowel, also appearance of healthy colon when partly loaded with fæces. The bulgings in the colon are due to accumulations of fæces. Compare with Fig. 30 (A), showing appearance of colon after bowel has been emptied naturally. Note normal appearance of longitudinal bands of muscle fibres and extent of puckerings in the loaded bowel.

extent or more particularly at certain areas. Ballooning of the small bowel was present in eight cases out of fourteen. The ballooning occurred usually in the ileum. The ballooned areas were as a rule multiple and of varying extent; in

some cases they were confined to an inch or two of the bowel (Fig. 29), in others much larger areas were involved. In one case (butter-fed), the whole gastro-intestinal tract from the stomach to the rectum was greatly ballooned. The

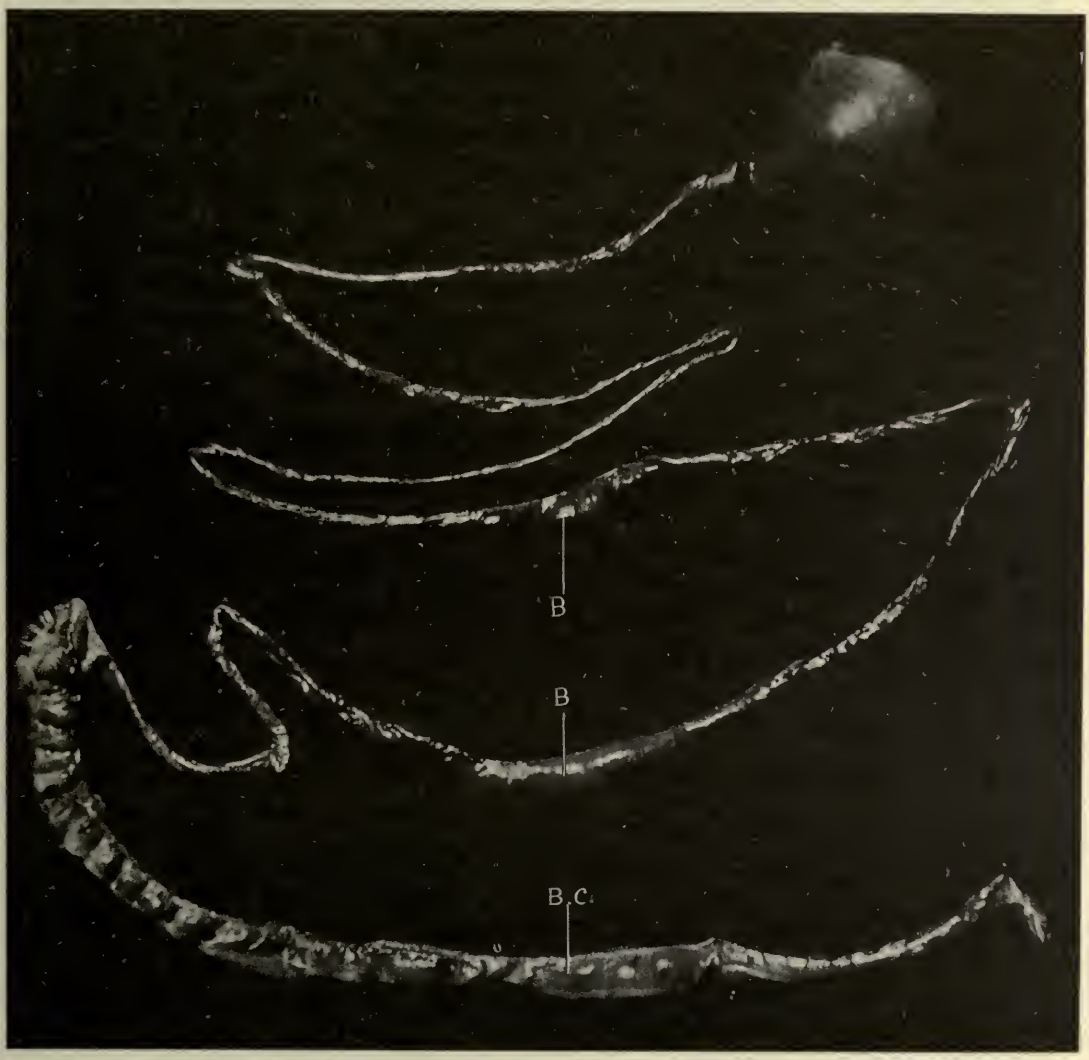

FIG. 29.—Photograph of the gastro-intestinal tract of monkey fed exclusively on autoclaved rice and water. Note great dilatation of the empty stomach, thinning of the small intestine, ballooned areas of small intestine at B, appearances of empty cæcum and colon, atrophy of the longitudinal muscular bands of colon, disappearance of puckerings in transverse and descending colon, ballooning of colon at area marked BC. The ballooning in this case was not due to accumulations of intestinal contents.

ballooning was not due to the accumulation of intestinal contents at these areas, but to excessive thinning and an atonic condition of the bowel walls.

Intussusception was present in ten cases out of fourteen. The invaginations

were usually multiple, invariably descending—the upper portion of the bowel being invaginated into the lower—often of small size, and never showing evidences of inflammation. They were found at all parts of the small intestine from the jejunum downwards; in one case only was the intussusception ileo-cæcal. The majority of these intussusceptions were no doubt manifestations of the death agony. In some, however, although no inflammatory changes had occurred, considerable constriction was present; the invaginated bowel being then much engorged and sometimes of a reddish-brown hue. It is concluded that such invaginations occurred at least several hours prior to death. I am disinclined to regard them as invariably agonal in origin; agonal intussusceptions are said to be usually ascending, those in the present experiment were invariably descending. It appears probable that the changes in the neuro-muscular mechanism of the bowel, presently to be described, were concerned in their origin.

Congestion of the small intestine was usually a prominent feature; small ecchymoses were frequently found widely distributed under the serous coat. Sometimes these ecchymoses involved the small bowel in its entire length; sometimes they were limited to the duodenum or to the lower end of the ileum or both. As a rule the congestive process was more marked in the duodenum than in other parts of the small intestine. A notable feature in monkeys fed on autoclaved rice *plus* butter was the pale yellow-white colour of the entire gastro-intestinal tube.

The external evidences of disease presented by the **large intestine** were the following: (1) Congestion and subperitoneal ecchymoses; (2) ballooning; (3) thinning and partial disappearance in places of the longitudinal bands of muscle.

The congestive process affected the great bowel in the same manner as the small. Sometimes subserous ecchymoses occurred throughout its entire length from the tip of the cæcum to the lower end of the rectum. More usually the ecchymoses were limited to certain areas, frequently to its last 4 to 6 inches. Occasionally grey-black lymphoid nodules of the size of a small pea projected into the serous coat. The colons of butter-fed monkeys were usually of a pale yellow-white tint, in marked contrast to the pink tinge of health.

The ballooning of the colon affected, in rare cases, the whole organ from the cæcum downwards. As a rule, however, it was limited to certain areas (Figs. 29 and 30). At those areas the characteristic puckerings of the great bowel, produced by the three longitudinal bands of muscular fibres, were wanting or much less prominent than in health. The colon was often elongated and its walls were greatly thinned, the longitudinal bands of muscle being less evident than in health. Sometimes the naked eye could only detect with difficulty the longitudinal bands at these areas; then they seemed to terminate abruptly at the upper extremity of the ballooned area and to commence again at its lower. When placed in formalin, however, the thinned bands could be clearly seen. As a rule the ballooned areas involved the whole circumference of the bowel, but

occasionally they were limited to one side of the bowel, resembling then a weak spot in an inflated inner cycle tube. They were not due to fæcal accumulations.

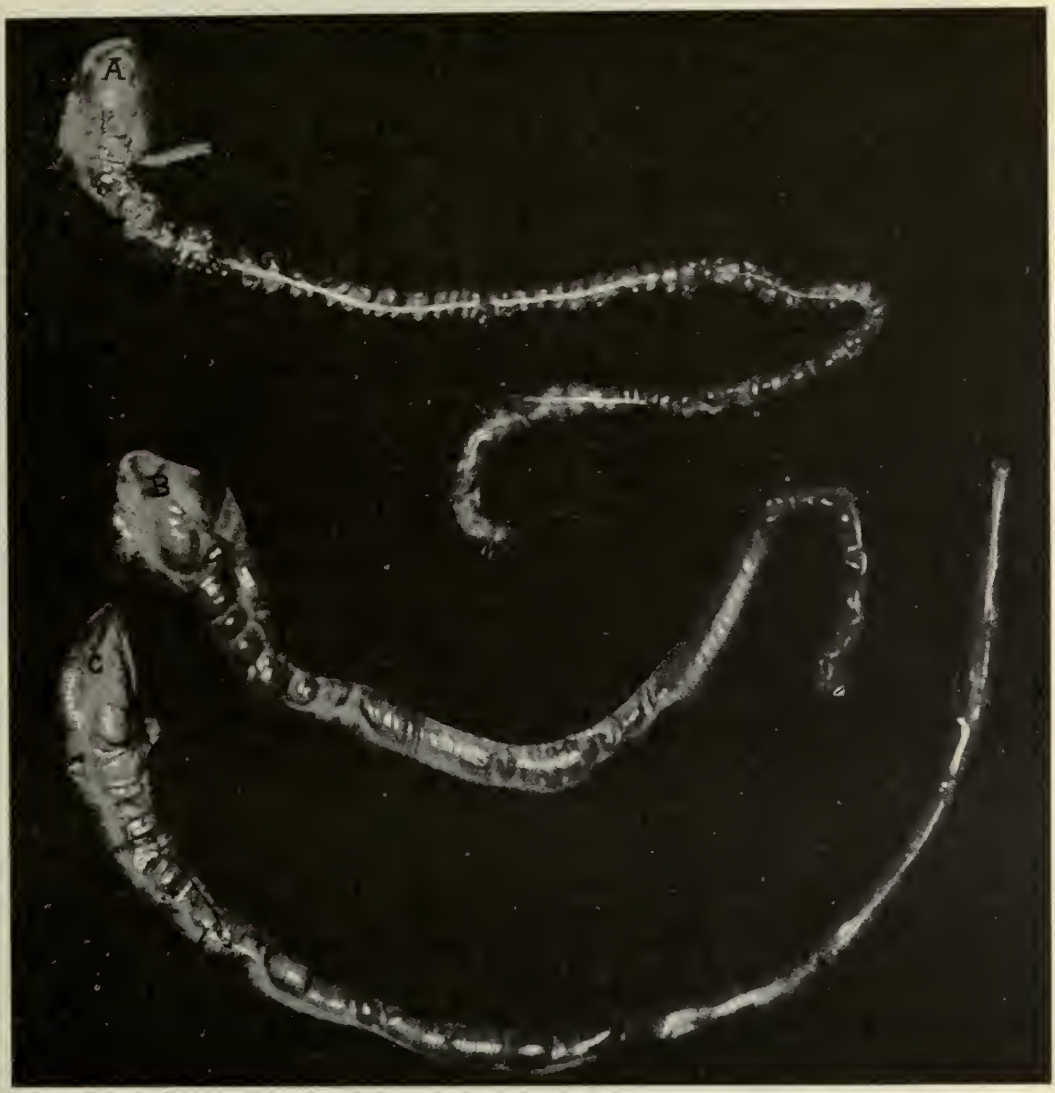

FIG. 30.—Photographs of : A, empty colon of healthy control monkey ; B, empty colon of monkey fed exclusively on autoclaved rice ; C, empty colon of monkey fed on autoclaved rice plus butter ; same scale. Note normal appearance of longitudinal muscular band and of puckerings of colon in A. Note atrophy of longitudinal muscular band, thinning and ballooning of bowel, loss of puckerings in transverse and descending colon in B ; whole colon unusually short in this case. Note similar appearances in C to those seen in B.

Between these ballooned areas the colon often presented a comparatively normal appearance with respect to its longitudinal bands and puckerings (Fig. 29).

The external appearances of the gastro-intestinal tract thus presented evidences of grave derangement of bowel function. Its internal appearances were as follows:

The Stomach was always greatly distended and quite empty (Figs. 28 and 29). The hand-lens showed its mucous membrane to be abnormally soft and necrotic. Ecchymoses were frequently present, usually at the pyloric end of the viscus. They varied in extent and in degree; in one case the whole mucous membrane of the stomach, with the exception of a small portion of the fundus, was covered with minute ecchymoses. In thirteen cases no ulcers were present; in the fourteenth an ulcer the size of a threepenny bit was present at the pyloric area.

The Duodenum.—Congestive and necrotic changes in the mucous membrane were the chief features observed; these changes were often very marked. No ulcers were met with. As a rule the ecchymoses of the mucous membrane were much more pronounced in the duodenum than in the stomach, and were sometimes seen to commence sharply, or more properly to be sharply accentuated, at the distal side of the pylorus. The whole surface of the duodenum was often studded with small pin-point hæmorrhages, the mucous membrane appearing as if it had been dusted with pepper. The upper part of the duodenum was, as a rule, more severely affected than the lower. The congestion and ecchymoses frequently extended to the **jejunum** and **ileum,** and in exceptional cases this "peppered" appearance of the bowel was continued to the ileo-cæcal junction. More usually, however, the congestion and ecchymoses were confined to the upper part of the small intestine or to the lower ileum, the intervening areas being comparatively free except where intussusceptions had occurred. In general the invaginated portions of the bowel were more congested than other parts of the small intestine—the duodenum excepted—the congestion in some intussusceptions being pronounced. Above areas where the more extensive invagination of the bowel had occurred, its lumen was often filled with a mucoid material resembling in appearance thin glue; this material was only present above the larger, and apparently older, intussusceptions, where it was sometimes bloodstained. Where ballooning had occurred, the walls of the bowel were often so thin as to be transparent, and here also a thin glue-like mucoid material was sometimes present in the bowel lumen. Often, however, these areas were empty of all contents, except gas.

As a rule the naked-eye changes in the mucosa were more pronounced in the **large intestine** than at any other part of the gastro-intestinal tract—the duodenum excepted. The changes were those of an intense colitis, but without ulceration. Although amœbic dysentery was present in a number of cases dying in consequence of the deficient dietary, no localized ulceration had occurred in any of them. The colitis sometimes involved the whole extent of the colon, but more usually it was confined to the last 6 inches of the great bowel; it usually corresponded in distribution to that of the subserous ecchymoses. In one case it assumed its maximum proportion at an isolated area of the mid-colon. The

FIG. 31.—Section of mucous membrane from pyloric end of stomach of healthy monkey, showing normal appearance of mucous membrane and pyloric glands. × 165.

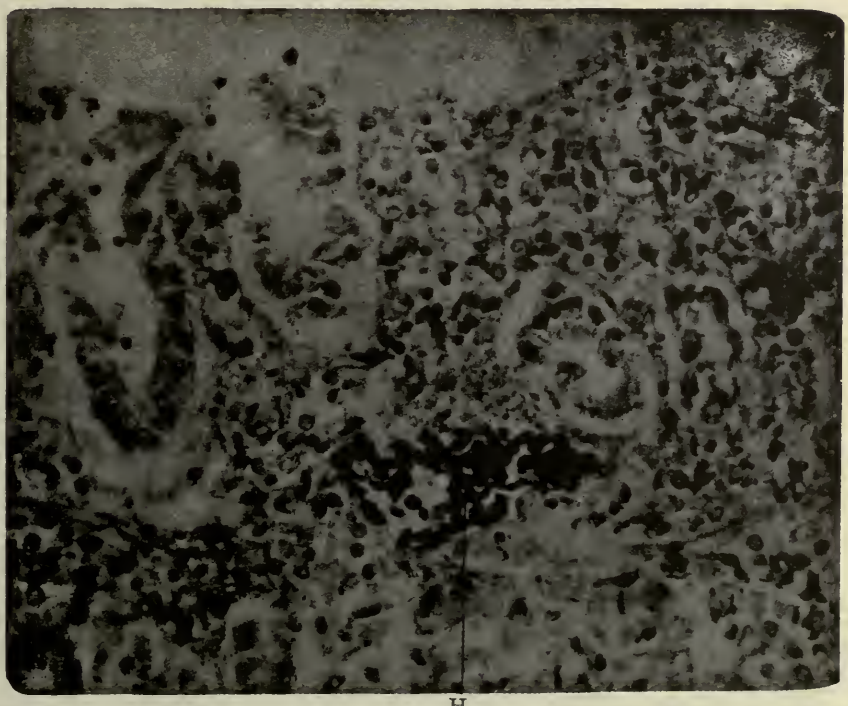

FIG. 32.—Section of mucous membrane from pyloric end of stomach of monkey fed exclusively on autoclaved rice. Note intense necrosis of glandular and epithelial elements with hæmorrhagic infiltration (H). The darkly-stained cells scattered throughout the necrotic mucous membrane are blood-corpuscles. × 165.

mucous membrane of the cæcum was usually moderately congested and ecchymotic, and often of a dark slate-grey colour. The lymphoid nodules of the colon were sometimes very prominent; in two cases they formed dark masses the size of a small pea, which projected into the lumen of the bowel and into its serous coat; one of these nodules showed, on section, numerous collections of small cocci. At areas where ballooning had occurred, the walls of the colon were excessively thin, often almost transparent. On opening the bowel at these points the walls collapsed like a burst balloon.

It is of interest to record that, amongst thirty-six wild monkeys in which the gastro-intestinal tract was minutely studied at autopsy, neither nematodes, cestodes, nor other intestinal worms were found.

In connexion with the pathological processes initiated in the gastro-intestinal tract by an autoclaved rice dietary, the post-mortem appearances found in two cases of beri-beri by Willcox during the Dardanelles campaign may be quoted: "The stomach showed marked redness of the mucous membrane, which was most marked in the pyloric half, where the colour was deep crimson. The duodenum showed intense crimson congestion of the mucosa, most marked in the upper part. The jejunum and ileum showed marked congestion, some petechiæ being present in the ileum. The large intestine showed congestion. Numerous small hæmorrhagic patches about ½ inch in diameter were present in the wall of the ascending colon. The mesenteric glands showed slight enlargement." The similarity of these changes to those found in monkeys fed on autoclaved rice is very striking.

The Histo-pathological Changes were studied in all fourteen cases, and were contrasted with the normal appearances in healthy monkeys.

In order to avoid post-mortem changes in the tissues, portions of the cardiac and pyloric ends of the stomach, of the duodenum, of the jejunum, of the lower ileum, of the ballooned areas of the small intestine, of the colon and of the ballooned areas of colon were taken for histological study in each case as soon after death as possible. The tissues were fixed in Zenker's fluid and stained by Mann's stain, Unna's methylene blue and eosin, and iron-hæmatoxylin.

The histo-pathological changes comprised:

(1) Congestion and hæmorrhage.
(2) Atrophy of the myenteron.
(3) Degenerative changes in the myenteric plexus of Auerbach.
(4) Atrophic, necrotic, and inflammatory changes in the mucous membrane.
(5) Bacterial invasion of the bowel walls.
(6) Partial disappearance of lymphoid elements of the mucous membrane.

Congestion and Hæmorrhage.—Where congestion occurred it was confined to the mucous, submucous, and serous coats of the stomach and bowel. The myenteron was not involved or but slightly. In this respect the appearances presented in sections were in marked contrast to those previously described in the case of pigeons and guinea-pigs. Small collections of effused blood-corpuscles

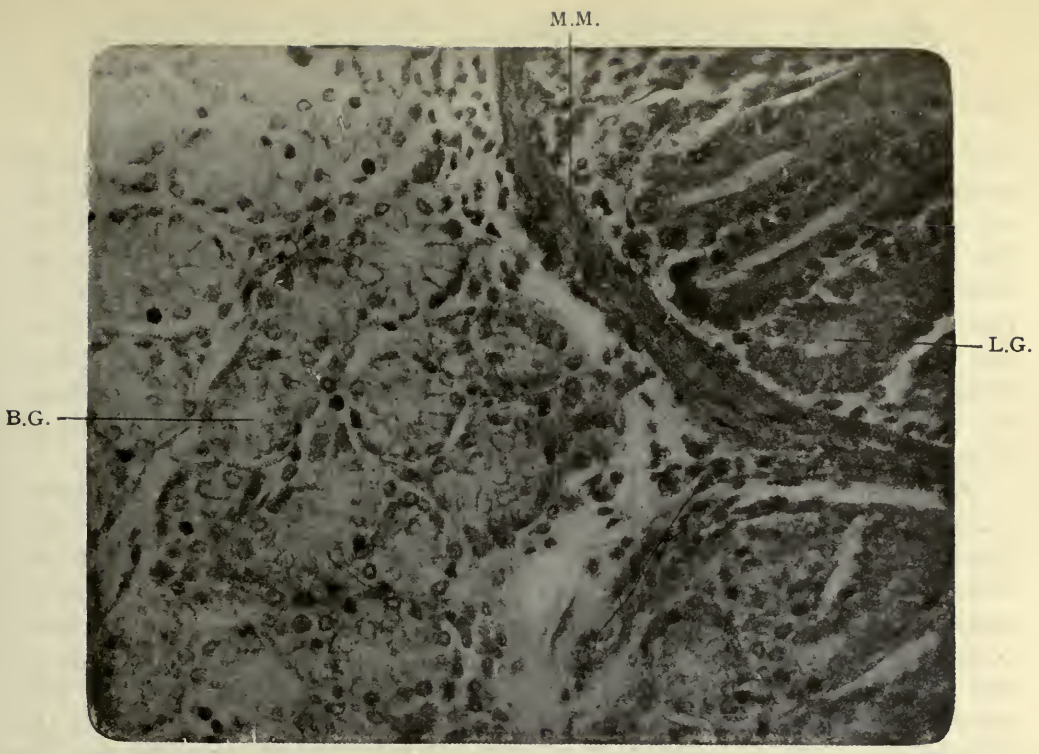

FIG. 33.—Section of mucous membrane of duodenum from a healthy control monkey. Note normal appearance of Brunner's glands (B.G.) lying beneath the muscularis mucosæ (M.M.), also bases of glands of Lieberkuhn (L.G.) above the muscularis mucosæ. × 165.

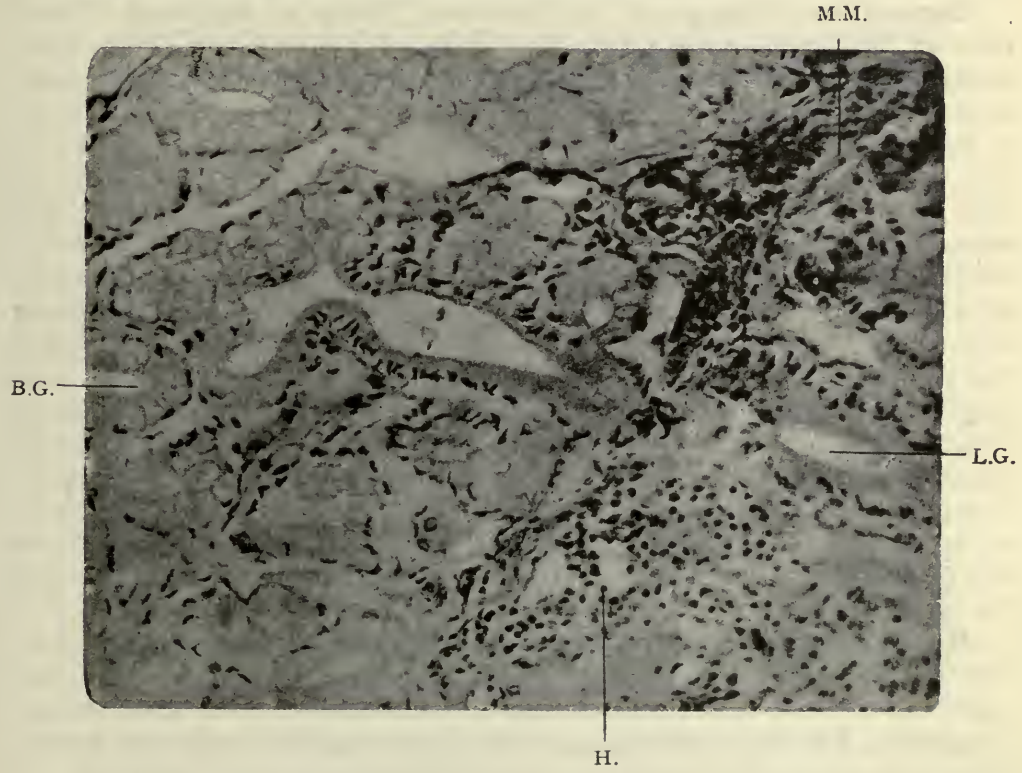

FIG. 34.—Section of mucous membrane of duodenum from a monkey fed exclusively on autoclaved rice. Note washed-out appearance of cells of Brunner's glands (B.G.) and karyolysis of their nuclei, almost complete disappearance of muscularis mucosæ (M.M.), atrophy and necrosis of glands of Lieberkuhn (L.G.), hæmorrhages (H) at bases of glands of Lieberkuhn. Compare with appearances previously recorded in pigeons and guinea-pigs fed on deficient diets. × 165.

were frequently encountered under the serous covering of the bowel—usually in sections from the duodenum and colon. It is to be noted that congestion did not occur uniformly throughout the entire digestive tube ; it was less marked in the mid-portion of the small intestine. The vessels of the duodenal and colonic submucosa were engorged, and actual hæmorrhages around the bases of the glands of Lieberkuhn were not uncommon. Free blood-corpuscles were often met with lying amongst the necrotic cells of the mucous membrane in sections from the stomach, duodenum, and colon. The photomicrographs illustrating the appearances seen in the diseased mucous membrane of the stomach (Figs. 31 and 32) sufficiently exemplify this point.

Atrophy of the Myenteron.—This atrophy varied in degree at different parts of the bowel. It was extreme in areas where ballooning had occurred. The dilatation of the stomach was probably less a matter of atrophy of its muscular coats than of their inability to contract. Apart from the ballooned areas of the bowel, where the myenteron presented extreme degrees of tenuity, the most remarkable changes were found in the longitudinal bands of the colon. Figs. 35 and 36 represent the degree of thinning of these bands. These sections were taken from approximately the same part of the colon in the healthy as in the diseased state ; the magnification is the same in both. It will be noted that the thinning of the longitudinal bands is due in part to their spread over the surface of the distended bowel ; in part to atrophy of muscle fibres.

Degenerative Changes in the Myenteric Plexus of Auerbach.—In all parts of the gastro-intestinal tract the ganglia of the myenteric plexus often presented appearances in marked contrast to those of health. Although the stains employed were not such as to bring out in minute detail the degenerative changes in individual cells, nevertheless they were sufficient to indicate the existence of such changes. The ganglia were much more prominent in the diseased bowel. In Figs. 35 and 36 the contrast in this regard between health and disease is well illustrated : in the healthy intestine (Fig. 35) the chain of ganglia lying between the longitudinal band and the circular layer of muscle can be seen with difficulty, whereas in the diseased bowel (Fig. 36) it is a prominent feature. The ganglionic cells were swollen, the cell membrane indistinct, frayed, or wanting. The nuclei had often disappeared or existed only as fragments of chromatin ; where complete nuclei were found they were often swollen. The nucleolus was frequently fragmented. Occasionally lacunæ empty of cells were found in the degenerating ganglia (Figs. 37 and 38). Ganglia were sometimes encountered in which no cell contained a normal nucleus ; others in which a few cells appeared relatively normal, and others in which degenerative changes were slight or absent. There can be no doubt that such changes would impair the neuro-muscular control of the bowel.

Necrotic and Inflammatory Changes in the Mucous Membrane.—These consisted in necrosis of all cellular elements of the mucous membrane. The necrosing cells were often surrounded by inflammatory cells and effused blood-corpuscles. The duodenum (Figs. 33 and 34) and colon (Figs. 39 and 40) were in

FIG. 35.—Section of longitudinal band of muscle (L.M.B.) from colon of a healthy control monkey, × 75. In the areolar tissue lying between this band and the circular muscular coat (latter not seen in photo-micrograph) a ganglion from the myenteric plexus of Auerbach is indicated by an arrow (G); high-power photo-micrograph of this ganglion is shown in Fig. 37.

FIG. 36.—Section of longitudinal band of muscle from greatly dilated colon of monkey fed exclusively on autoclaved rice, × 75. Compare with Fig. 35, and note great thinning of longitudinal muscular band (L.M.B.), which is spread out at its margins over surface of circular muscular layer (C.L.). Note also the prominent chain of swollen ganglia (G), including four large oval ganglia, lying between longitudinal and circular layers of muscle. High-power photo-micrograph of one of these ganglia is shown in Fig. 38. Much of the areolar tissue between the muscular coats has disappeared. Hæmorrhages into the serous coat are indicated at H.

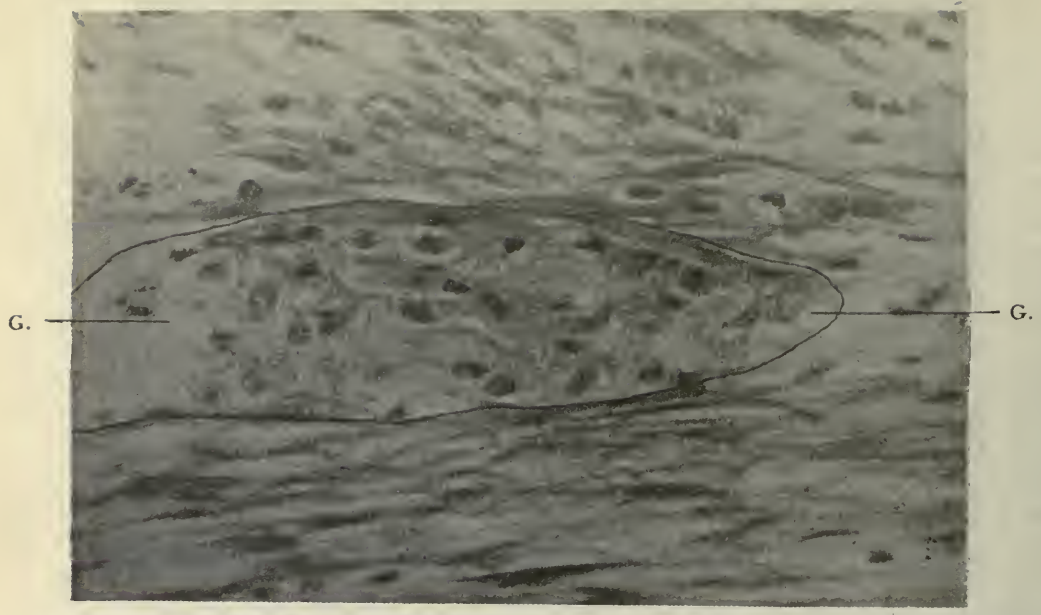

FIG. 37.—Section of ganglion from Auerbach's plexus in colon of healthy control monkey: outlined in Indian ink, × 165. Note oval appearance, normal outline of ganglionic cells, size and staining characters of the nuclei. See also Fig. 35. Stain: iron-hæmatoxylin.

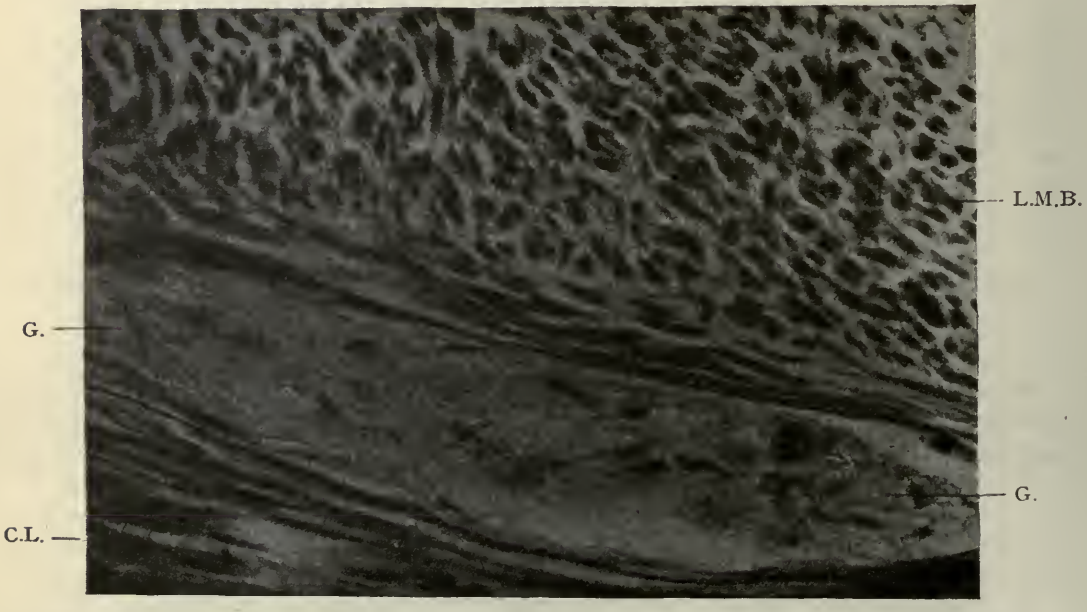

FIG. 38.—Section of ganglion (G) from Auerbach's plexus in colon of monkey fed on autoclaved rice: outlined in Indian ink, × 165. Compare with Fig. 37. Note loss of outline of swollen ganglionic cells, swelling and disappearance of the nuclei, débris-like character of cells, and their disappearance in places. See also Fig. 36. Stain: iron-hæmatoxylin.

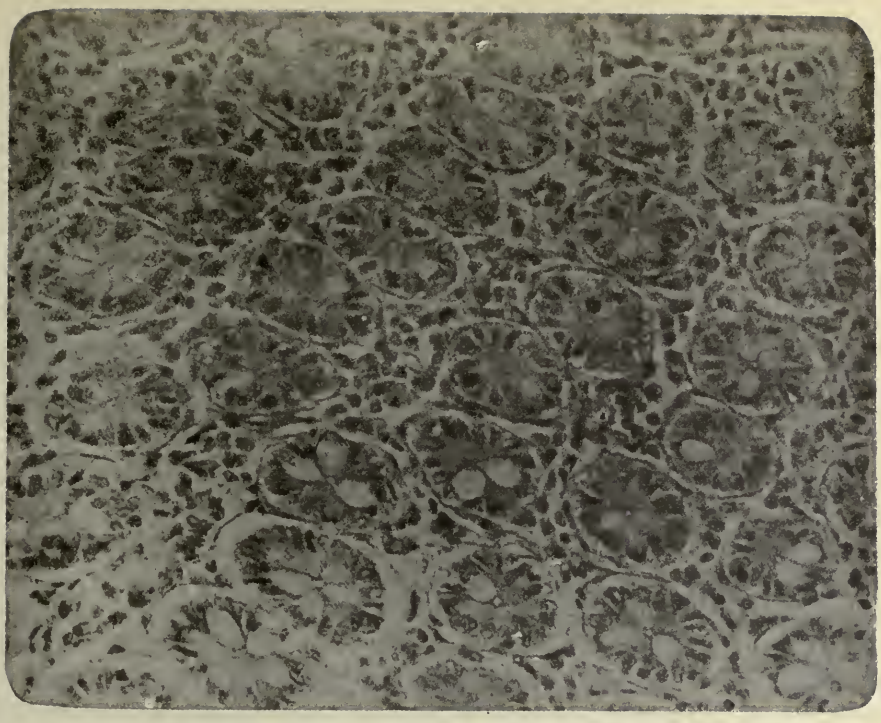

FIG. 39.—Transverse section of mucous glands of colon of healthy control monkey. × 165.

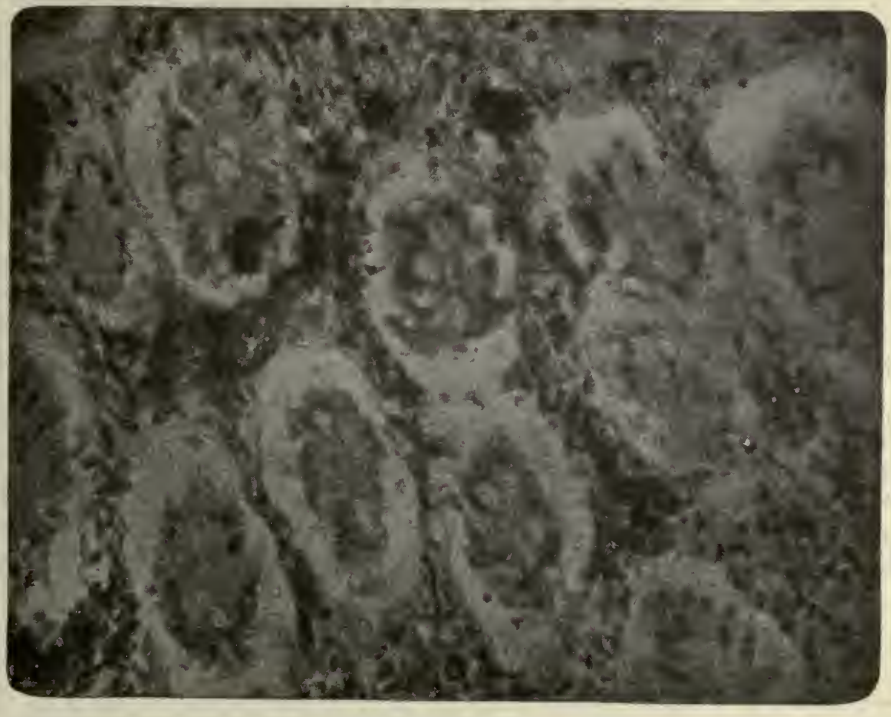

FIG. 40.—Transverse section of mucous glands of colon of monkey fed on autoclaved food, butter, and onion, × 225. • Compare with Fig. 39, and note the intense necrotic changes and hæmorrhagic infiltration around glands.

general more severely affected in this regard ; some degree of colitis was present in the great majority of cases. The mucous membrane of the stomach often exhibited necrotic and congestive changes (Figs. 31 and 32). In ballooned areas of both small and large bowel, only remnants of mucous membrane were met with. All glandular elements of the gastro-intestinal tract were affected in greater or lesser degree—the gastric and pyloric glands (Figs. 31 and 32), the glands of Brunner and of Lieberkuhn, in the duodenum (Figs. 33 and 34), and the mucous glands of the colon (Figs. 39 and 40). Throughout the entire intestinal tract the muscularis mucosæ was greatly thinned (Figs. 33 and 34), the atrophy in places constituting actual breaches in its continuity. The photo-micrographs illustrate so clearly the appearances seen that no further description of them is called for.

It is to be emphasized that considerable variation in the severity of the lesions in different animals and in different parts of the same gastro-intestinal tract may occur.

Bacterial Invasion of the Bowel Walls was encountered in a number of suitably-stained specimens, especially from the colon. Bacteria in large numbers were often seen deep in the mucous membrane ; sometimes they formed a bacterial capsule around the desquamated cells of the glands ; as for example, around those of the mucous glands of the colon. Frequently they were seen scattered throughout the submucosa, and mycelium-like organisms were, in several specimens, found lying in small cavities in this coat of the bowel. In some sections from the colon the bacterial invasion was seen to extend to the muscular layers, and bacteria in considerable numbers were found lying in and between the layers of the myenteron. More rarely organisms were found in the serous coat or in blood-vessels. Large collections of cocci were found in an enlarged lymphatic nodule taken from the colon. The organisms as seen in sections of the colon, were of four varieties : (1) cocci ; (2) short rods resembling *B. coli* ; (3) longer rods, usually found in and between the muscular coats ; and (4) mycelium-like organisms and their spores, usually found in small cavities in the submucosa.

Atrophy of Lymphoid Elements.—Although in the colon the lymphoid nodules were frequently swollen in general the lymphoid elements of the intestinal mucous membrane were greatly reduced in numbers. In health the lymphoid cells are very abundant whether collected into nodules or filling in the spaces between the glands of Lieberkuhn. The thinning of the protective layer of lymphocytes no doubt facilitated the development of infective processes in the mucous membrane.

Clearly all these changes are such as would greatly favour hæmic infection from the diseased bowel.

VII. EFFECTS OF AUTOCLAVED FOOD DIETARIES IN MONKEYS

These were in general similar to those noted in the case of monkeys fed on autoclaved rice. There were, however, a number of differences which may be recorded as follows:

(1) Dilatation of the stomach was less frequent and less pronounced (compare Figs. 41 and 42). Gastric catarrh was also less common. Ulcer of the stomach was present in two cases as compared with one in animals fed on autoclaved rice. Carcinoma of the pylorus, not detectable on naked-eye examination, but discovered histologically, was present in one case.

(2) Duodenal catarrh and subserous ecchymoses were less frequent, as were degenerative changes in the mucous membrane.

(3) Congestive changes in the jejunum and ileum, subserous ecchymoses of these viscera, and ballooning of the small bowel were less frequent and, indeed, were comparatively rarely encountered, although atrophy and thinning of the walls of the small intestine were notable features in 50 per cent. of cases. Degenerative changes in the mucous membrane of the small intestine were also less marked.

(4) Intussusceptions involving large areas of small bowel were less frequent, although occasionally met with (Fig. 42).

(5) In butter-fed animals receiving autoclaved food the whole intestinal tract was usually of the same peculiar yellow-white tinge noted in animals fed on autoclaved rice and butter.

(6) Colitis and great ballooning of the colon, with atrophy of the muscular coats of the viscus, great thinning of its walls, loss of the characteristic rugæ, and a thin paper-like texture of the viscus were the most conspicuous features found in animals fed on autoclaved food. These appearances were very pronounced (Fig. 42) in all six animals fed on autoclaved food and onion, and in two out of five animals fed on autoclaved food, butter, and onion. The colitis was as a rule both extensive and severe, small ulcers with adherent sloughs were often present; a condition not found in animals fed on autoclaved rice. In some cases the colitis involved the whole colon from the cæcum downwards, the serous coat being often ecchymotic. More commonly it was limited to the lower part of the colon and to the rectum, while occasionally a patchy colitis was present affecting limited areas, especially of the mid-colon. In one case a diffuse, apparently cancerous, infiltration of the submucous coats of the rectum was found in a monkey fed on autoclaved food, butter, and onion. The bowel wall was, at this area, much thickened and tough to the scissors. On histological examination occasional fine epithelial projections into the submucous coat were noted, as well as groups of epithelial cells scattered throughout a fibrous infiltration of the submucous coat. The colitis was invariably associated with enlargement and discoloration of the mesenteric glands.

It is obvious, then, that pathological changes of great importance can occur in the gastro-intestinal tract of monkeys as a result of deficiency of vitamin B

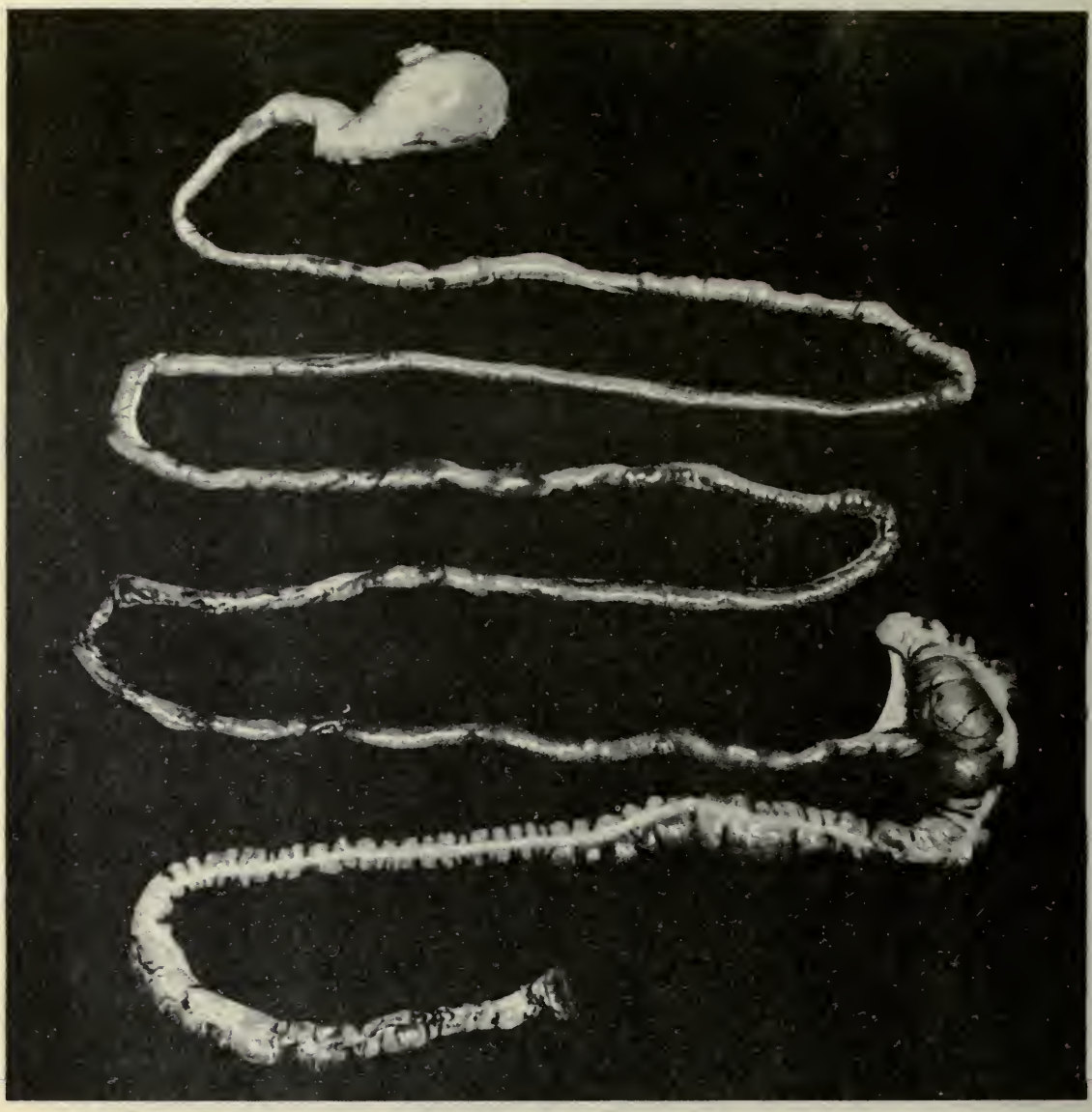

FIG. 41.—Photograph of gastro-intestinal tract of control monkey (No. 18, Table II). Killed on 104th day of the experiment, 15 hours after last meal. Stomach and mid-colon empty, cæcum loaded, lower bowel contains small amount of fæcal matter. Bowel evacuated before death. Same scale as Fig. 42, with which compare.

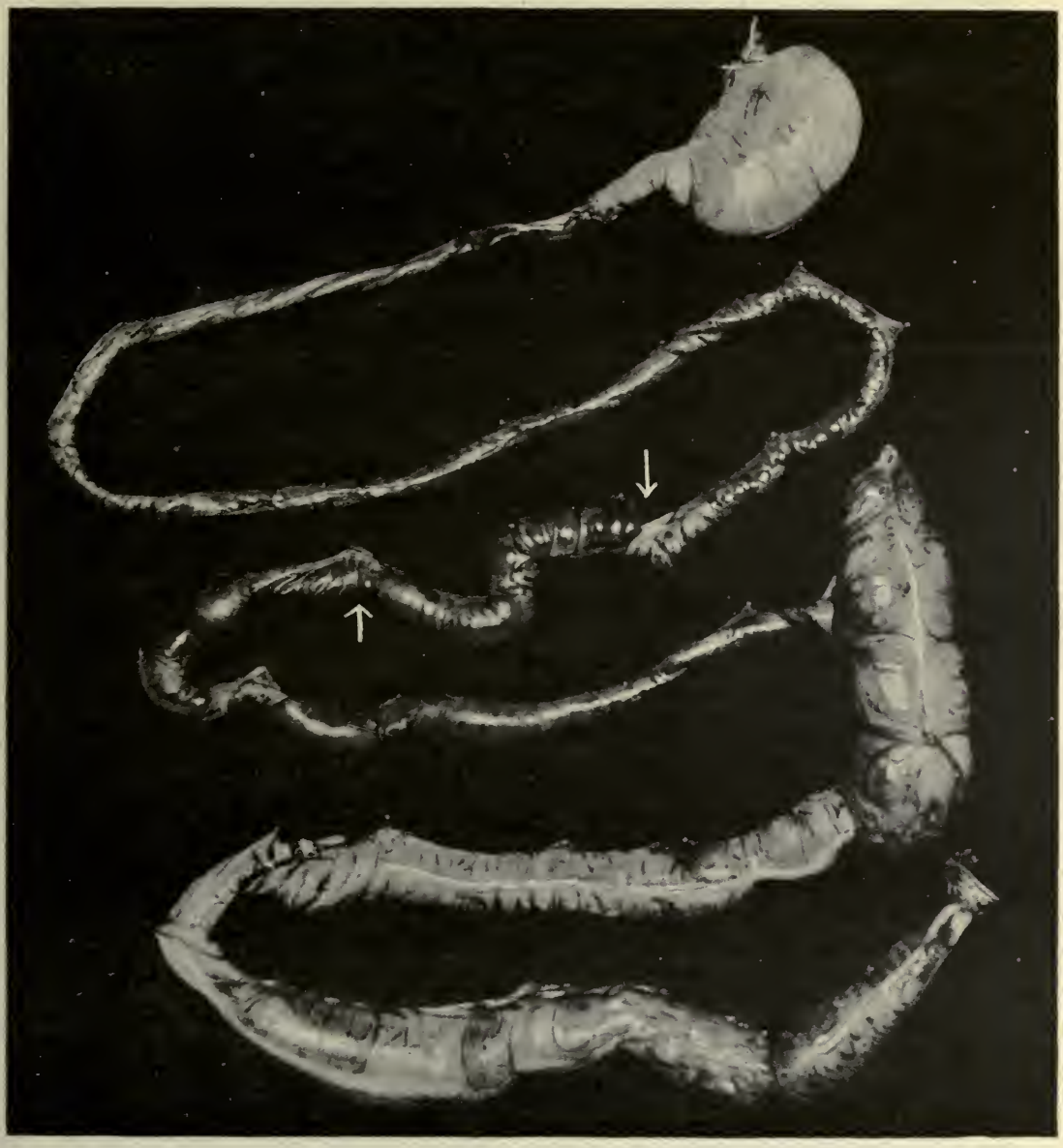

FIG. 42.—Photograph of gastro-intestinal tract of monkey (No. 22, Table II), fed exclusively for a period of 67 days on autoclaved food and onion. The animal (an adult female) died on the same day as her young, which was similarly fed. Note dilatation of empty stomach, also of cæcum and large bowel. Large ileal intussusception is indicated by arrows. Note inert appearance of greatly dilated colon. Intense colitis was present throughout the whole length of the viscus. The subserous ecchymosis, especially at lower part of the colon, can just be made out in the photograph. Compare with Fig. 41.

alone. Of these the most constant, as well as the most severe, is colitis. These changes are, especially as regards the stomach and small intestines, more frequent in the presence of an excess of starch and a want of vitamin C in the deficient dietary. Similar changes in the colons of sufferers from war œdema have been described by Oberndorfer.[1]

In one control monkey only was the gastro-intestinal tract not in perfect health. In this animal (No. 16) a small area of mid-colon was congested, giving to the mucous membrane a rose-pink tinge; no erosion of the mucous membrane was present nor ecchymosis of the serous covering of the bowel. The hyperæmia was limited to the mucous coat. The animal had been constipated, and was one of those which had suffered from jaundice. In no control animal was colitis present. Table XI shows the state of the digestive organs in monkeys fed on the four classes of deficient dietaries:

TABLE XI

Lesions.	Controls.	Autoclaved Rice.	Autoclave Rice and Butter.	Autoclaved Food and Onion.	Autoclaved Food, Onion, and Butter.
Number of animals	8	10	4	6	5
Atrophy of submaxillary glands *	Nil	6	4	5	2
Dilatation of stomach	Nil	10	4	4	2
Gastric catarrh	1 (No. 16)	7	3	3	2
Ulcer of pylorus	Nil	Nil	1	2	Nil
Carcinoma of pylorus	Nil	Nil	Nil	Nil	1
Duodenal catarrh	Nil	7	3	2	1
Subserous ecchymosis of duodenum	Nil	5	1	1	1
Duodenal ulcer	Nil	Nil	Nil	Nil	Nil
Congestive changes in jejunum	Nil	8	1	1	1
Congestive changes in ileum	Nil	7	2	Nil	Nil
Subserous ecchymosis of jejunum	Nil	5	Nil	1	Nil
Subserous ecchymosis of ileum	Nil	3	1	Nil	Nil
Ballooning of small bowel	1 (No. 16)	6	4	2	2
Thinning of bowel walls	1 (No. 16)	10	4	2	4
Intussusception	Nil	6	4	5	3
Colitis	Nil	10	3	6	2
Subserous ecchymosis of *whole* colon	Nil	2	Nil	1	1
Subserous ecchymosis of *lower* colon only	Nil	5	1	3	2
Ballooning of colon	1 (No. 16)	6	3	4	3
Atrophy of colon walls	Nil	10	4	3	4
Enlargement of mesenteric glands	1 (No. 16)	10	4	6	4
Atrophy of omentum	Nil	10	4	6	5
Atrophy of pancreas *	Nil	6	2	4	2

* *Notes.*—(1) Cases are noted as having atrophic submaxillary glands and pancreas when the weight of these organs was less than the lightest amongst controls.

(2) Intussusceptions are noted in every case in which they were present. The majority of them were agonal in origin, while a proportion, as judged by their size and appearance, had probably occurred some time prior to death.

The occurrence of a recently-developed *cancer of the pylorus* in one of the monkeys fed on autoclaved food, butter, and onion calls for mention. Reports as to the effect of vitamins on tumour growth are conflicting. Some maintain that diets deficient in vitamins reduce the rate of growth of tumours (Benedict

[1] *Münch. Med. Woch.*, 1918, LXV. 1191.

and Rahe)[1]; others that vitamin-rich diets favour tumour growth (Corson-White)[2]; others that it is not practically possible to restrict the growth of experimental cancers by limitation or selection of diets, and that starvation of such new growths is apparently impossible without starvation of the host (Drummond).[3] It is reported further that in England some diminution in the number of deaths from cancer occurred during the year 1918, in both males and females, when rationing was general (Registrar-General's Reports). A lower death-rate from cancer during the same year has also been reported from Berlin. The evidence against the deficiency of vitamin in the present instance having had anything to do with the genesis of the pyloric carcinoma would thus appear to be overwhelming. Nevertheless I report the observation, for if the dietetic fault had nothing to do with it, the circumstance is interesting in another connexion—namely, that carcinoma of the pylorus was present before the experiment commenced, and therefore may occur in a wild and apparently perfectly healthy monkey.

The facts of the case are these. The monkey was an adult female. She was at the onset of the experiment in vigorous health, having only just left her native jungle. She weighed 2,400 grams, and on the conclusion of the experiment, 51 days later, 1,950 grams; thus losing 450 grams, or 19 per cent. of original body-weight—a loss by no means extreme. For the first 10 days she was fed on autoclaved rice and butter—120 grams of the former and 15 grams of the latter. The rice was autoclaved for an hour and a half at 130° C. Of this food she ate freely at first, more sparingly towards the end of the 10 days. On the eleventh day the diet was changed to autoclaved food, fresh butter, and fresh onion prepared in the proportions and manner previously described. The food mixture thus contained an adequate supply of vitamin A and vitamin C, but was deficient in vitamin B. Its nutritive value may have been altered in other regards by the autoclaving. The animal exhibited during the course of the experiment the following symptoms: diarrhœa, progressive anæmia, asthenia, and during the last nine days severe dysentery. Autopsy was performed immediately after death.

The stomach was greatly dilated, but presented no other naked-eye evidences of disease. Following my laboratory routine in such cases, a portion of it 1 centimetre square, embracing all coats of the viscus, was removed from the neighbourhood of the pylorus for histological examination. The tissue was fixed in Zenker's fluid, embedded in paraffin, sectioned and stained with hæmatoxylin. Three such specimens were examined. In one the appearances seen under a low power of the microscope (Zeiss Obj. AA. Oc. 4) are represented semi-diagrammatically in the drawing (Fig. 43). An obvious carcinoma was present. It was of small area, covering in a transverse direction three and a half fields of this power of the microscope. The surface of the growth was flush with the

[1] *Jour. Cancer Res.*, 1917 (April), II. 159.
[2] *Pennsylvania Med. Jour.*, 1918–19 (March), XXII. 348.
[3] *Brit. Med. Jour.*, 1920 (July 31), p. 147.

mucous surface of the stomach, and exhibited no excrescences towards the cavity of the viscus. Numerous epithelial down-growths (accurately represented in the drawing) projected into the submucous coat. This coat appeared somewhat thickened beneath the growth. The down-growths had not penetrated deeply into the submucosa ; the vertical area occupied by them scarcely exceeded that which would have been occupied by the glandular elements they replaced. The

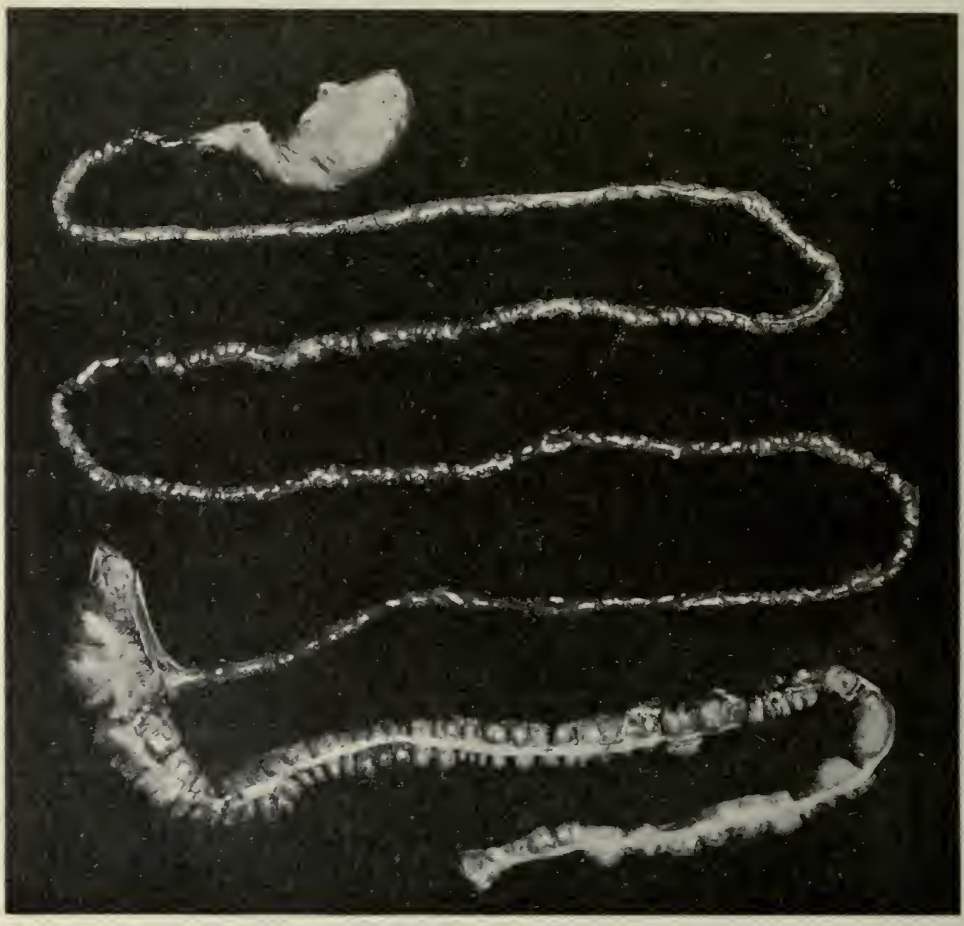

FIG. 41*a*.—Gastro-intestinal tract of healthy adult male monkey (No. 20, Table II).

cells near the advancing edge of the growth stained well, their staining capacity gradually diminishing towards the mucous surface of the stomach. The older cells were of hyaline appearance, their nuclei having disappeared or having failed to retain the stain (Fig. 44). The two remaining specimens were not in series with the first ; they showed but occasional microscopic nodules of the carcinoma, one of which is seen in the photo-micrograph Fig. 44). Further sections taken from the same block showed no growth.

The discovery of this area of carcinoma was largely a matter of chance, since

there was no naked-eye evidence of its presence. Such small cancerous growths may very easily be missed unless microscopical search is made for them throughout serial sections of the organ. It may be that this carcinoma was the only case of cancer of the stomach in my series of monkeys; on the other hand, it is

FIG. 42*a*.—Gastro-intestinal tract of adult male monkey (No. 9, Table II) which was fed for the first 28 days of experiment on autoclaved rice, and thereafter until the point of death, on the eighty-second day, on autoclaved food and onion. Note the great dilation of the stomach, and small intestine, the " air-locks " in the small bowel, the lengthening of the colon and the atrophy of its longitudinal muscular bands. Intense colitis was present. Compare Fig. 41*a*.

possible that I may have missed others. It seems probable that the carcinoma was of recent origin, since the area of pyloric mucosa involved by it was of very small size, and the underlying coats of the viscus were not invaded by it. The suspicion therefore arises that the malignant growth may have developed during the fifty-one days of the experiment.

COMPARISON OF THE GASTRO-INTESTINAL CHANGES IN THE THREE SPECIES

The data afforded in this and the preceding chapter indicate that the profound changes resulting in the gastro-intestinal tract, in consequence of the various

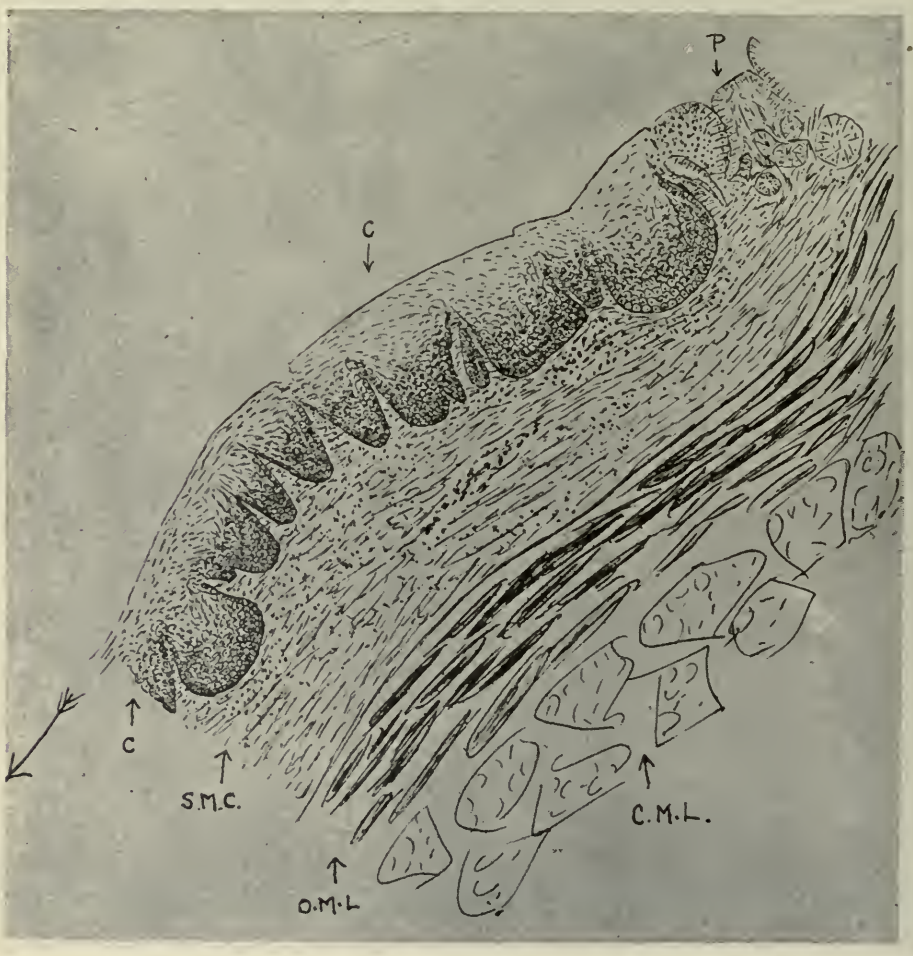

FIG. 43.—Semi-diagrammatic drawing of section from pyloric end of stomach of a monkey fed on autoclaved food, butter, and onion, showing C, carcinoma; P, pyloric glands; S.M.C., submucous coat; O.M.L., oblique muscular layer; C.M.L., circular muscular layer. Drawing represents one complete field under Zeiss objective AA and ocular No. 4. The growth extended for an additional two and a half fields of the microscope in the direction of the large arrow.

deficient foods employed, are similar in kind in the three species; it may be expected, therefore, that they will be similar in kind if not in degree in human beings whose dietaries have faults similar in kind if not in degree to those used in these experiments. Without attempting to analyse them too closely or to

attribute to each deficiency or fault a specific effect, it is obvious that certain broad conclusions can be drawn :

(1) The health of the gastro-intestinal tract is dependent on an adequate provision of accessory food factors : especially vitamins B and C. The absence of vitamin B is capable of producing pathological changes in the tract which frequently assume the clinical form of colitis. This observation is of the highest importance in view of the frequency of this malady. Vitamin C, in association

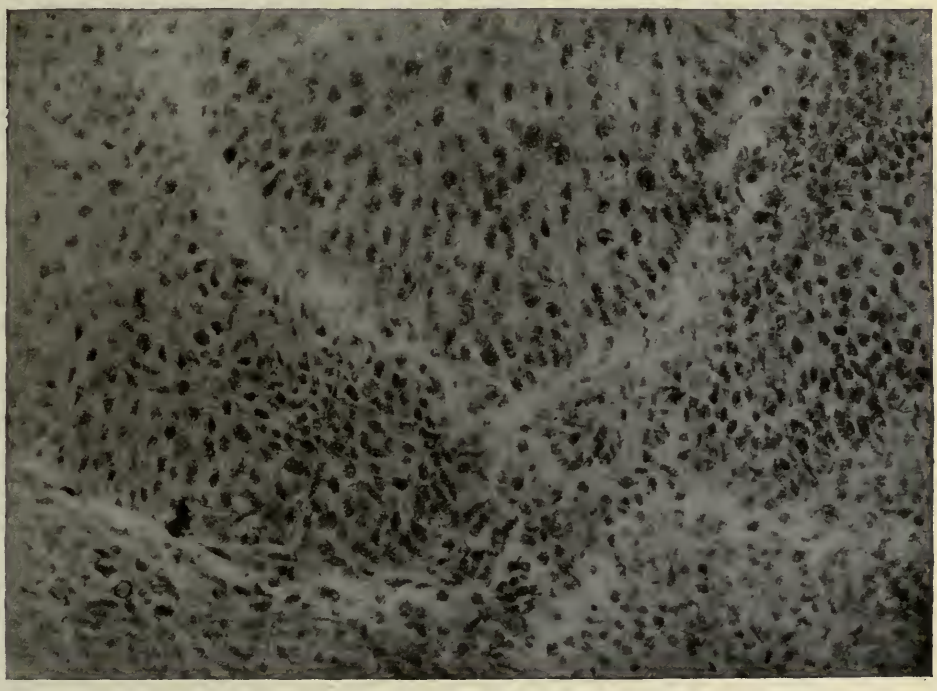

FIG. 44.—Micro-photograph, × 165, of recently developed carcinoma of the pylorus in a monkey fed for 51 days on food almost wholly devoid of vitamin B.

no doubt with a too scanty provision of vitamin B, is especially concerned in the production of congestive and hæmorrhagic lesions in the tract, and evidences of these may be found in animals which have not exhibited during life any of the clinical manifestations of scurvy in noteworthy degree. A state of ill-health of the gastro-intestinal tract may thus be a pre-scorbutic manifestation of disease due to insufficient vitamin intake, especially when associated with an excess of starch or fat or of both in the food.

(2) The disorder of the gastro-intestinal tract is enhanced when the deficient food is ill-balanced.

(3) In general the disorders resulting in this situation from deficient foods are :

(*a*) Congestive, necrotic, and inflammatory changes in the mucous membrane; sometimes involving the entire tract, sometimes limited to certain areas.

(*b*) Degenerative changes in the neuro-muscular mechanism of the tract, tending to dilatation of the stomach, ballooning of areas of small and large bowel, and probably also to intussusception.

(*c*) Degenerative changes in the secretory elements of the tract—of the gastric glands, the pyloric glands, the glands of Brunner, the glands of Lieberkuhn, and of the mucous glands of the colon. These changes are such as must cause grave derangement of digestive and assimilative processes.

(*d*) Toxic absorption from the diseased bowel as evidenced by the changes in the mesenteric glands.

(*e*) Impairment of the protective resources of the gastro-intestinal mucosa against infecting agents, due to hæmorrhagic infiltration, to atrophy of the lymphoid cells, and to imperfect production of gastro-intestinal juices. This impairment results not only in infections of the mucous membrane itself, but permits of the passage into the blood-stream of micro-organisms from the bowel.

(4) It is to be emphasized that the pathological changes found in the gastro-intestinal tract are more marked in some individuals than in others; and that, while all of them may occur in one and the same subject, it is usual to find considerable variation in the incidence of particular lesions in different individuals.

These observations demonstrating the dependence of digestive functions on the presence in the food of an adequate supply of vitamins were made during the years 1918 and 1919.[1] They have since been confirmed by the work of Lumière.[2]

[1] *Brit. Med. Jour.*, 1919, I. 177, and II. 36.

[2] Lumière, A., *Bull. de l'Académie de Médecine*, 1920 (January, March, and August); *La Presse Médicale*, May 1920.

CHAPTER XI

OTHER DIGESTIVE ORGANS

The Salivary Glands.—These organs, as represented by the submaxillary glands, undergo some degree of atrophy in consequence of all the deficient dietaries employed (Fig. 15).

In healthy monkeys their average weight per kilogram of original body-weight is 1·01 gram ; in those fed on autoclaved rice it is 0·80 gram ; in those fed on autoclaved rice and butter it is 0·70 gram ; in those fed on autoclaved food and onion it is 0·82 gram ; in those fed on autoclaved food, butter, and onion it is 0·78 gram (Table IX). The atrophy was thus most marked in animals whose deficient dietary was disproportionately rich in fats. Wide variations in the degree of atrophy occur in different individuals. In some the average weight per kilogram of original body-weight has been as low as 0·60 gram ; in others it has approached closely to, and in one case equalled, the average weight in healthy controls.

It seems probable that in cases presenting the highest degree of atrophy, impairment of function is present, and that in consequence digestion is impeded at its very outset. Some evidence in this connexion is available from the literature. Sullivan and Jones [1] find the saliva of pellagrous subjects to be of a peculiar ropy consistency, which makes its presence in the mouth most obvious. Its sulphocyanate content is much reduced in comparison with that of normal persons. These observers remark that, since the sulphocyanate arises from the metabolism of protein and the detoxicating action of the system whereby poisonous cyanides are converted into the relatively innocuous sulphocyanate, in pellagra there is both a lessened intake of protein and a detoxicating power feebler than normal. The reaction of saliva in pellagrins is somewhat more alkaline than normal. The parotitis described by Enright [2] amongst German pellagrins in Egypt is interesting in this connexion, since no doubt the debilitated organ is more susceptible to infection than in health. It is of interest also to note that Muckenfus [3] reports the presence in normal saliva of a small amount of vitamin B.

The Liver.—This organ undergoes greater or lesser degrees of atrophy in all species :

The atrophy is to a considerable extent masked by the passive hyperæmia which so frequently accompanies it. As determined by weight, it amounts in pigeons fed exclusively on rice to about one-tenth part of the normal weight of the organs. In birds

[1] *Public Health Reports*, 1919 (May 16), XXXIV. 1068.
[2] *Lancet*, 1920 (May 8), p. 1003.
[3] *Jour. Am. Chem. Soc.*, 1918 (Oct.), XL. 1606.

receiving butter in addition to the rice the atrophy is less pronounced. The organ loses almost one-third of its weight, and vacuolation is marked in guinea-pigs fed on a scorbutic diet (Fig. 45). In monkeys fed on autoclaved rice the loss in weight is approximately one-tenth part of the normal; in those receiving butter in addition to the rice the atrophy is less marked. In both these respects the results observed in pigeons and in monkeys are the same. The atrophy is more pronounced in monkeys fed on autoclaved food. In cases where both vitamin B and vitamin A were wanting, the loss of weight amounted approximately to one-fourth part of the organ's normal weight; where vitamin B alone was wanting, it amounted approximately to one-sixth. A similar atrophy of the liver occurs in war œdema, in which the organ may be reduced in weight to 950 grams (Oberndorfer.)[1]

Certain concurrent infections—tuberculosis, *B. suipestifer*, and septicæmias of intestinal origin—cause the liver, as observed in pigeons, to undergo great enlargement. Thus, in cases of polyneuritis columbarum associated with tuberculosis, the weight of the organ has been found to be practically double that of health; while such infections as *B. suipestifer* may increase its weight by one-half. This observation is of importance in connexion with beri-beri: when this malady is due solely to food deficiency the liver should be reduced in size; if it be enlarged, there is an infectious element in the case. Scheube and Bentley record that in human beri-beri the liver is almost invariably enlarged, a circumstance which would seem to indicate that human beri-beri is rarely of the purity of polyneuritis columbarum, and that bacterial agencies influence the character of its final phases even if they do not influence its earlier phases.

The changes in the liver have been studied histologically in pigeons. They consist in: (1) Necrobiosis of the liver cells with karyolysis; (2) necrosis in cases complicated by infection; (3) passive congestion.

The necrobiosis has no definite focal distribution; it affects single cells or small groups of cells. It varies in degree within wide limits in livers from different cases, and in different parts of the same organ. The number of liver-cells showing normally-staining nuclei may not exceed one-tenth to one-fifth of the total cells of the organ. I have encountered several cases in which the number was considerably less. Cells containing nuclei which have lost in great measure their staining characters, owing to partial disappearance of the nuclear chromatin, may constitute as many as three-fifths of the total liver-cells; in many such cells, in hæmatoxylin-stained sections, the nuclei could only just be distinguished under high powers of the microscope as faint rings empty of chromatin. Cells from which the nuclei have wholly disappeared may number one-fifth to one-third of the total cells of the organ; in exceptional cases their numbers have been much higher. The cell-body becomes homogeneous, or the cell-wall may enclose but a granular débris.

Extensive and more rapid death of cells occurs in cases where polyneuritis columbarum is associated with septicæmic states. In such cases necrotic changes in the liver-cells may be very pronounced, the degenerated cells being separated

[1] *Münch. Med. Woch.*, 1918, LXV. 1191.

one from another and from their basal attachments. In septicæmic cases bacteria were sometimes seen, in sections of the organs, lying amongst the liver-cells, and were readily detected in smears from its cut surface.

Both necrobiosis and necrosis are usually associated with greater or lesser degrees of passive congestion. The vessels are engorged, and a fairly uniformly distributed hæmorrhagic infiltration may occur amongst the liver-cells. In the graver cases of necrosis associated with septicæmia, the degree of congestion

FIG. 45.—Section of liver from guinea-pig fed on a scorbutic diet. Note marked vacuolation.

and of hæmorrhagic infiltration may be extreme and the liver be greatly enlarged in consequence.

I interpret these changes as indicating a gradual starvation of the cells, the process of necrobiosis and karyolysis being aided by passive congestion of the organ. It is possible that toxic substances produced in the course of a deranged metabolism, or absorbed through the debilitated intestinal mucosa, may contribute to the result; malnutrition of the cells with failure of regeneration is, I believe, the essential factor concerned. These changes are sufficient evidence of this organ's impairment of function in a relatively high proportion of cases. Biliary insufficiency no doubt contributes to a state of acidosis, and facilitates the passage of toxic substances from the digestive tract into the blood-stream.

The organ's content of glycogen is reduced in " war œdema " (Masse and Zondek). In monkeys the gall-bladder was sometimes distended with a pale-coloured bile.

The dependence of the functional perfection of the liver on an adequate supply of vitamins is an observation of much importance, since this organ is so profoundly concerned in the maintenance of metabolic harmony. The fact that in health it is rich in vitamins of every class is an indication of its need for these indispensable substances.

The Pancreas.—The atrophy of this organ is a notable effect of food deficiencies. It varies greatly in different animals:

In healthy male pigeons the average weight of the pancreas is 0·95 gram; in healthy females, 0·89 gram, the range of weight in the former being from 0·7 to 1·4 gram, in the latter from 0·7 to 1·6 gram. In birds fed on polished rice the organ may weigh as little as 0·3 gram, and but rarely exceeds 0·7 gram; its average weight being 0·58 gram.

In polyneuritis columbarum the pancreas is frequently of a dead white colour, which may be universal throughout its entire length or confined to limited areas. It has rarely preserved the typical coral pink appearance of health. Occasionally it is dark slate-grey in colour, and ecchymoses, sometimes of considerable size, and necrotic-like areas may be found on its surface. The comparative absence of gross pathological changes might lead one, in a cursory examination, to regard the organ as practically normal; but when care is taken to contrast its appearance microscopically with that of a healthy pancreas, the degree of its abnormality is at once obvious. I lay stress on these points, since one commonly reads in post-mortem reports of persons dying of deficiency disease that, " apart from generalized atrophy, the organs appeared normal." Such a statement is probably misleading. An organ which presents in animals the appearances I have described is not likely to be always normal in human beings subjected to similar food deficiencies, nor is it likely to exercise a normal function. Further; to be functionally imperfect, it is not necessary that the pancreas should present such gross lesions as inflammations and hæmorrhages into its substance. One may have a headache without a fractured skull. I regard pancreatic insufficiency as one of the more important of the effects of food deficiency.

In monkeys the atrophy of this organ is less marked than in pigeons, but is still very considerable, especially in animals whose deficient food is excessively rich in fats.

In controls the weight of the organ ranges between 2·4 and 3·9 grams; in animals fed on autoclaved rice it ranges between 1·09 and 2·8 grams; in those fed on autoclaved rice and butter, between 1·8 and 2·4 grams; in those fed on autoclaved food and onion, between 1·3 and 2·9 grams; and in those fed on autoclaved food, butter, and onion, between 2 and 3·5 grams.

In none of the deficiently-fed animals does the maximum weight of this organ exceed appreciably the minimum weight in health, except in those of the last

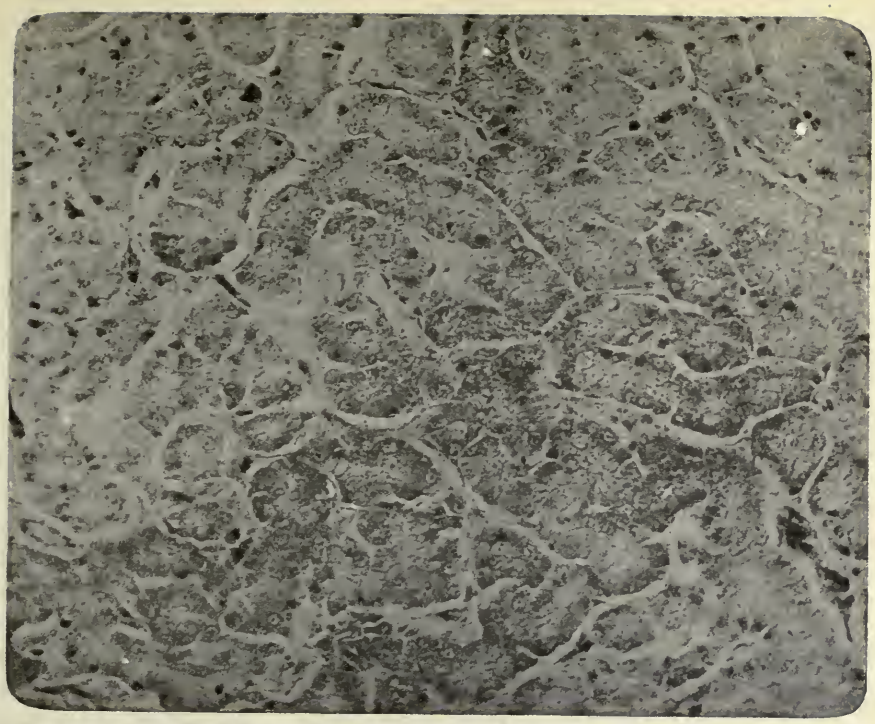

FIG. 46.—Section of pancreas from a case of experimentally-produced poiyneuritis columbarum, × 165. This specimen presents appearances closely resembling the normal. Note alveolar structure, granular outer half and clear inner half of cells. A slight degree of necrobiosis and karyolysis is present, although not easily detected in the photo-micrograph.

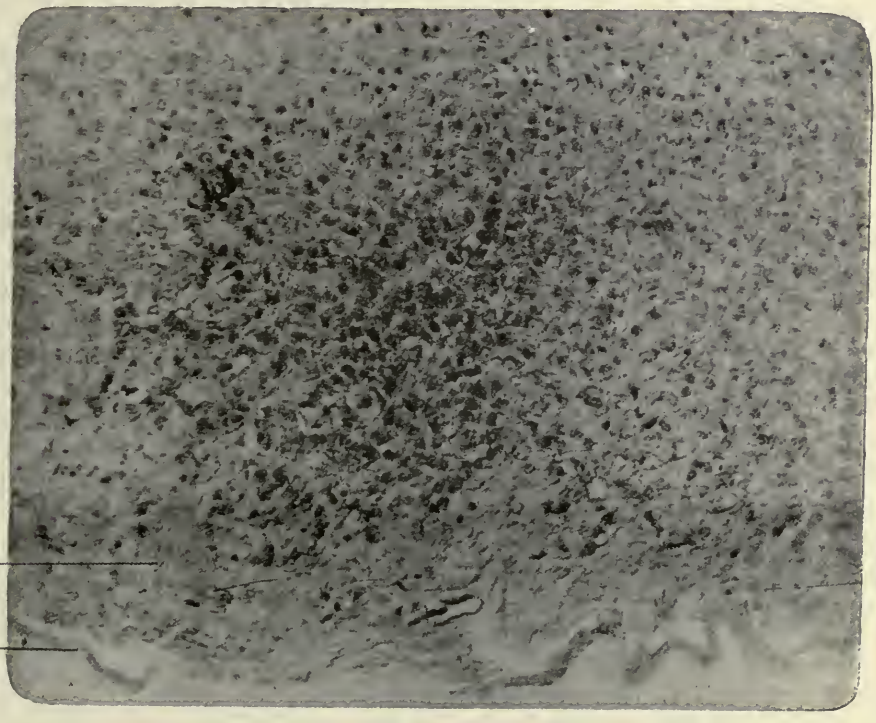

FIG. 47.—Section of pancreas from a case of experimentally-produced polyneuritis columbarum, × 165, taken from the periphery of the organ. Note shrunken capsule (C), necrosis of cells (N) underlying capsule, compression of alveoli, smaller size of alveolar cells giving rise to appearance of larger number of nuclei area for area than in Fig. 46. Necrobiosis of cells is more marked in this specimen than in Fig. 46.

category. In monkeys, as in pigeons, this organ may exhibit marked atrophy in certain subjects; it is usually more marked in the tail end of the organ. Apart from atrophy, increased pallor, and softer consistency, no gross lesions. with the exception of occasional small hæmorrhages, have been encountered in the pancreas of deficiently-fed monkeys.

The histological appearances presented by this organ have been studied in both pigeons and monkeys. In general the texture of the organ is less open, its lobules are less distinct, and its parenchyma-cells appear shrunken and collapsed. The alveoli are more closely packed, and the shrunken cells appear to be functionally less active; they seldom exhibit granular evidence of an efficient output of work. Their nuclei are often more indefinite in staining characters than in health; while cells from which the nuclei seem to have disappeared are not uncommonly met with. A certain amount of necrobiosis of parenchyma-cells occurs; but having regard to the normal processes of degeneration and renewal of cells which go on in this organ in health, the degree of necrobiosis was not marked in about one-third of the total number examined. In the remaining cases it was more pronounced, and involved either single cells or groups of cells, especially at the periphery of the organ (Figs. 46 and 47). Collections of round cells were occasionally encountered, and in some cases there was a relative increase of interstitial tissue. The latter were especially frequent, in pigeons, at the periphery of the organ. Occasionally varying degrees of congestion and hæmorrhagic infiltration were seen, and in a few pigeons these appearances were pronounced. No marked changes were found in the islets of Langerhans, although in a few cases in monkeys these structures appeared to form a higher proportion of the sections than in health. In general the impression left on the mind by a study of this organ was that the functional capacity of its cells was depressed; they appeared to have lost their capacity for work. The normal processes of renewal of cells seemed to be in abeyance. In this connexion it is of interest to note the finding of Voegtlin and Myers [1] that vitaminic extracts prepared from brewer's yeast cause, on intravenous injection, an increased flow of pancreatic secretion, their action in this regard being similar to that of secretin. In cases of digestive disorder, associated with the habitual use of deficient and ill-balanced foods, which I have so far had an opportunity to treat in the light of these observations, I have noted a striking improvement in pancreatic and biliary function following the use of vitamin-containing extracts made from the yolks of eggs.

Mackenzie Wallis [2] has recently directed attention to the similarity of the changes found by him in cases of infantile diarrhœa to those described by me as resulting from food deficiency. These changes appear also to present a number of features in common with the condition described by Oertel [3] as "essential atrophy of the pancreas." In this state there exists an atrophy due to loss and

[1] *Jour. Pharm. and Expt. Therap.*, Baltimore, 1919, XIII, No. 4, p. 301.
[2] *Brit. Med. Jour.*, 1920 (July 31), p. 160.
[3] *Jour. Med. Res.*, 1919, XL, No. 3, p. 289.

collapse of parenchyma, associated with irregular, diffuse, abortive regeneration. This condition leads anatomically to a definitely recognizable entity and to a considerable degree of pancreatic insufficiency. It is important, then, to recognize that atrophy of the pancreas may result from avitaminosis, especially when associated with an excess of starch and fats in the food. The impairment of function so produced will be manifestly greater should the organ be attacked by such infecting agents as pneumococcus, streptococcus, or staphylococcus, all of which are peculiarly prone to cause toxic necrosis of the acinar cells of this organ.

CHAPTER XII

THE ENDOCRINE ORGANS

Evidence has been advanced of the deleterious effects of food deficiencies on the organs responsible for digestion and assimilation; it is now necessary to examine their effects on the endocrine regulators of metabolism. So important is the part played by the endocrine organs in controlling the metabolic activities of the digestive system that it is impossible fully to appreciate the significance of the changes occurring in the latter without a knowledge of those that occur in the former. The endocrine organs influence those of digestion both by their hormones and through the sympathetic nervous system. Food deficiency deranges both the normal production of hormones and the functional perfection of the sympathetic nervous control; consequently, the digestive organs are deprived of the full advantage of that efficient regulation and correlation which normally they would derive from healthy endocrine action. Attention has been drawn to the frequency with which the duodenum is involved in consequence of food deficiency. It seems probable that this may lead to interference with the normal production of secretin and of pancreatic secretion. But hormones from more distant organs also influence the health and activities of the digestive apparatus. Thus that from the thyroid promotes the flow of gastric juice and of succus entericus. It is known that hypothyroidism may lead to hypo-acidity, to impaired secretion of gastro-intestinal juices, to the production in both stomach and duodenum of such lesions as patechial hæmorrhages, superficial hæmorrhagic erosions, acute ulcer and diffuse inflammation, as has been shown by Ivy [1] in the case of thyro-parathyroidectomized dogs. The severity of these lesions is directly proportionate to the length of time for which the animal survives operation. Friedman [2] also has found that thyroid insufficiency causes in dogs and in rabbits acute ulcers of the stomach and duodenum, and occasionally appendicular lesions; and concludes that thyroid insufficiency in man may lead to similar results. Adrenal insufficiency also may cause profound disturbance of digestive and gastro-intestinal function; such, for instance, as imperfect secretion of gastric juice, the development of gastric ulcers,[3] and derangement of the glycogenolytic process. Failure of the

[1] Ivy, A. C., *Arch. Intern. Med.*, 1920, XXV, No. 1, pp. 6–31.
[2] Friedman, G. A., *Jour. Med. Res.*, 1918, XXXVIII, No. 1, p. 69.
[3] Ibid., 1915, XXXII, No. 2, p. 287.

inhibitory action exercised by epinephrine over the muscle of the stomach and intestine may favour the production of vomiting, and of dilatations of various parts of the gastro-intestinal tract. The pituitary body, too, by means of the hormone produced in its posterior lobe, has an important influence over the intestinal muscle, an influence which seems to come more especially into play in states of temporary paralysis of the muscle of the bowel. A striking example of this action is afforded by the effect of pituitrin in dispelling accumulations of flatus from the distended atonic bowel.

These examples suffice to emphasize the close relation of derangement of endocrine function to disorder of digestive function. It is necessary, therefore, to take cognisance of any disturbance of endocrine function in relation to the changes in the gastro-intestinal tract, the salivary glands, the liver, and the pancreas, which have been under consideration in the preceding chapters.

But the effects of disordered endocrine function on the digestive organs are not all; for such disorder will profoundly influence the processes of metabolism in general. Consider, for example, the importance of any agency which is capable, directly or indirectly, of deranging the functional perfection of the thyroid gland, which is to the human body as the draught is to the fire; or, of the parathyroids which control the metabolism of calcium and the efficient calcification of teeth and bone; or, of the adrenal medulla whose hormone is believed to be concerned in the maintenance of vascular tone, and in the excitation of sympathetic nerve terminals throughout the body; or, of the adrenal cortex with its relation, as we shall see, to lipoid metabolism, and to the development of the sex organs; or, of the pituitary body, an organ concerned with skeletal development, the acceleration of physical and mental growth, and the excretory function of the convoluted tubules of the kidney; or, of the reproductive organs, which have such a profound effect on development and on psychic function.

Whatever be the true nature of vitamins, they resemble in their action that of hormones, whose function is to stimulate metabolism. This similarity of action is illustrated by the fact that such endocrine extracts as those of the duodenum,[1] the thyroid, and the anterior part of the pituitary body (tethelin)[2] can delay in their onset and alleviate, although not permanently dispel, the symptoms of polyneuritis in pigeons resulting from deprivation of vitamin B. The beneficial effect of these extracts appears to be due as much to their action as metabolic stimulants as to any vitamins they may contain, because synthetic thyroxin and pilocarpine hydrochloride [2] exert it also.

The disturbances of metabolism resulting from avitaminosis are bound up with, and are in considerable measure dependent on, the disturbance of endocrine function which results from the same cause. This fact is exemplified by the retardation or hastening of the onset of symptoms of deficiency disease, which may be brought about by factors that influence favourably or unfavourably the resources of the endocrine organs; such, for instance, as rest and warmth, which

[1] Friedman, loc. cit.

[2] Dutcher, R. A., *Proc. Nat. Acad. Sciences*, 1920, VI. 10–14.

retard the onset of symptoms, and cold, fatigue, and infection, which precipitate it. Such factors, too, as age and sex operate in regard to the onset of symptoms through the medium of endocrine action. It is true that all of these may influence the onset of symptoms by conserving or expending the calories available for the needs of the individual; but underlying this, or associated with it, is conservation or expenditure of endocrine resources.

My studies have provided some interesting contrasts in the behaviour of certain endocrine organs in the presence of food faults. Thus, the adrenal glands tend to undergo enlargement while the thyroid tends to atrophy in the presence of food deficiencies. When, on the other hand, the food is excessively rich in proteins and fats without any deficiency of vitamins, the thyroid tends to enlarge and the adrenals to diminish in size. In the former case the body appears to need more adrenal and less thyroid hormone; in the latter, more thyroid and less adrenal hormone. The combination of effects produced in the thyroid and adrenal glands in the presence of food deficiency is paralleled by the observation of Herring [1] that in rats fed on thyroid extract the adrenals almost double their weight, while their epinephrine-content is also increased, and by his more recent observation that the adrenals increase and the thyroid diminishes in size in consequence of pregnancy.[2] The pituitary enlargement—occurring as it does in the pars anterior—calls to mind the enlargement of this part of the organ resulting from thyroidectomy and from castration, the similarity being carried further when the thyroid and testicular atrophy resulting from avitaminosis are remembered.

It seems, therefore, that both the functional perfection and the correlations of the endocrine organs are dependent upon a properly balanced and vitamin-containing food-supply; dietetic deficiency means endocrine insufficiency.

The effects of food deficiency on the pancreas have already been dealt with. There remain to be considered those on other endocrine structures, with which, for the sake of convenience, I shall include the thymus and the spleen, although there is no unequivocal evidence that either of these produces an internal secretion.

[1] *Quart. Jour. Exp. Phys.*, 1917, XI. 47.
[2] *British Med. Jour.*, 1920 (Dec. 11), p. 886.

CHAPTER XIII

THE THYMUS AND SPLEEN

The Thymus.—The extreme atrophy of this organ—to which attention was first drawn by Funk and Douglas [1]—is one of the most remarkable of the effects of food deficiency.

In pigeons the thymus consists of a chain of glands, resembling a string of sausages, stretching from the base of the skull to the entrance of the thoracic cavity. It lies on either side of the neck, adjacent to the wall of the œsophagus and external to the vascular and nervous trunks. In the healthy pigeon it varies considerably in size, and in rare cases—3 in 35—it was present only in traces which were not weighable. Its variations in the male range between 0·1 and 1·702 gram; in the female between 0·085 and 0·776 gram. It is, on the average, twice as large in males as in females; weighing in the former 2·324 grams, and in the latter 1·201 grams, per kilogram of body-weight. *In monkeys*, also, wide variations in the size of this organ in health have been found; the range lying between 0·6 gram and 2·45 grams. In these animals, too, it is, on the average, heavier in males than in females.

Excluding a scorbutic diet, with regard to whose effects on the thymus no observations were made, all other deficient dietaries employed in my experiments gave rise to intense atrophy of this organ. As a rule the whole of its cellular elements disappeared, leaving only its fibrous covering. This disappearance was as marked in monkeys deprived only of vitamin B as in those in which the avitaminosis was complete. The balance of the food with respect to proteins, fats, carbohydrates, and salts appears to make little difference in the disappearance of the thymus in the absence of vitamin B. It seems, therefore, that its atrophy is the direct result of deprivation of this substance. Not only does the thymus atrophy for want of vitamin B, but it undergoes regeneration when this accessory food factor is provided to pigeons previously deprived of it. The intensity of its atrophy is paralleled only by the disappearance of adipose tissue throughout the body. These facts would appear to indicate that the body, when deprived of vitamins requisite for normal metabolism, or when there is an increased demand for them during periods of metabolic stress, finds them for a time in the thymus, and uses them to the point of complete disappearance of this organ. The rapid involution of the thymus during pregnancy, which has recently been demonstrated by Herring in white rats, may possibly be illustrative of this fact. If the thymus be a storehouse of vitamins, its store of

[1] *Jour. Physiol.*, 1914, XLVII. 475.

these substances is not sufficiently great to protect animals from the effects of their absence for long periods; for once the supply of vitamins in the food is cut off, the organ offers but a feeble resistance to the onset of morbid states resulting from their deficiency. Indeed, in those instances in which experimental trial has been made of thymic tissue as a prophylactic and curative agent either in polyneuritis columbarum or in human beri-beri, the results have not been such as to justify great importance being attached to the vitaminic resources of this organ. Some degree of protection and some degree of alleviation are afforded by its employment in such cases, but its continued use cannot wholly protect against or cure the malady.

In pigeons the thymus undergoes intense atrophy in inanition and under the metabolic stress of septicæmic invasion.

It is of interest, in connexion with the disappearance of this organ consequent on deprivation of vitamin B, to recall the experiments of Tarulli and Lo Monaco, who observed that, when the thymus was excised in young hens 2 to 5 days old, these birds suffered from weakness of the legs, tremor of the entire body, and a somnolent condition which ended in death.

The Spleen.—This organ in pigeons, guinea-pigs, and monkeys reacts somewhat differently to food deficiencies. Its changes in the three species will be considered separately.

In Pigeons.—A reference to Table VII and to Figs. 12 and 13 reveals the enormous degree of atrophy, amounting roughly to three-quarters of its former volume, which occurs in this organ when the diet consists of autoclaved rice.

The average weight of the spleen in healthy males per kilogram of body-weight is 1·162 grams; in healthy females, 1·071 grams. In cases of polyneuritis columbarum the corresponding weights are in males 0·295 gram, and in females 0·252 gram. When butter is added to the rice dietaries the atrophy is still greater; then the average weight amounts to 0·225 gram, both sexes being taken together.

The degree of splenic atrophy is out of all proportion to the loss of body-weight. It may be that, in pigeons, the spleen, like the thymus, also holds a store of vitamins which is drawn upon when these substances are deficient in the food. It is interesting to note that the thymus atrophies with greater rapidity than the spleen, a fact which was demonstrated by killing pigeons at various stages of subjection to the deficient dietaries.

The histological changes in the spleen consist in (1) thickening of the capsule and contraction of the organ; (2) atrophy of splenic pulp and partial disappearance of lymphoid elements; (3) increased deposits of pigment; and (4) thickening of the walls of the arteries. These make up a picture more remarkable than that presented by any other organ of the body, with the exception of the thymus, the testicles, the adrenals, and the intestines. They are illustrated in Figs. 48 and 49.

In consequence of the atrophy of the splenic pulp and the reduction in numbers of the lymphoid elements of the organ, its fibrous trabeculæ and arterial system stand out in sections with abnormal prominence. The capsule is much

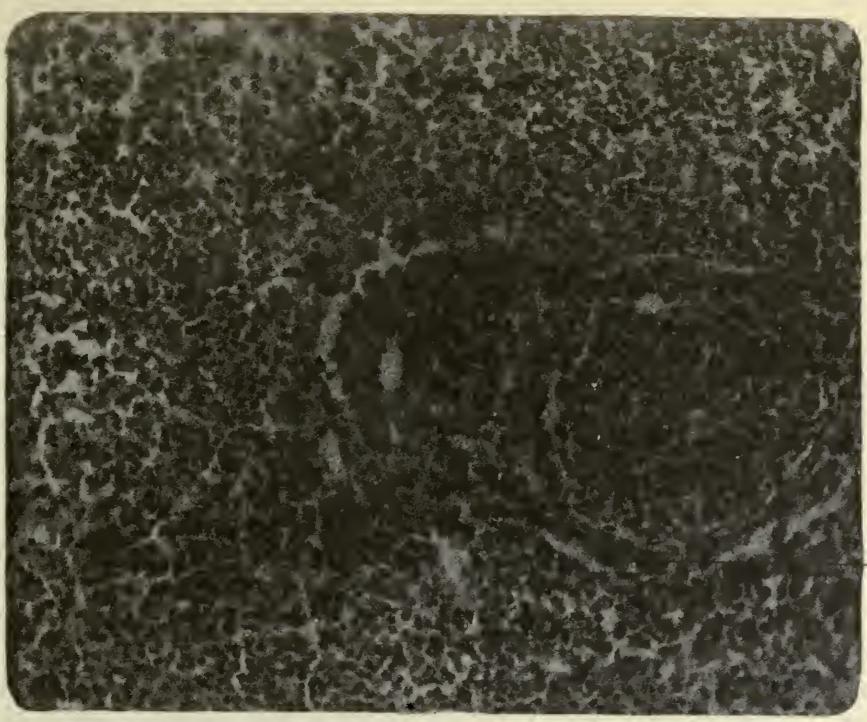

FIG. 48.—Section of normal spleen of pigeon, × 165. Note normal appearances of healthy organ, thickness of small artery in centre of section, and normal distribution of pigment (P).

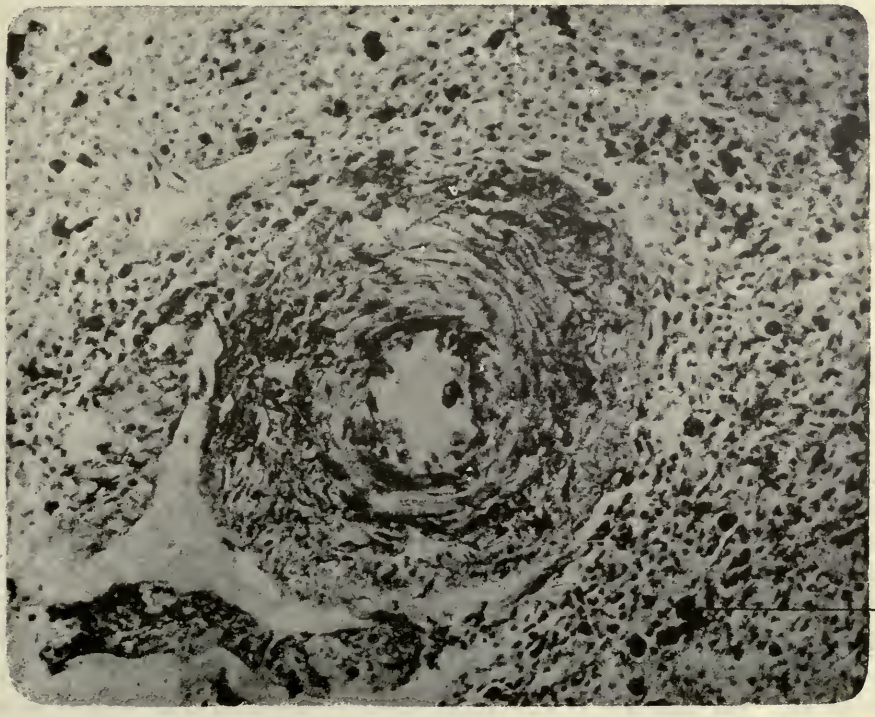

FIG. 49.—Section of spleen from a case of experimentally-produced polyneuritis columbarum, × 165 Note great loss of cellular elements, greater deposit of pigment (P), great thickening of all coats of the artery in centre of section.

thickened and the organ contracted, both changes resembling closely those which occur in the testicles.

The pigment in the atrophic spleen appears to be increased. It is possible that its increase may be only relative, the same quantity being collected into the smaller compass provided by the contracted organ. It seems probable, however, that the increased blood destruction, which occurs in consequence of the deficient diet, may to some extent be responsible for the increased deposit of pigment.

The lymphoid cells and the cells of the pulp are involved in a process of necrobiosis and absorption; they are greatly reduced in numbers. The nuclei lose their staining characters, a gradual karyolysis occurs, and the cytoplasm ultimately disintegrates (Figs. 48 and 49). In the more atrophic spleens, only traces of Malpighian corpuscles are to be found.

The vessels are involved in a process of proliferative arteritis, often leading to great thickening of their walls and to constriction of their lumen (Figs. 48 and 49). The thickening of the vessels suggests that the pathological changes may in some part be due to the prolonged action of toxic substances generated in the course of a highly abnormal metabolism.

In Guinea-pigs.—Pronounced atrophy of the spleen occurs in guinea-pigs fed on a scorbutic diet. The atrophy amounts to approximately one-half of the original weight of the organ. In healthy animals its average weight per kilogram of original body-weight is 0·64 gram, in those fed on the scorbutic diet, 0·30 gram. Histologically, the changes differ somewhat from those seen in pigeons. The capsule is but little thickened, and no notable thickening of the artery walls occurs. The changes comprise atrophy of the splenic pulp and disappearance of a high proportion of lymphoid elements. The cells of the Malpighian corpuscles are much disorganized, and are largely replaced by red blood-corpuscles. The atrophic organ contains many more red blood-cells than the healthy organ. In sections the loss of cellular elements is very striking.

In Monkeys.—In these animals the atrophy of the spleen is much less marked than in pigeons similarly fed. It is most evident in those which received butter in addition to the deficient food (Fig. 15); in this respect the result is in agreement with that noted in pigeons (Fig. 13). The greater atrophy of the spleen in pigeons is all the more remarkable since the weight of the organ per kilogram of body-weight is practically the same in healthy animals of the two species: in pigeons it is 1·48 grams, in monkeys 1·5 grams. This observation provides an example of the varying reactions of the same organ in different species to the same food deficiencies. Histologically, the spleen in deficiently-fed monkeys presents similar appearances to those in polyneuritic pigeons. There is, however, no thickening of the vessel walls.

The atrophy of the spleen produced by avitaminosis no doubt impairs its hæmatopoietic and hæmatolytic functions, and diminishes the resources of the subject to infections. Enright [1] reports a great reduction in size of the spleen in cases of "war œdema" not complicated by malaria; the organ sometimes

[1] *Lancet*, 1920 (Feb. 7), p. 314.

weighing only 3 ounces (86 grams). Oberndorfer,[1] also, has recorded a similar observation; he has found that the weight of the spleen may be as low as 50 grams as compared with 150–180 grams in health.

Although in deficiency disease, uncomplicated by infections, atrophy of the spleen is the rule, it is often enlarged in cases of polyneuritis columbarum when concurrent septicæmias are present. The point is one of interest in connexion with human beri-beri; if the spleen be enlarged in this disease, some infection is almost certainly present. In practice this is usually malaria, but in the absence of malaria any enlargement of the spleen should excite suspicion of an infectious element in the case.

[1] *Münch. Med. Woch.*, 1918, LXV. 1191.

CHAPTER XIV

THE REPRODUCTIVE ORGANS

The Gonads in Pigeons.—In healthy and full-grown pigeons *the testicles* are large, but vary considerably in size with season and food-supply. They lie on the surface of the kidneys, side by side, separated only by the adrenal glands, which are closely adherent to their

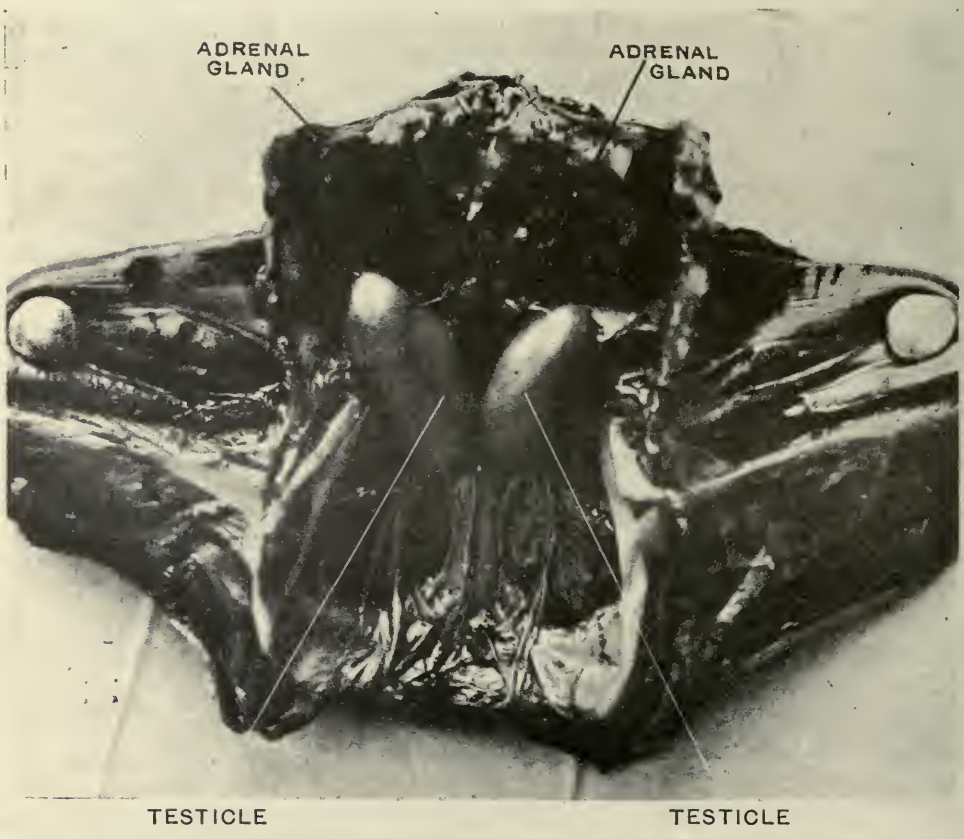

FIG. 50.—Testicles and adrenals of a healthy pigeon *in situ* : the black arrows point to the adrenals : upper poles of testicles slightly everted to expose the underlying adrenals, same magnification as Fig. 51, with which compare.

inner and anterior borders. They are oval bodies round in section, and vary in length from 1·5 to 2·0 cm. The capsule is very thin, and is intersected by a fine capillary network which is more marked on the external and lateral surfaces of the organ.

One of the most remarkable results of foods deficient in vitamins is the constant and very pronounced atrophy of the testicles. It occurs in extreme degree whether the dietary is exclusively composed of autoclaved rice or whether butter and onions are added; in the latter circumstances the atrophy is slightly less extreme. It appears, then, to be one of the most specific of the effects of avitaminosis in pigeons. Fig. 50 shows the normal appearance of the testicle in an adult pigeon; the upper poles have been slightly everted to expose the

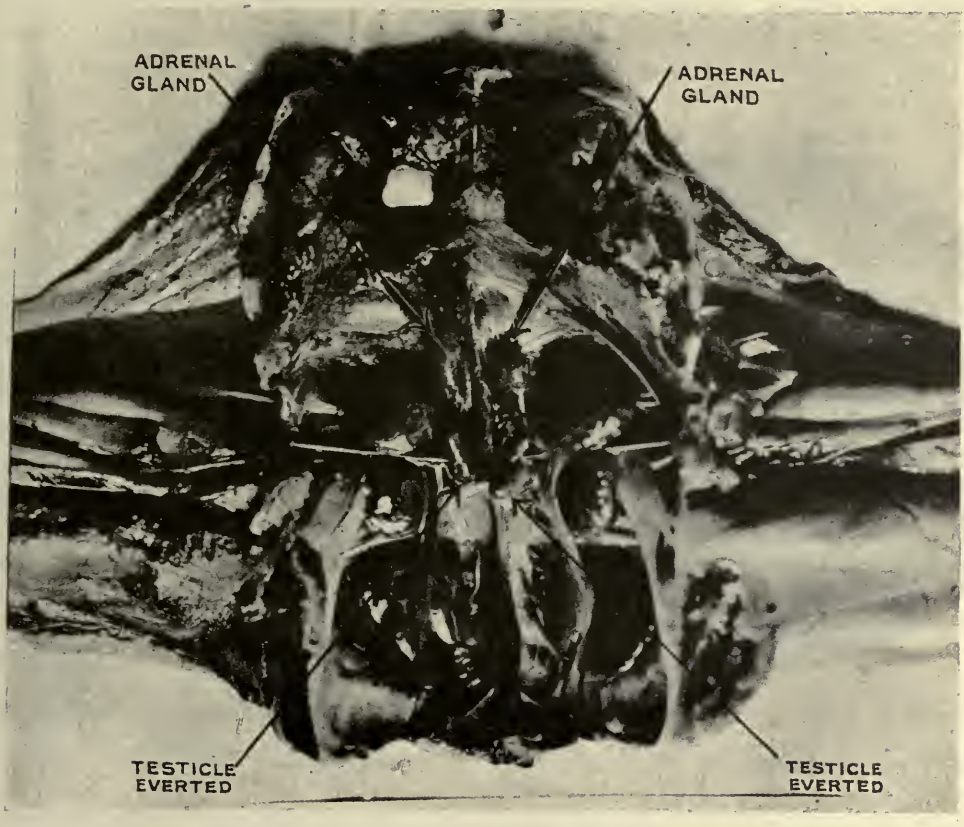

FIG. 51.—Testicles and adrenals from a case of polyneuritis columbarum. Compare with Fig. 50. Note the great atrophy of the testicles as compared with that of healthy bird, also the hypertrophy of the adrenals. The testicles have been detached from the adrenals and their upper poles turned downwards.

underlying adrenals. Fig. 51 shows the testicles from a case of polyneuritis columbarum, in which they have diminished to less than the size of a grain of polished rice, and are actually no larger than the hypertrophied adrenals. The average weight of the testicles in the early spring months, in healthy controls, is 1·355 grams, in polyneuritis columbarum it is but 0·119 gram; or a reduction in size to about one-eleventh part of their original weight.

Histological examination shows a complete cessation of the function of sper-

matogenesis. The capsule of the organ and the intertubular trabeculæ are greatly thickened; the diameter of the tubules is lessened; spermatozoa, spermatids, and spermatocytes are wholly absent. The tubules are lined by a single but often incomplete layer of cells which still preserve, in a considerable proportion of their numbers, nuclei which, from their appearance and staining reactions, seem capable of regeneration (Figs. 52 and 53).

Special interest attaches to the changes in the intertubular tissue, since the interstitial cells of Leydig, on which are dependent the development of the secondary sexual characters, lie in this tissue outside the seminal tubules. Evidence on this point is available from the literature. Houlbert,[1] in agreement with

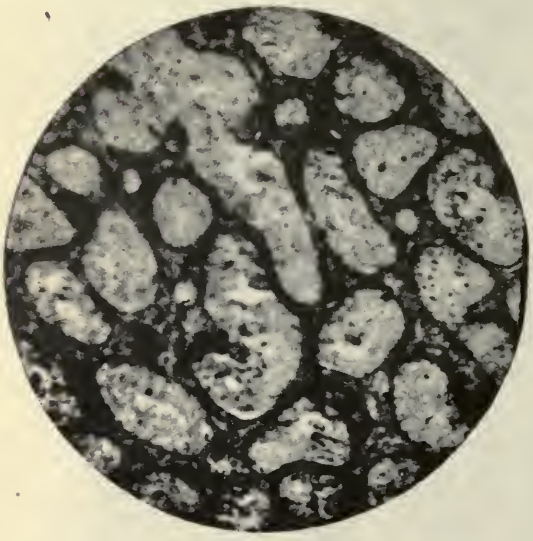

FIG. 52.—Testicle of pigeon, × 95, showing the effects of a diet of autoclaved rice. Note narrowing of tubules, great thickening of intertubular tissue, and almost complete absence of sperm elements.

FIG. 53.—Normal testicle of pigeon, × 95.

other observers, found that in chickens deprived of vitamins the testicles were very small, and on histological examination showed an arrest of the cellular divisions and metamorphoses which should normally occur in the seminal tubules at the date at which the chickens were killed. The interstitial cells exhibited a very pronounced infiltration of pigments, which, as Bouin and Ancel have shown, occurs in the interstitial cells of glands whose endocrine activity is on the decline. Houlbert found that the chickens showed an arrest of growth and of development of the secondary sex characters (spurs, comb, and tail feathers). On the other hand, he noted that the glands of internal secretion, whose activity had been arrested by experimental avitaminosis, "resumed their normal evolution when

[1] *Paris Méd.*, 1919 (Dec. 13).

vitamins were restored to the diet."[1] Drummond,[2] also, has found similar testicular degeneration in rats fed on a synthetic food deficient in vitamin B. He observed that they exhibited lower sex activity, and were indeed sexually impotent. Deficiency of this vitamin thus results in insufficient determination and maintenance of reproductive elements, as well as of elements yielding hormones necessary for development and mental efficiency. It is known that in cases of prolonged cachexia, in injury to the brain and spinal cord, in chronic alcoholism, and in certain infections—such as pneumonia, measles, and influenza—testicular atrophy may occur; but there is, so far as I am aware, no etiological influence, apart from X-rays, which is capable of causing such profound changes in the testicles as lack of vitamins. It may, indeed, be that the testicular atrophy of prolonged cachexias and of tuberculosis is due to the lack, failure of assimilation, or excessive waste of these essential substances. It may be considered, on the other hand, that the testicular atrophy is a neurotrophic phenomenon comparable to that which may follow injury to the brain and cord. The evidence brought forward indicates, however, that this is not the case, and that we have in this remarkable result of vitamin-deficiency a new and potent etiological factor in relation to the genesis of reproductive inefficiency.

It may be noted that Schaumann[3] found, when bull's testicles were given to polyneuritic pigeons, a pronounced curative and prophylactic influence was exerted on the experimentally-produced disease.

The ovary also undergoes atrophy. In healthy birds the organ weighs on the average 0·953 gram per kilogram of body-weight, whereas in cases of polyneuritis columbarum it weighs but 0·305 gram. The atrophy is less marked when butter has formed part of the deficient dietary; the average weight of the ovary is then 0·356 gram per kilogram of original body-weight.

The Sex Organs in Monkeys.—The atrophy of *the testicles* is much less marked in monkeys than in pigeons. It is most pronounced in those fed on autoclaved food and fresh onion (Fig. 14)—that is to say, in animals deprived of vitamin A as well as of vitamin B.

The ovaries also undergo atrophy. To the naked eye they often appear congested, and ecchymoses or minute hæmorrhages may be present under their serous covering. On histological examination the organs appear shrunken, and exhibit atrophic and degenerative changes in the Graafian follicles and in their contained ova.

The uterus, too, is distinctly smaller than in healthy animals. It was commonly flattened antero-posteriorly, having lost in great measure its plump, pear-shaped appearance. It was frequently congested; congestion and muscular atrophy being the chief features noted on histological examination.

Bearing on these changes, as observed in the ovary and uterus of deficiently-fed monkeys, and confirmatory of them, are certain recently published observations on the alteration of the œstrous rhythm in guinea-pigs induced by

[1] *Brit. Med. Jour., Epit.*, 1920 (Jan. 31), p. xx.
[2] *Biochem. Jour.*, 1919, XII. 25. [3] *Arch. Schiffs und Tropen-Hygiene*, 1910, XIV. 325.

underfeeding. "Under well-regulated food conditions the œstrous cycle in the guinea-pig is almost uniformly 16 to 17 days in duration. G. N. Papanicolaou and C. R. Stockard, of the Rockefeller Institute, find that underfeeding with a diet of 20 grams of carrots per day produces a prolongation of the dicestrum, and at the same time a congestion of the ovary and uterus, with degeneration of the Graafian follicles; the extent of the prolongation depends upon the stage at which the animal is underfed. Underfeeding during the first 5 to 7 days of the dicestrum has only a slight effect, the next œstrus being postponed for one or two days, while underfeeding during the latter part of the dicestrum—that is, 12 to 17 days after an ovulation and œstrus—leads to a delay of about seven days, the ovum being expressed at the twenty-third to twenty-fifth day, instead of at the seventeenth day. Should an animal be underfed for seven days—from the tenth to the seventeenth day—after œstrus, the next ovulation and œstrus are postponed for 10 to 11 days, arriving at the twenty-seventh or twenty-eighth day, instead of at the seventeenth day. These variations are associated with the fact that the conditions of the ovary vary at the different times. Shortly after an ovulation the ovary contains almost entirely small primary follicles, not so unfavourably affected by food conditions as are the large Graafian follicles, which begin their growth and development during later stages of the dicestrum. A large follicle at the height of its development seems to require much better nutrition than does a small primary follicle, and the lack of proper food arrests its progress very readily; thus late underfeeding has the more injurious effect, and the postponement of the next œstrus is correlated with a retarded development of new ripe follicles in the ovary. The entire œstrous activity depends on the conditions prevailing in the ovary. The delay of ovulation for 11 days following late and long underfeeding and after the underfeeding has been stopped is in accord with experiments which show that, after removal of all young corpora lutea following an ovulation, the next ovulation arrives in about 11 days instead of 16 to 17. This acceleration of 5 to 6 days is due to the absence of the corpora lutea, which, if present, evidently inhibit the maturation or prolong the time necessary for the development of ripe follicles in the ovary. These experiments all demonstrate the sensitiveness of the follicles in the ovary to environmental conditions. Extreme variations in the œstrous cycles have been observed in rats, and may in part be due to variations in diet." [1]

These observations in animals under experimental conditions find confirmation in the great increase of amenorrhœa and sterility which occurred amongst women of childbearing age during the late war; these conditions, it is said, are at the present time prevalent among the Russians. During the later stages of the war, German periodicals referred to "War Amenorrhœa" with alarm, all authors commenting on its great increase. It was attributed to defective nutrition, and to the fact that many women were called upon to do men's work. During the year 1917, according to Strickel,[2] cases of amenorrhœa were seven times more

[1] Quoted from the *Lancet*, London, 1920 (Oct. 2), p. 727.
[2] *Brit. Med. Jour.*, 1917 (Dec. 1), p. 734.

frequent at the Charité-Frauenklinik in Berlin than before the war. So grave was the outlook thought to be that Cordes, a Berlin gynæcologist, feared that, by leading to sterility, it would constitute a serious danger to the desired increase in population.[1] The effects of the war in this regard are further illustrated by the observations of Holmberg,[2] who has investigated the incidence of amenorrhœa at a gynæcological clinic before, during, and after the war. He found, excluding cases due to tuberculosis, heart disease, and other causes unassociated with the food, as well as cases in which menstruation had never occurred, that among 1,356 patients seen in 1912, there were 12 cases of amenorrhœa of indefinite origin, or 0·9 per cent. In 1913 and 1914 the percentages were 0·7 and 1·3. During 1915 and 1916 there was little change, the figures for the two years being 1·5 and 1·6 per cent. respectively. But in 1917 there was a sudden rise to 5 per cent., and in 1918 to 9 per cent.; coincident with a return to more normal conditions there was, in 1919, up to November 1, an abrupt fall to 1·7 per cent.[3]

Defective nutrition, underfeeding, anxiety or physical strain, cold and wet, and enforced celibacy are among the possible causes advanced by German physicians to account for "War Amenorrhœa." The list is comprehensive, for it brings into prominence not only the nutritional factor, which is the fundamental cause of the ovarian insufficiency, but directs attention also to the influence of other factors of a nature calculated to depress the functional capacity of the endocrine organs in general, on which perfection of ovarian function is so largely dependent. These observations are of significance in gynæcological practice. Disturbance of ovarian function requires consideration from several points of view: (1) From that of nutrition in general; (2) from that of the vitamin-content of the food in particular; and (3) from that of the functional derangement of other endocrine organs consequent on food deficiencies. The application in practice of the information recorded in this chapter should yield valuable results. The importance of these observations to stock-breeders and poultry farmers is obvious also.

[1] *Lancet*, 1918 (May 18), p. 712.
[2] *Svenska Lä Karesälls, Förhandl.*, 1919 (Dec. 31).
[3] Quoted from *Brit. Med. Jour., Epit.*, 1920 (March 6), p. xxxix.

CHAPTER XV

THE THYROID AND PARATHYROID GLANDS

THE changes resulting in these organs require separate consideration in the three species.

In Pigeons.—The thyroid glands atrophy to a moderate extent.

In health they are small organs of the size and shape of a canary-seed, lying below the root of the neck at its entrance to the thorax. They are situated one on either side of the neck under cover of the sternum, about ½ inch within the thoracic cavity; their blood-supply is extraordinarily rich, and for this reason they appear, when removed from the body, somewhat smaller than when *in situ*. The average weight of both thyroids per kilogram of body-weight in healthy male pigeons is 84·7 milligrams; in healthy females 85·5 milligrams, or practically the same in both sexes.

In cases of *polyneuritis columbarum* induced by an exclusive diet of autoclaved rice, the average weight of both thyroids per kilogram of original body-weight is 76 milligrams in males, 75·8 milligrams in females, or the same in both sexes. In cases resulting from a diet of autoclaved rice *plus* fresh butter and onions, the corresponding weight is 69·7 milligrams, both sexes being taken together; it is thus considerably less than in pigeons fed exclusively on autoclaved rice.

The atrophy of the thyroid brought about by inanition is greater than that induced by either of the deficient dietaries whose basis was rice; in birds starved to death the average weight of the thyroids per kilogram of original body-weight is only 59 milligrams.

Histological Appearances.—Owing to the great variations in the histological appearances of the thyroid glands in health,[1] it is impossible to form a right estimate of the degree of histological change induced by food deficiencies unless large numbers are examined. The present account is based on an examination of serial sections of the thyroids from thirty cases of polyneuritis columbarum and from thirty healthy pigeons.

In healthy and non-goitrous pigeons in a locality 6,000 feet above sea-level the thyroids fall into two main groups, and into variants of these: (1) Colloid or resting glands; and (2) actively secreting glands. Between these two extremes many different appearances are seen according as the organ is assuming the phase of active secretion from the colloid or resting state, or reverting from the phase of active secretion to the colloid or resting state. In regard to the phases of the normal thyroid glands' activity, these organs in pigeons differ in no respect from those of mammals in which I have hitherto studied them.[1]

[1] McCarrison, *The Thyroid Gland in Health and Disease*, London, 1917.

In the thirty healthy pigeons examined, rather more than one-half had thyroids of the colloid or resting class (Fig. 55); the remainder came within the category of actively secreting glands (Fig. 59) or of glands reverting to the colloid state. In cases of polyneuritis columbarum, on the other hand, the thyroids fell into four main groups: (1) Colloid glands—nine; (2) actively secreting glands—seven; (3) reverting glands—nine; and (4) "infected" glands—five.

Colloid glands were less often met with in cases of polyneuritis than in health.

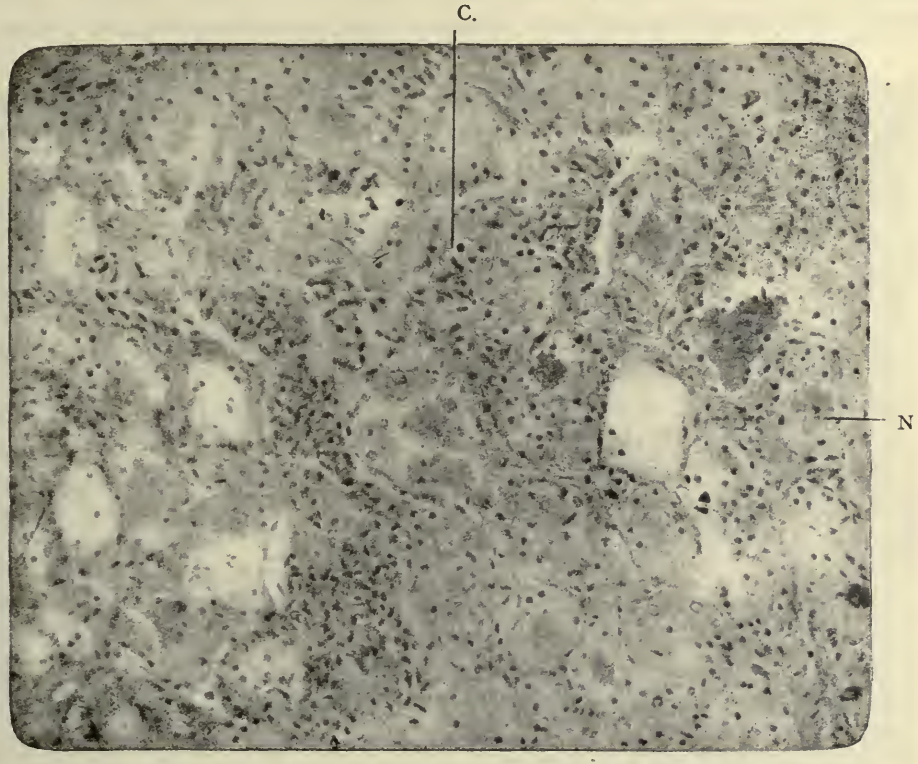

FIG. 54.—Section of thyroid from a case of experimentally-produced polyneuritis in pigeon, × 165. An "infected" gland from a case associated with septicæmia. Note generalized congestion, marked necrosis of cells, separation of acinar cells from the peri-acinar vascular connective tissue envelope, disappearance of acinar structure in places, small colloid content: a characteristic appearance in infected pigeons.

Under low powers of the microscope they differed little, or not at all, from similar colloid glands from healthy birds. Higher magnification of the acinar epithelium sometimes revealed cells in which necrobiotic changes had undoubtedly occurred, constituting interruptions in the continuity of the uniform row of nucleated cells lining the acini. Having regard, however, to the fact that degeneration and renewal of acinar cells is a normal process in the thyroid gland, such appearances cannot be considered abnormal unless they are excessive. In general the evidences of departure from normal were scanty, and in some cases they were

actually wanting. The colloid substance did not appear to differ histologically from normal.

Thyroids falling within the category of *actively secreting glands* comprised less than one-fourth of the cases examined. In some of these the vascular connective-tissue envelope surrounding the acini appeared more prominent than in health, moderate degrees of congestion being usually present. In general the nuclei of the acinar cells stained less clearly, an abnormal proportion showing karyolysis. Apart, however, from slight congestion, several thyroids were met with in this category which I was unable to distinguish from healthy glands.

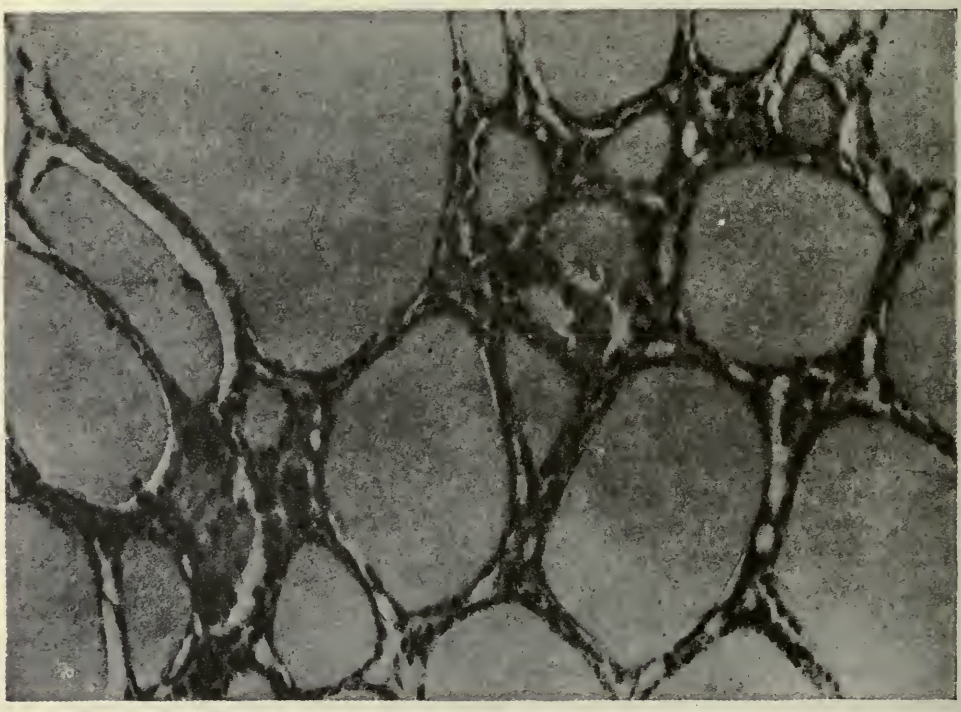

FIG. 55.—Thyroid gland, colloid type, not enlarged, from monkey fed on autoclaved rice. A similar histological picture was seen in 35 per cent. of controls. × 265.

Thyroids in the stage of reversion to or from the colloid state made up the major part of the remaining cases. In these a moderate or slight degree of congestion was the most constant abnormal feature. In some cases evidence of necrobiotic change was present in a proportion of the acinar cells; but in this category, also, thyroids were encountered which differed little, or not at all, from the glands of healthy pigeons.

The thyroid glands were examined in five cases in which polyneuritis columbarum was associated with septicæmia; in these cases they invariably came within the category of *infected glands*. The changes seen in such glands (Fig. 54) are distinctive and pronounced; the organ is congested in marked

degree; the alveolar cells are necrotic, and separated from one another and from their basal attachment; disintegrating cells occupy the acini, which, owing to denudation of their epithelial lining, are often obscure in outline; colloid is scanty, absent, or existing as isolated, acidophile globules lying free amongst the necrotic and necrosing cells. I have found it possible, with only a small percentage of error, to distinguish between simple polyneuritis columbarum and that associated with septicæmia by the histological appearances of the thyroids alone.

Excluding, then, infective processes, which so constantly reveal their presence

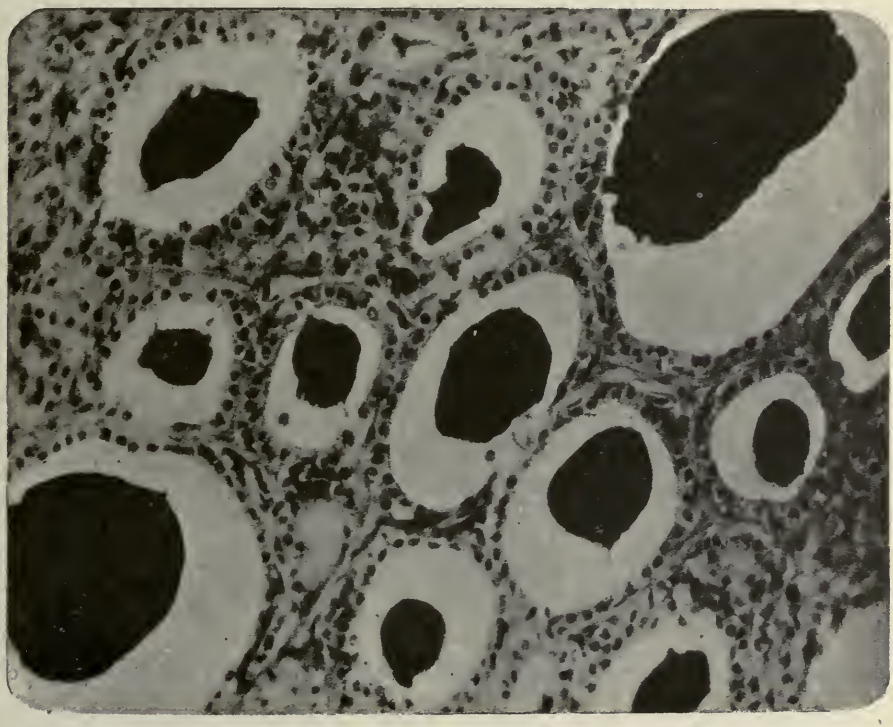

FIG. 56.—Thyroid gland, not enlarged, from monkey fed on autoclaved food, butter, and onions. × 265. A similar histological picture was seen in several control animals.

in the body by initiating pathological changes in the thyroid gland, I find this organ, so far as can be judged by histological study, to be often amongst the least affected of all organs by the deficient dietary. The changes which are attributable to this cause consist in mild or moderate degrees of congestion and in necrobiosis of a relatively small proportion of the secreting cells. Confusion as to the changes directly attributable to the dietetic deficiency is apt to occur unless complicating infections are excluded. It is to these that pronounced congestion, necrosis, and denudation of the alveolar epithelium are directly due, and not, as I had previously concluded,[1] to the dietetic deficiency, although such deficiency

[1] McCarrison, *The Thyroid Gland in Health and Disease*, London, 1917, p. 39.

is indirectly responsible for them, since it renders the thyroid very liable to attack from bacterial agencies. To what extent the chemical activities of the thyroid gland may be altered by the deficient dietary I am unable to say.

The histological appearances of the thyroid gland of pigeons fed on autoclaved rice, butter, and onions do not differ materially from those above described.

No notable changes were observed in the *parathyroids* in either category in the absence of concurrent infections. When such infections were present, the parathyroids shared in the congestion and necrosis of cells found at the same time in the thyroid.

In Monkeys.—In healthy control monkeys of the species *Macacus sinicus*, the average weight of the thyroid per kilogram of body-weight is 83 milligrams, or

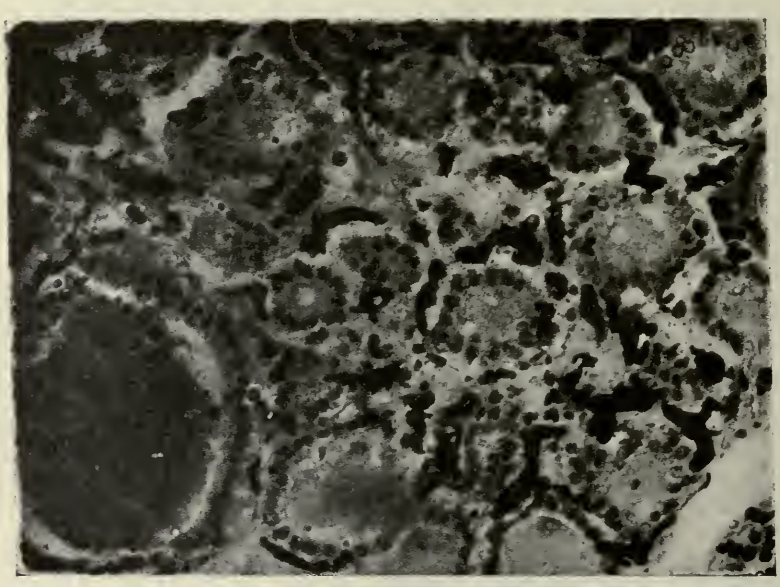

FIG. 57.—Thyroid from monkey fed on autoclaved rice and butter. Note great engorgement of peri-acinar capillaries. The darker-staining cells are blood-corpuscles. × 210.

approximately the same as in pigeons. The effects on the organ of the various deficient dietaries may conveniently be recorded separately.

(1) *A Diet of Autoclaved Rice.*—The effects of this dietary were studied in twelve monkeys. The amount of atrophy to which it gave rise was slight. The average weight of the organ per kilogram of original body-weight was 81 milligrams as compared with 83 milligrams in controls. The gland presented the same varying histological pictures seen in health (Figs. 55, 56, and 59), colloid glands preponderating. The evidences of pathological change were comparatively slight, and limited to congestion, such as that seen in Fig. 57, and to a greater proportion of cells showing evidence of necrobiosis. Congestion was not present in all cases; the number so affected in monkeys was five out of twelve. The most notable pathological appearance was found in animals presenting hæmic infections, a

not infrequent consequence of this dietary. Then the organ showed marked congestion, desquamation of acinar epithelium, varying degrees of necrosis of parenchyma-cells, and complete or partial disappearance of colloid.

(2) *A Diet of Autoclaved Rice and Butter.*—The effects of this dietary were studied in four monkeys. The degree of atrophy was considerable, having regard to the rapidity with which the animals died (fifteen days). The average weight of the organ was 73 milligrams per kilogram of original body-weight, as compared with 83 milligrams in healthy controls. In all four cases in this category the glands were of the colloid type, or of a type showing a tendency to reversion from the colloid state. The vesicle walls consisted of a single layer of cuboidal epithelial cells; the acini contained a pale pink staining colloid in which a few vacuoles,

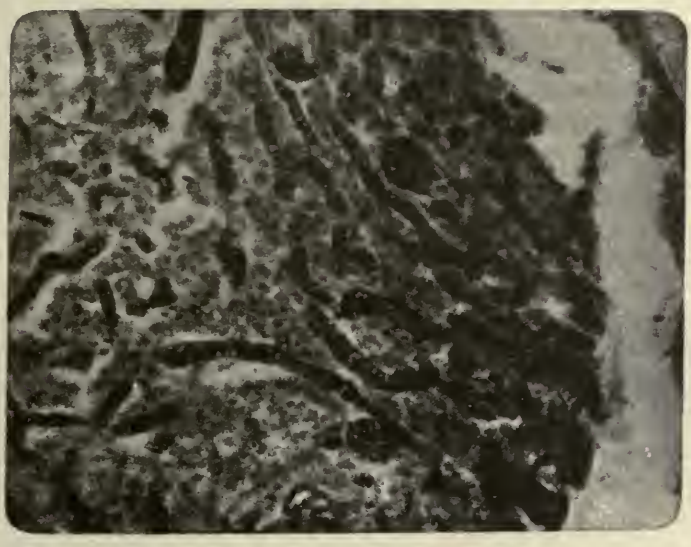

FIG. 58.—Parathyroid from monkey fed on autoclaved rice and butter. Note great engorgement of capillaries. × 210.

indicating absorption of colloid, were present. In all cases the peri-acinar capillaries were much distended (Fig. 57), each acinus being sharply outlined, in part of its circumference, by a capillary envelope of pink-staining blood-corpuscles. The intervesicular parenchyma was very scanty, and necrobiosis of parenchyma-cells was slight. The *parathyroids* in three cases, in which they were found in sections, were intensely congested (Fig. 58), and in one hæmorrhagic infiltration had caused disruption of the compact masses of polygonal cells composing the gland, and death of many of them. Similar changes in these organs have been encountered on one other occasion only in my experimental experiences; in the parathyroids of newborn rats whose mothers were fed daily through pregnancy on anaerobic cultures of fæcal bacteria.[1] The cause of the hæmorrhagic infiltration of the parathyroids was probably the same in both instances. In the one,

[1] McCarrison, *The Thyroid Gland in Health and Disease*, London, 1917, p. 153.

the micro-organisms, or their products, operated through the medium of the maternal blood; in the other, the deficient dietary caused such changes in the intestinal mucosa as subjected the parathyroids to the noxious effects of micro-organisms, or of their products, derived from the intestinal tract. It is remarkable that only in this category were the parathyroids found to be notably altered by morbid change; the excessive richness of this deficient food in fat would appear to be particularly harmful to the thyroid apparatus.

(3) *A Diet of Autoclaved Food and Onion.*—The effects of this dietary were studied in six monkeys. The atrophy of the thyroid was considerable; its average weight per kilogram of original body-weight amounted to 69 milligrams, as compared with 83 milligrams in healthy controls. Histologically the thyroid presented more definite evidences of departure from normal than in other categories. Whereas in the control animals the number of thyroids of the colloid type (Fig. 55) exceeded those of the actively secreting type (Fig. 59); in monkeys fed on autoclaved food and onion, the histological appearances were in all six animals of the latter type, and colloid was invariably scanty. In addition to this preponderance of glands of the actively secreting type, there was present, area for area, a greater number of nuclei. Thus the nuclear count in the normal actively secreting gland (Fig. 59) was 175 to a given field, whereas it was 275, 195, 250, and 238, respectively, in four animals fed on autoclaved food and onion. This piling up of nuclei might be regarded as indicative of hyperplasia, but in no case did I detect evidences of nuclear division. A section of the thyroid from one such case is shown in Fig. 60. While, therefore, there is in animals of this category an appreciable loss of weight of the thyroid gland, there is no histological evidence of atrophy of its parenchyma-cells; the tendency is rather to hyperplasia of these cells. No notable changes were observed in the parathyroids.

(4) *A Diet of Autoclaved Food, Butter, and Onion.*—The effects of this dietary were studied in five monkeys. The diminution in weight of the organ was considerable, the average being 70 milligrams per kilogram of original body-weight as compared with 83 milligrams in controls. The histological pictures did not differ appreciably from the normal. There was a tendency for glands of the actively secreting type to preponderate (Fig. 60). No notable changes were observed in the parathyroids.

In Guinea-pigs.—A diet of crushed oats and autoclaved milk causes the thyroid gland to increase in weight.

The average weight of the organ per kilogram of body-weight in controls was 95 milligrams. In those fed on the scorbutic diet it was 218 milligrams per kilogram of original body-weight, and 295 milligrams per kilogram of final body-weight, or from two to three times the weight of the healthy organ.

On histological examination, the organs were greatly congested and hæmorrhagic infiltrations were frequent. It would be of considerable interest to know whether the thyroid enlarges in infantile scurvy.

Summary.—In general, then, the effects of food deficiency on the thyroid

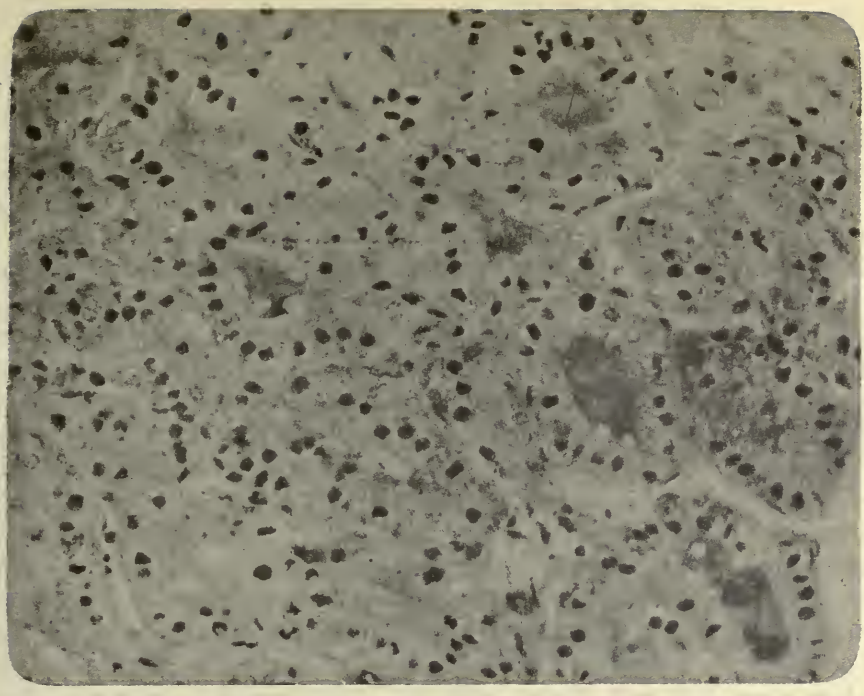

FIG. 59.—Normal actively secreting thyroid from a control monkey. Note increase in height of acinar cells, vacuolation, and absorption of colloid. × 265.

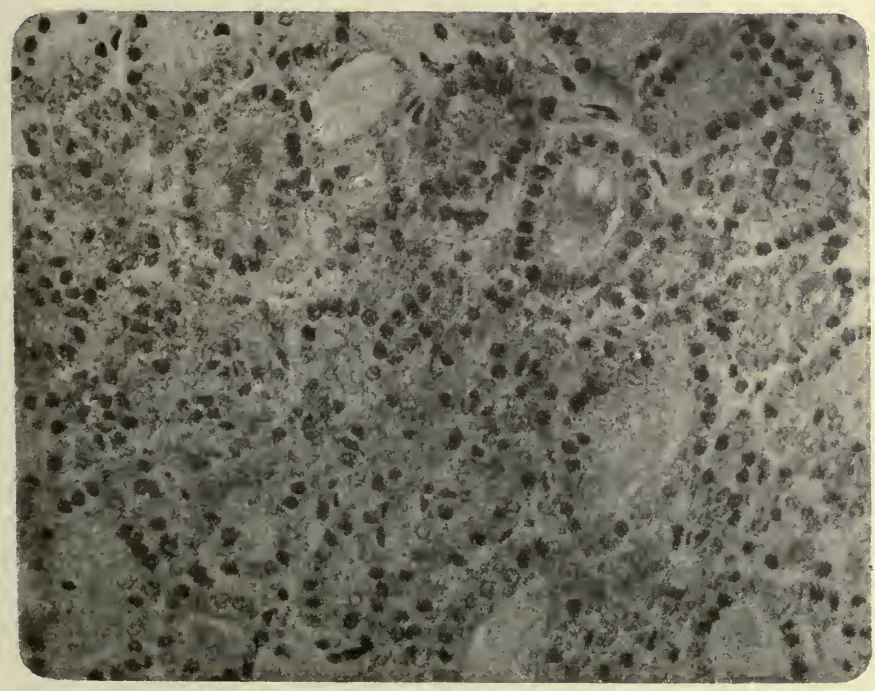

FIG. 60.—Non-enlarged thyroid from a monkey fed on autoclaved food and onions. Note increase in height of acinar cells, increased number of nuclei (compare with Fig. 59), vacuolation of colloid, and small size of many vesicles. × 265.

gland are to cause a slight reduction in size and weight in all classes of deficiency excepting that of vitamin C. The organ is, in consequence of the food fault, rendered peculiarly susceptible to injury by bacterial and toxic agencies, which may cause extensive degenerative changes in its cells, and congestion. Hæmorrhage into the parathyroids is apt to occur when the deficient food is excessively rich in fats and starch; this combination of faults appears to enhance the susceptibility of these organs to the action of intestinal anaerobes. Without going too far, it may safely be concluded that, in the presence of food deficiency, the functional perfection of the thyro-parathyroid mechanism is very prone to be impaired. These observations have an important bearing on the occurrence of tetany and on disturbances of calcium metabolism in improperly-fed children.

They are of interest also in connexion with the deficiency disease syndrome known as "hunger-osteopathy."[1] This condition is characterized by sharp pains in the pelvis, epigastrium, and lower thorax. There is in some cases a marked tendency to spasmodic contractions of muscles reaching a degree similar to that of tetany, and associated with Chvostek's or with Trousseau's phenomenon. The hæmorrhagic lesions found to result in the parathyroids of some animals from deficient feeding no doubt provide the pathological explanation of some of the phenomena met with in this malady. The frequent occurrence of tetany in association with rickets is also of interest in this connexion.

[1] Porges and Wagner, *Wien. Klin. Woch.*, 1919 (April 10), p. 385.

CHAPTER XVI

THE PITUITARY BODY

In Pigeons.—This organ is peculiar in that it tends to hypertrophy in consequence of food deficiency, a tendency especially notable in males.

The average weight of the pituitary body in healthy male pigeons is 5·3 milligrams, in healthy females 5·9 milligrams. As estimated per kilogram of body-weight the organ weighs in males 18·3 milligrams, and in females 22·1 milligrams. It is thus considerably heavier in females than in males. *In inanition* the pituitary body weighs more in males than in females; its weight, per kilogram of original body-weight, in the former being 17·8 milligrams, in the latter 14·4 milligrams. It would seem that, in consequence of inanition, the organ actually atrophies in females; but as the number of birds on which the effects of inanition were studied is small, too much stress cannot be laid on this observation, especially as the small size of the organ and the difficulty of its removal intact introduce considerable sources of error.

In polyneuritis columbarum resulting from an exclusive diet of rice, the average weight of the pituitary body per kilogram of original body-weight is 19·6 milligrams in males and 22·4 milligrams in females. There is thus no noteworthy alteration in the average weight of this organ in females in consequence of an exclusive rice dietary, whereas in males there is a tendency to increase in weight. While this is true on the average, it is to be noted that individual cases in both males and females show wide variations in the weight of this organ.

The same tendency to increase in weight of the pituitary body in males is observed in cases of polyneuritis resulting from a diet of autoclaved rice, butter, and onions; then its average weight is 19·4 milligrams per kilogram of body-weight, a figure practically identical with that obtained in the previous category. In females, also, in this category the organ is slightly above the average weight of health.

Histological Appearances.—These refer only to the glandular part of the organ, and to its grosser changes, as observed in pigeons. Moderate congestion is the main histological feature. In healthy pigeons the gland sometimes shows minute acini containing droplets of colloid-like material. In cases of polyneuritis, these colloid accumulations are in general less often seen. The vessels are usually engorged; slight hæmorrhagic infiltration between the parenchyma-cells is sometimes present. In some cases the nuclei are present in greater numbers in individual fields of the microscope than in health, giving the impression of hyperplasia, but I have been unable to find evidences of nuclear division. Figs. 61 and 62, in which the thickness of the sections and their magnifications are the same, illustrate these points. Evidences of karyolysis or karyorrhexis were occasionally encountered, but in general nuclear changes were scanty. It is difficult to say,

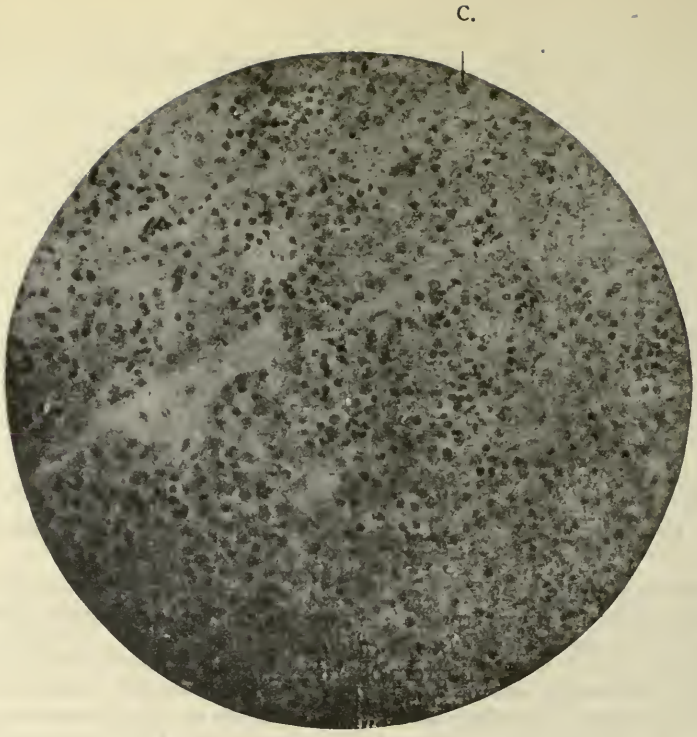

FIG. 61.—Section of glandular part of pituitary body from a healthy pigeon, × 165. The specimen shows one droplet of colloid at C.

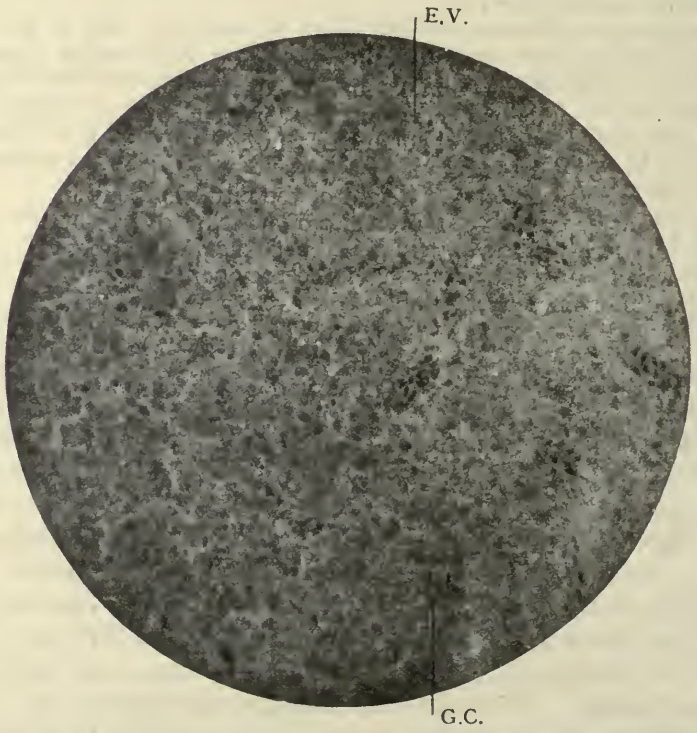

FIG. 62.—Section of glandular part of pituitary body from a case of experimentally-produced polyneuritis columbarum, × 165. Note engorgement of vessels (E.V.), and generalized congestion of the gland (G.C.).

from the gross histological appearances, to what extent and in what direction the function of the organ is affected. Special methods of study are required to determine these points; these I was unable to undertake.

In Monkeys.—In healthy control monkeys of the species *Macacus sinicus* the average weight of the pituitary body per kilogram of body-weight is 14 milligrams; in those fed on autoclaved rice, 15 milligrams; in those fed on autoclaved rice and butter, 15 milligrams; in those fed on autoclaved food and onion, 16 milligrams; and in those fed on autoclaved food, butter, and onion, 11·8 milligrams (Fig. 14). It is thus seen that in the first three categories the organ tends to increase in weight; an observation which confirms that already recorded for pigeons. On analysing the figures further, it is found that the average weight of the organ per kilogram of body-weight is 13·3 milligrams in healthy males; 14·4 milligrams in healthy females. It is thus considerably larger, on the average, in females than in males—a fact also noted in pigeons. While, however, it enlarges in male monkeys fed on autoclaved rice (to 15·3 milligrams), it does not do so in females to the same extent; in these the weight of the organ is 14·7 milligrams per kilogram of original body-weight. In monkeys, as in pigeons, individuals exhibit wide variations in the weight of the pituitary body. An observation for which I can offer no explanation at present is the marked drop in the weight of the pituitary body in monkeys fed on autoclaved food, butter, and onions.

Histological Appearances.—In monkeys fed on autoclaved rice diets, the anterior part of the organ presents similar appearances to those seen in pigeons, its sinus-like capillaries being frequently engorged. Oxyphil granules appeared, also, to be less abundant. In monkeys fed on autoclaved food the degree of departure from normal was slight or nil.

Summary.—The pituitary body thus presents two remarkable effects of food deficiency, namely (1) its tendency to enlargement when all other endocrine structures—the adrenals excepted—atrophy; and (2) its difference in response to the food deficiency in the two sexes. Jackson and Stewart [1] have also observed a sexual difference in the weight of the pituitary body in consequence of underfeeding.

From the available evidence, I am inclined to regard the reaction of the organ to food deficiency as an attempt at compensatory hypertrophy. Its tendency to enlargement is of interest in connexion with the enlargement of the adrenals, presently to be described; these organs are said mutually to facilitate each other's action on the blood-vessels,[2] although their mode of action differs. In all probability the object of their enlargement is the same.

[1] *Minnesota Medicine*, 1918 (Nov.).

[2] Kepinow, L., *Compt. rend. Soc. de biol* (Paris), 1920, LXXXIII. 1134.

CHAPTER XVII

THE ADRENAL GLANDS

THESE organs are, of all endocrine structures, the most susceptible to dietetic defects. The most remarkable result emerging from my studies is the demonstration of their enlargement in inanition, and also in consequence of all classes of food deficiency in the three species of animals employed for experimental purposes. Indeed, it may be said that adrenal derangement is one of the most important of all the effects of food deficiency on the animal organism. It will be convenient to record the observations as they were made.

IN PIGEONS

The adrenal glands are situated in the middle line of the body, between the upper poles of the kidneys. They are closely applied to the spinal column, to which they are bound down by areolar tissue. They lie side by side, and separated only by the main vascular trunks. The tissues of the adrenals and kidneys are not continuous or intermingled one with the other, but are divided by a space, filled with loose areolar tissue, varying in width from 0·2 to 0·5 cm. In shape these organs are pyriform or roughly triangular; the base being uppermost as the bird lies on the dissecting-table. They are of a yellow-ochre or dull-yellow colour, and average about 0·6 cm. long by 0·4 cm. at their widest part: at the upper or broad extremity they are about 0·2 cm. thick. One organ is occasionally slightly larger than the other; when this is the case the left is commonly the larger of the two. Their consistency in health is quite firm. In the male they are closely adherent to the posterior and inner border of the testicles, which overlie them. In healthy males the weight of the adrenals ranges between 18 and 49 milligrams; any enlargement over this limit is highly suggestive of septicæmic or tubercular processes. The average weight in control males is 29·2 milligrams, or 100·3 milligrams per kilogram of body-weight. In control females the weight of the adrenal ranges from 11 to 37 milligrams; the average being 24 milligrams, or 90 milligrams per kilogram of body-weight. In healthy pigeons the glands were slightly larger in males.

1. **The Effects of Inanition.**—The adrenal glands enlarge in consequence of inanition (Table VII). Whereas their average weight per kilogram of body-weight in healthy controls, both sexes taken together, is 95 milligrams, in pigeons starved to death it is 125 milligrams. The enlargement is associated with a corresponding increase in their content of medullary secretion—epinephrine—as determined by kymographic methods of observation. The adrenal glands of two pigeons, dying in consequence of inanition, were removed from the body immediately after death, weighed and pounded up in a sterile mortar with 5 c.c. of a 0·85 per cent. solution of NaCl. In two other cases the birds were killed

when at the point of death, the glands weighed and emulsified in saline. The emulsions were injected into the left jugular vein of two sheep under ether anæsthesia, kymographic tracings of the arterial blood-pressure being taken from the right carotid. The observations were controlled either by injecting into the same sheep the emulsified adrenal glands of healthy birds, or by the injection of $\frac{1}{10}$ milligram of adrenalin, the commercial solution (1 in 1,000) being employed for the purpose. The results are shown in Table XII.

TABLE XII

SHOWING EFFECTS ON ARTERIAL BLOOD-PRESSURE OF SHEEP OF THE INTRAVENOUS INJECTIONS OF EMULSIFIED ADRENALS FROM HEALTHY AND STARVED PIGEONS

No. of Pigeon.	Healthy or Diseased.	Weight of Adrenals in mgrms.	Weight of Sheep in lbs.	Initial B.P. in mm. of Hg.	Primary Rise of B.P. in mm. of Hg.	Succeeding Fall of B.P. in mm. of Hg.	Final Rise of B.P. in mm. of Hg.
158	Healthy	16	35	120	Nil	18	8
	$\frac{1}{10}$ mgrm. adrenalin		35 (Same sheep)	108	12	22	34
127	Inanition	28	35 (Same sheep)	110	22	14	46
116	Polyneuritis: Hydro-pericardium	72	35	114	24	20	72
124	Inanition	28	33	74	35	2	100
111	Polyneuritis: Œdema	53	33 (Same sheep)	86	38	Nil	124
123	Inanition	40	33 (Same sheep)	60	Nil	Nil	102
	$\frac{1}{10}$ mgrm. adrenalin		33	54	Nil	Nil	82
122	Inanition	31	33	54	Nil	Nil	68

These kymographic results (Fig. 63) indicate that the adrenal enlargement of inanition is associated with a corresponding increase of epinephrine. It will be observed from Table XII that sheep vary greatly in their susceptibility to adrenalin introduced intravenously; $\frac{1}{10}$ milligram causing a rise of blood-pressure of 34 mm. of Hg in one and of 82 mm. in another. This variation is dependent in some measure upon the initial blood-pressure of the animal at the time of observation. Metabolic idiosyncrasy, however, is mostly responsible for it.

These results have been confirmed by Vincent and Hollenberg [1] not only as regards pigeons, but also in rats and dogs. In dogs, after a somewhat longer period of inanition than 15 days, the adrenal bodies are almost double the normal weight. In rats the hypertrophy is considerably greater than in pigeons and dogs, even when inanition is carried out for a shorter period. Vincent [2] has also found that the abdominal chromophil body in the dog is markedly increased in dimensions after fourteen days' inanition, but the chrome reaction was less intense than in the normal dog.

2. **The Effects of an Exclusive Diet of Milled and Autoclaved Rice.**—Enlargement of the adrenal glands, often great, results in consequence of this dietary.

[1] *Endocrinology*, 1920, IV, No. 3, 15, p. 408.
[2] *Proc. Roy. Soc.*, London, 1910, LXXXII, B, p. 502.

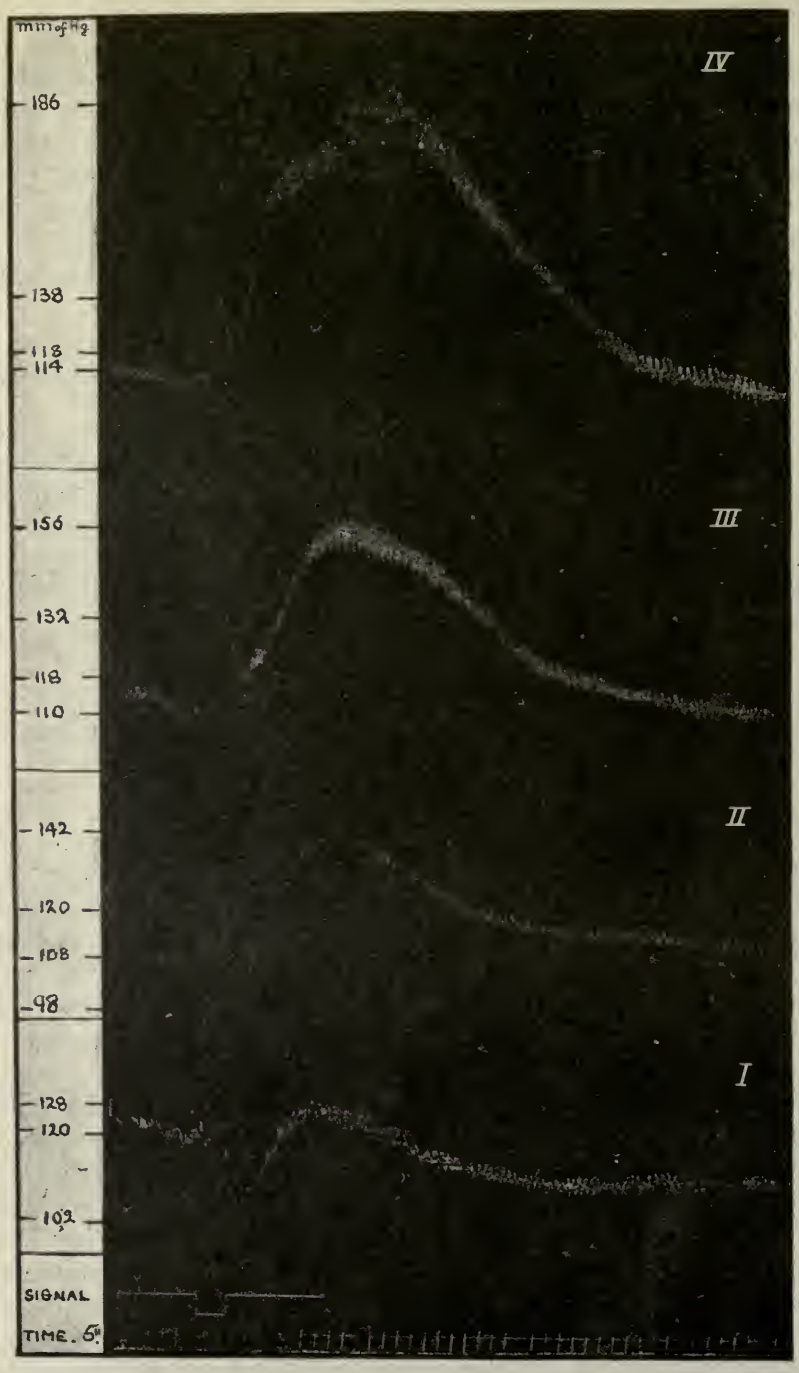

FIG. 63.—Kymographic tracings of arterial blood-pressure, in a sheep weighing 35 pounds, showing effects of—I, injection of an emulsion of both adrenal glands, weighing 16 milligrams, from a healthy pigeon; II, 0·1 milligram of adrenalin; III, an emulsion of both adrenal glands, weighing 28 milligrams, from a case of inanition; IV, an emulsion of both adrenals, weighing 72 milligrams, from a pigeon with large hydropericardium resulting from an *autoclaved rice* diet. All injections made into the left jugular vein.

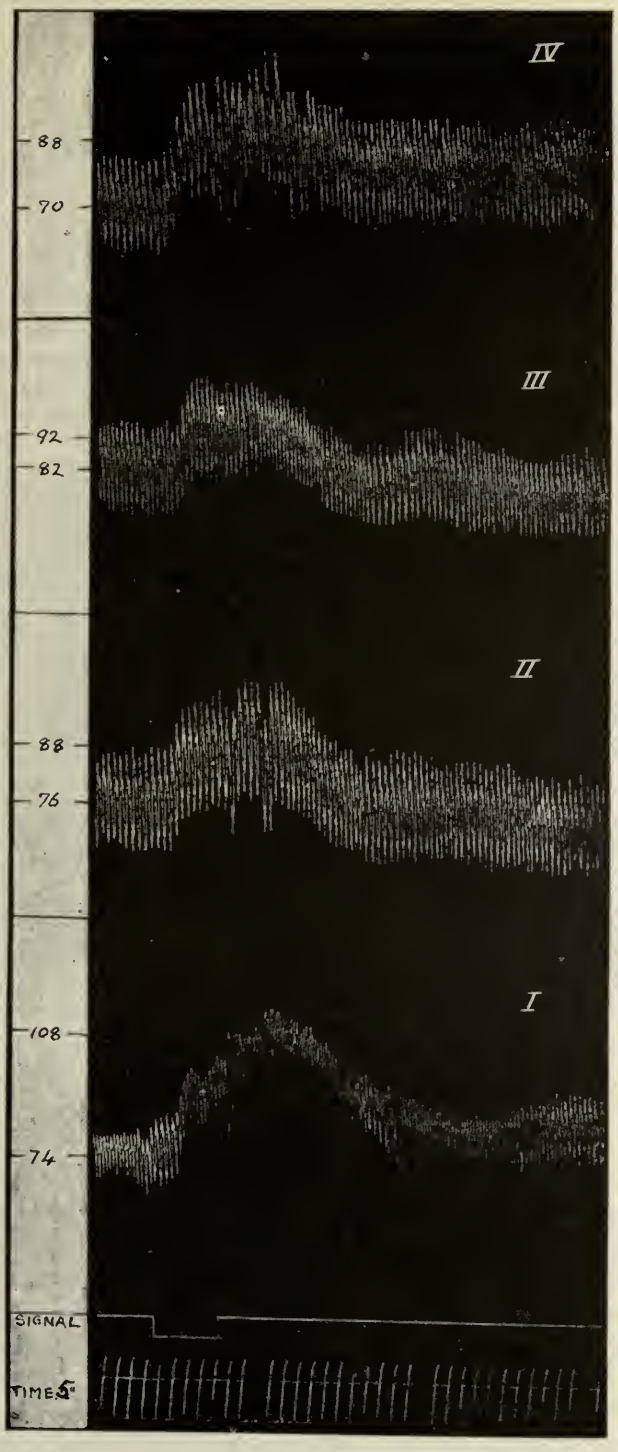

FIG. 64.—Kymographic tracings of arterial blood-pressure in sheep weighing 44 pounds, showing effects of injecting—I, an emulsion of both adrenal glands, weighing 20 milligrams, from a healthy pigeon; II, an emulsion of both adrenals, weighing 28 milligrams, from a case of polyneuritis columbarum; III, an emulsion of both adrenals, weighing 32 milligrams, from a case of polyneuritis columbarum; IV, 0·01 milligram of adrenalin. Polyneuritis columbarum was produced in these cases by a diet of *autoclaved rice, butter, and onions*. All injections made into the left jugular vein.

On removing the liver, stomach, and intestines the increase in size of the adrenals is at once apparent, and is in marked contrast to the atrophy of the gonads. In the male the atrophic testicles may actually be smaller than the neighbouring hypertrophied adrenals, whereas in health they are approximately 50 times larger (Figs. 50, 51). The adrenals in male polyneuritic pigeons range in weight between 27 and 70 milligrams, as compared with 18 and 49 milligrams in health; their average weight is 42 milligrams, or 139·5 milligrams per kilogram of original body-weight. In ten cases out of twenty males in this series the adrenals weighed 40 milligrams or over; that is to say, they equalled or exceeded the maximum weight in health in 50 per cent. of cases. In females the range of weight lay between 18 and 91 milligrams as compared with 11 and 37 milligrams in health; their average weight is 41·9 milligrams, or 149 milligrams per kilogram of original body-weight. The adrenals exceeded the maximum weight in health in six cases of polyneuritis out of fifteen occurring in females. Thus in polyneuritis columbarum the range of weight of these organs is higher and wider, and their average weight is greater than in health, while they are more enlarged in females than in males.

The enlarged glands are swollen, prominent, and of a yellow-red, or more commonly reddish-brown, colour. They are often hyperæmic, diffluent, and easily torn; and frequently weigh less than their size leads one to expect. Much of the yellow-ochre colour of health has disappeared, or is only found in patches.

Histological Observations.—For the information of those who are not familiar with the histological characters of the normal adrenals in birds, it may be said that they are not separated into a peripheral or cortical and a central or medullary area, as is the case in mammals. They consist of columns of cortical and of medullary cells intermingled one with another, and usually, but not always, separated by fine areolar tissue, in which the capillaries ramify.

The glands from cases of polyneuritis resulting from an exclusive diet of rice were examined in ten cases. Chrome salt fixation, which stains the adrenalin yellow, was employed. The organs were embedded in paraffin and stained by Delafield's or Mann's stain. No especial study was made of the cortical lipoids, as the necessary apparatus was not available. The results of this preliminary histological survey were as follows: (1) The enlargement did not appear to be due to hyperæmia *per se*; the organs often showed evidence of congestion, which was very marked in some cases; the venous stasis arises subsequent to the initial enlargement of the organ. (2) In some of the larger glands intense congestion had caused destructive changes in the glandular tissue; this was especially noticeable at the central parts of the organ, peripheral areas retaining much of their normal character. (3) There appeared to be little or no diminution of the chrome-staining granules—epinephrine—of the medullary columns, except in very large and hyperæmic glands. (4) The cortical columns appeared to form a greater proportion of the section in diseased than in healthy birds (Fig. 65). The cortical enlargement is associated with a loss of definition of the lipoid granules (Kellaway).[1] (5) The nuclei of both medullary and cortical cells were fewer in number, area for area, in the diseased organs. (6) The nuclei often appeared more vesicular, larger, and frequently more shadowy

[1] *Proc. Roy. Soc.*, 1920, Series B, XC, No. B642, p. 6.

in outline, while cells without nuclei, or containing only shadow nuclei, were commonly seen. (7) Some cells of the cortex showed small, uniformly dark-staining nuclei which were in marked contrast to the more vesicular nuclei of the normal cortex; these were possibly recent division forms. (8) Some diseased glands showed many cells with brightly-staining eosinophile granules when stained by Mann's stain. (9) The cortical cells were often elongated, reminding one of the high columnar cells seen in the hyperplastic thyroid (Fig. 66). (10) Many cells in both cortex and medulla appeared to differ little from normal. (11) Sections of the organ from healthy pigeons occasionally exhibited appearances suggestive of various stages in the process of

FIG. 65.—Adrenal gland, healthy pigeon, × 165, showing normal proportions of cortical and medullary columns; lighter areas are medullary, darker areas are cortical columns.

FIG. 66.—Hypertrophied adrenal gland from pigeon fed on autoclaved rice, × 165. Note cortical hypertrophy. Medullary cells (M) are loaded with chrome-stained epinephrine.

secretion in the cortical cells: some being packed with particles whose nature was not clear, others, lying side by side with them, having an empty cytoplasm. These appearances seem to indicate that the cortex in pigeons secretes a substance which is discharged into the medullary areas of the gland. (12) Sections have frequently shown sympathetic ganglia closely adherent to the periphery of the gland; with the stains used, some of the large cells of these ganglia have presented appearances—changes in the nuclei, and diffuse staining of the cell-body—indicative of pronounced degrees of degeneration (Fig. 81). The adrenal glands are said to be the chief storehouse or manufactory of body lipoids; and since these substances are intimately concerned with the nutrition of the myelin of medullated nerve fibres and enter into the composition of all cells, it may be presumed that the adrenal cortex will undergo some notable change in

polyneuritis columbarum. Cramer,[1] having confirmed my observation as to the effect of avitaminosis on the adrenals, has recently found that there is an almost complete disappearance of lipoids from the cortex in rats fed on a synthetic diet devoid of vitamins.

Kymographic Observations.—The enlargement of the adrenals is accompanied by a corresponding increase in epinephrine-content of the enlarged organs, as demonstrated by kymographic observations of the arterial blood-pressure in sheep. The adrenals used in these observations were as far as possible removed from the body immediately after death, so as to avoid oxidation of their epinephrine. They were then weighed and emulsified in about 5 c.c. of a 0·85 per cent. solution of sodium chloride. The emulsions were injected into the left jugular veins of sheep under ether anæsthesia; the kymographic tracing being taken from the right carotid. The observations were controlled in most cases, either by the injection into the same sheep, after the lapse of an appropriate interval, of the emulsified organs of a control bird or of 0·01 c.c. of the commercial solution of adrenalin, equivalent to $\frac{1}{10}$ milligram of the drug. In the later observations the procedure followed was first to inject the emulsion of the glands from a control bird, then, after a suitable interval, the adrenal emulsions from the diseased birds, and finally $\frac{1}{10}$ milligram of adrenalin. Seventeen observations were made. The results are shown in Table XIII (Fig. 63).

TABLE XIII

Showing Effects on Arterial Blood-pressure of Intravenous Injections into Sheep of Emulsified Adrenals from Healthy Pigeons and from Cases of Polyneuritis Columbarum; Controlled by Pure Adrenalin

No. of Pigeon.	Weight of Adrenals in mgrms.	Weight of Sheep n lbs.	Rise of Blood-pressure in mm. of Hg.	Other Details.
77	32	46	12	Healthy bird
112	39	47	38	Polyneuritic bird: no œdema
86	45	43	38	Polyneuritic bird: œdema } same sheep
87	49	43	42	Polyneuritic bird: œdema }
155	37	39	38	Polyneuritic bird: no œdema } same sheep
—	—	39	56	$\frac{1}{10}$ mgrm. of adrenalin }
128	18	32	24	Healthy bird } same sheep
130	18	32	28	Healthy bird }
162	15	47	32	Healthy bird
85	43	47	26	Polyneuritic bird: œdema: dead 72 hours: epinephrine oxidized } same sheep
83	29	47	10	Polyneuritic bird: no œdema: dead 72 hours: epinephrine oxidized }
—	—	47	64	$\frac{1}{10}$ mgrm. of adrenalin }
158	16	35	8	Healthy bird
116	72	35	72	Polyneuritic bird: œdema } same sheep (Fig. 63)
—	—	35	34	$\frac{1}{10}$ mgrm. of adrenalin }
111	53	33	124	Polyneuritic bird: œdema } same sheep
—	—	33	82	$\frac{1}{10}$ mgrm. of adrenalin }

[1] *Proc. Phys. Soc.*, 1920 (May 15); *Jour. Phys.*, LIV; and *Brit. Jour. Exp. Path.*, 1920 (Aug.) I, No. 4, p. 1.

The following conclusions emerge from these kymographic observations:

(1) Sheep vary greatly in their susceptibility to adrenalin administered intravenously. Single observations in different sheep are not strictly comparable.

(2) The averages of five observations in which the adrenals of healthy birds were employed, and of six in which the adrenals from freshly-killed cases of polyneuritis columbarum were used, are as follows:

(*a*) 20 milligrams of healthy adrenals caused a rise of blood-pressure of 21 mm. of Hg in 38-pound sheep.

(*b*) 50 milligrams of adrenals from cases of polyneuritis caused a rise of blood-pressure of 58 mm. of Hg in 40-pound sheep.

The total epinephrine-content was thus proportionate to the increase in size of the glands—that is to say, it was approximately area for area, the same as in health.

(3) The adrenal glands from cases of polyneuritis columbarum with associated œdema were larger, and had a total epinephrine-content greater, than in polyneuritis without œdema.

(4) The greater part of the epinephrine-content of these organs is destroyed by oxidation within 72 hours after death. Confirmation of these kymographic observations by chemical methods of epinephrine-estimation will be recorded in a subsequent chapter.

3. The Effects of a Dietary of Autoclaved Rice, Butter, and Onions.—This dietary also causes enlargement of the adrenal glands in pigeons.

The average weight of the enlarged organs per kilogram of original body-weight was in one experiment 161 milligrams, as compared with 95 milligrams in health, and with 69 milligrams in healthy pigeons receiving butter and onion in addition to their natural food. To the naked eye the organs are usually of a lighter colour than in health, resembling often pale butter or margarine; congestive changes may obscure their pale tint in some cases.

Histological Observations.—The adrenals from ten cases of polyneuritis resulting from the dietary were examined histologically: fixation in chrome salts and staining with Delafield's hæmatoxylin and iron-hæmatoxylin were employed. No study of the organs' content of lipoids could be undertaken. The chief histological abnormalities noted were (1) a preponderance of cortical over medullary columns; (2) the almost constant engorgement of the medullary areas. This engorgement appeared to commence in the areolar tissue between the columns, and to extend, in cases of greater severity, into and among the cells of the medulla, leading sometimes to destruction of many of them (Figs. 66, 67). During this process the cortical columns, as will be seen from the photo-micrographs, maintained a comparatively normal appearance as determinable by the staining methods employed. The regularity of the medullary congestion, while the cortex remains practically untouched, was the most characteristic feature in these glands.

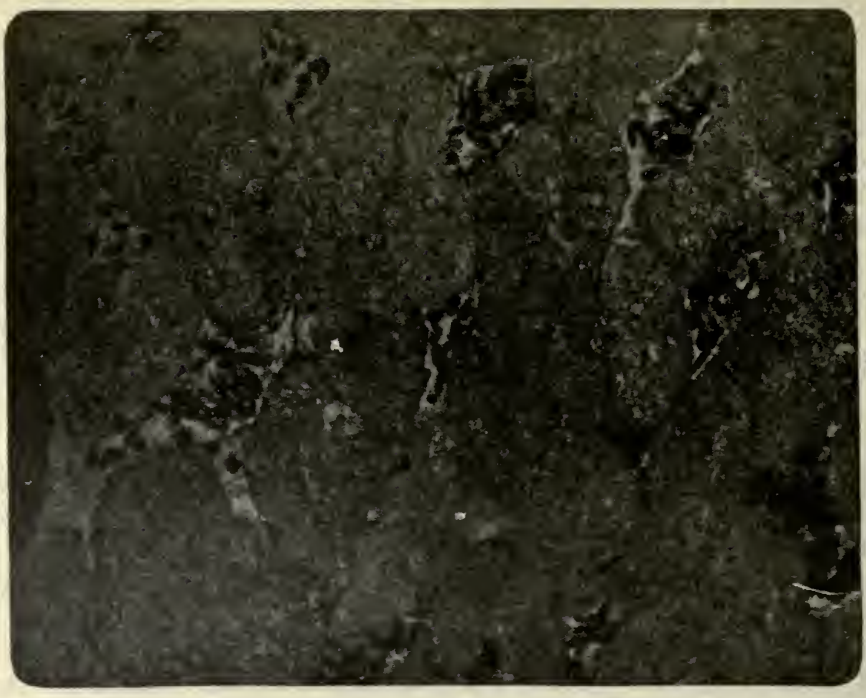

FIG. 67.—Adrenal gland from pigeon fed on autoclaved rice, butter, and onion, × 165. Note congestion.

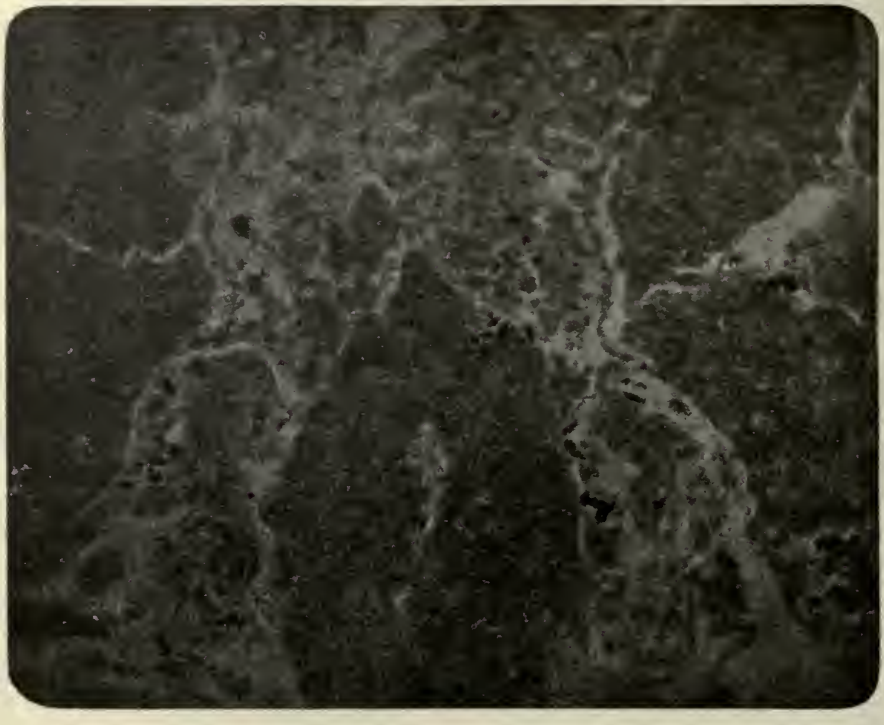

FIG. 68.—Adrenal gland from pigeon fed on autoclaved rice and butter, × 165. Note degeneration of medullary columns.

Kymographic Observations.—These were made in sheep in the manner above described, the emulsions of the glands being prepared and injected in the same way. Seven observations were taken with emulsions of glands from polyneuritic cases, two with a solution containing $\frac{1}{10}$ milligram of adrenalin, and seven with emulsions of glands from healthy controls. The results are shown in Table XIV.

TABLE XIV

SHOWING THE EFFECTS ON ARTERIAL BLOOD-PRESSURE OF THE INTRAVENOUS INJECTION INTO SHEEP OF EMULSIFIED ADRENALS FROM HEALTHY PIGEONS, AND FROM CASES OF POLYNEURITIS COLUMBARUM DEVELOPING IN CONSEQUENCE OF A DIET OF AUTOCLAVED RICE, BUTTER, AND ONIONS.

No. of Pigeon.	Weight of Adrenals in mgrms.	Weight of Sheep in lbs.	Rise of Blood-pressure in mm. of Hg.	Other Details.
77	32	46	12	Healthy bird
128	18	32	24	Healthy bird } Same sheep
130	18	32	28	Healthy bird }
162	15	47	32	Healthy bird
188	20	44	12	Healthy bird }
206	28	44	14	Polyneuritic bird } Same sheep (Fig. 64)
218	32	44	14	Polyneuritic bird }
—	—	44	24	$\frac{1}{10}$ mgrm. adrenalin }
186	21	39	34	Healthy bird }
208	51	39	10	Polyneuritic bird } Same sheep
220	60	39	12	Polyneuritic bird }
201	31	39	18	Polyneuritic bird }
179	15	37	56	Healthy bird }
207	35	37	64	Polyneuritic bird } Same sheep, very sensitive to adrenalin
214	37	37	64	Polyneuritic bird }
—	—	37	90	$\frac{1}{10}$ mgrm. of adrenalin }

The following conclusions emerge from these kymographic observations:

(1) The averages of seven observations in which the adrenals of healthy birds were employed, and of seven in which the adrenals from cases of polyneuritis columbarum were used, are as follows:

(*a*) 19·8 milligrams of healthy pigeons' adrenals caused a rise of blood-pressure of 28·3 mm. of Hg in 39·6-pound sheep.

(*b*) 39·1 milligrams of adrenals from cases of polyneuritis columbarum caused a rise of blood-pressure of 28 mm. of Hg in 39·8-pound sheep.

(2) In cases of polyneuritis resulting from a dietary of autoclaved rice, butter, and onions, there is no increase in the epinephrine-content of the enlarged adrenals proportionate to their increase in size. On the contrary, the gland-content of this substance per gram of gland is approximately one-half of that found in health. This observation has been confirmed by chemical methods of epinephrine estimation.

The remarkable fact thus emerges that, while an exclusive dietary of autoclaved rice, and a dietary of autoclaved rice to which fresh butter and fresh onions are added, are both capable of causing polyneuritis columbarum and enlargement of the adrenal glands, the enlargement resulting from the former dietary is associated with an increase of the epinephrine-content of the adrenals corresponding

to their increase in size, whereas the enlargement resulting from the latter dietary is not. (Compare Figs. 63 and 64.)

4. Effects of an Exclusive Diet of Rice Polishings.—The adrenal glands enlarge in consequence of this diet, being 147 milligrams per kilogram of body-weight as compared with 95 milligrams in health.

5. Effects of Concurrent Infections on the Adrenal Glands in Cases of Polyneuritis Columbarum.—Concurrent infections, when associated with food deficiency, frequently accentuate the enlargement of the adrenal glands. Thus, remembering that the average weight of both adrenals per kilogram of body-weight is in health 95 milligrams, and in polyneuritis resulting from an exclusive rice dietary 144 milligrams (both sexes being taken together), the weight of both adrenals was increased to 189, 403, 478, and 500 milligrams respectively in four cases presenting concurrent infections. Despite this enormous increase in size, the rise of blood-pressure caused by the injection of the glands in emulsified form into the jugular vein of sheep amounted only to 22, 24, 14, and 14 mm. of Hg respectively. Concurrent infections thus lower the epinephrine-content of the adrenal glands.

IN MONKEYS

The suprarenal glands enlarge in consequence of all classes of deficient dietaries.

In *Macacus sinicus* the average weight of both adrenals per kilogram of body-weight is in health 0·190 gram. The right adrenal is about one-seventh part lighter than the left. In monkeys fed on autoclaved rice the glands average 0·352 milligram per kilogram of original body-weight; in those fed on autoclaved rice and butter, 0·293 gram; in those fed on autoclaved food and onion, 0·258 gram; in those fed on autoclaved food with butter and onion, 0·266 gram. The organs thus enlarge in consequence of all four classes of deficient dietaries.

The enlargement is greatest in those fed on the autoclaved rice dietaries, and least in those fed on the autoclaved food dietaries, although the period of subjection to the deficient foods was much longer in the latter than in the former. It follows, then, that more perfect balance of the food diminishes the tendency to enlargement of these organs in the presence of avitaminosis.

The epinephrine-content of the enlarged adrenals was high in monkeys fed exclusively on autoclaved rice, whose blood was sterile at the time of death, low in those presenting hæmic infections at autopsy; being 0·000393 gram per kilogram of original body-weight in the former, 0·000264 gram in the latter, as compared with 0·000301 gram in healthy control animals. In monkeys fed on autoclaved rice and butter the epinephrine-content of both adrenals amounted to 0·000224 gram per kilogram of original body-weight, being thus lower than normal, a result which confirms that already recorded for pigeons.

Owing to the exhaustion of my supply of reagents, which could not be replenished in India, I was unable to complete the estimations of epinephrine in the suprarenals of monkeys fed on autoclaved food. Such as were made,

however, showed that their content of this substance *per gram of gland* was rather lower than in health. It is thus seen that, in monkeys as in pigeons, the nature of the animals' food has a profound influence on the adrenal glands.

IN GUINEA-PIGS

The Influence of a Scorbutic Diet of crushed oats and autoclaved milk on the adrenal glands was studied in five guinea-pigs.

The animals were isolated in separate cages. The experiment was continued until death occurred. Autopsies were performed with the attention to detail previously described. Aerobic cultures of the heart's blood at autopsy gave negative results in four cases, positive results in one (No. 5, Table XV). In this case the organism isolated failed to kill guinea-pigs on subcutaneous injection in large dosage.

Increase in size of the adrenal glands, together with greater or lesser degree of congestion, were the main naked-eye changes observed. The yellow colour of the organs was usually found to have given place to a reddish-yellow tinge. The superficial vessels presented varying degrees of engorgement. Minute hæmorrhagic effusions under the serous coat were frequently encountered.

The weight of the adrenals was approximately double that of health (Table XV).

Whereas the gross weight of both organs in healthy guinea-pigs ranged between 0·390 and 0·520 gram, with an average weight of 0·467 gram, in guinea-pigs fed on the scorbutic dietary the weight of both glands ranged between 0·850 and 1·150 grams, with an average weight of 0·955 gram. The increase in weight due to the scorbutic diet was even more marked when the weight of the glands was calculated per kilogram of original and of final body-weight (Fig. 69).

The epinephrine-content of the enlarged suprarenals was estimated by the method of Folin, Cannon, and Dennis.[1]

In each case one gland was used for epinephrine estimation, the other for histological study. On the presumption that both organs were affected in like degree, the total epinephrine-content of both adrenals was calculated from the results obtained with one gland. In some instances the right gland was used for the estimation, in others the left.

The results of these estimations are shown in Table XV, and are illustrated graphically in Fig. 69.

It is seen from Table XV that—

(1) The total quantity of epinephrine in both glands in guinea-pigs fed on a scorbutic diet was less than half that present in healthy guinea-pigs (col. 7). although the weight of the organs was more than twice as great in the former as in the latter (cols. 5 and 6).

(2) Similarly, the total epinephrine per kilogram of *original* body-weight was little more than half that of health (col. 8).

[1] *Jour. Biol. Chem.*, 1912–13, XIII. 477.

TABLE XV

SHOWING THE EPINEPHRINE-CONTENT OF THE ADRENAL GLANDS, THE TOTAL EPINEPHRINE PER KILOGRAM OF BODY-WEIGHT, IN (*a*) FIVE GUINEA-PIGS FED ON A SCORBUTIC DIET, AND (*b*) IN FOUR HEALTHY GUINEA-PIGS FED ON NORMAL FOOD

	Number.	Original Weight of Guinea-pig in grams	Final Weight of Guinea-pig in grams.	Weight of Adrenals in grams.	Weight of Adrenals per Kilogram of Original Body-weight in grams.	Weight of Adrenals per Kilogram of Final Body-weight in grams.	Total Epinephrine in Both Adrenal Glands in grams.	Total Epinephrine per Kilogram of Original Body-weight in grams.	Total Epinephrine per Kilogram of Final Body-weight in grams.	Total Epinephrine per Gram of Gland.	Experimental or Control Animal.
a	1	550	390	0·850	1·545	2·179	·000113	·000205	·000289	·000132	Experimental
a	2	520	400	1·029	1·978	2·572	·000143	·000275	·000357	·000139	,,
a	3	500	320	0·850	1·700	2·656	·000096	·000192	·000300	·000112	,,
a	4	550	320	0·900	1·636	2·812	·000116	·000210	·000362	·000128	,,
a		520	390	1·150	2·211	2·948	·000086	·000165	·000220	·000074	,,
—		528	364	0·955	1·814	2·633	·000110	·000209	·000305	·000117	Averages
b	7	570	620	0·390	0·684	0·629	·000253	·000443	·000408	·000648	Control
b	8	610	610	0·520	0·852	0·852	·000216	·000354	·000354	·000415	,,
b	9	610	610	0·460	0·754	0·754	·000253	·000414	·000414	·000550	,,
b	10	670	670	0·500	0·746	0·746	·000233	·000347	·000347	·000466	,,
—		615	627	0·467	0·759	0·745	·000238	·000389	·000380	·000519	Averages

(3) When calculated against the *final* body-weight (col. 9) of the guinea-pig, the total epinephrine per kilogram was found to be less markedly reduced.

(4) The total epinephrine per gram of gland was less than one-fourth of that found in health (col. 10).

(5) It will be noted that in guinea-pig No. 5, in which a coliform organism was cultured from the heart's blood at autopsy, the epinephrine-content was considerably less than in the other four animals, in which no infection was detected by aerobic methods of culture.

A pronounced reduction in the amount of epinephrine in the suprarenal glands was thus found to result in guinea-pigs from a scorbutic diet of crushed oats and autoclaved milk.

In connexion with these observations, it is of interest to direct attention to the fact that the total epinephrine per gram of gland in healthy pigeons is ten times greater (0·0023 gram), than in healthy guinea-pigs (0·00023 gram). This greater proportion in birds may bear some relationship to the fact that they excrete uric acid as such.

Histological Observations.—The histological changes resulting from a scorbutic dietary comprise (1) hæmorrhagic infiltration, and (2) degenerative changes in the cellular elements of the cortex and medulla.

Hæmorrhagic Infiltration.—There are two features of importance in connexion with the hæmorrhagic infiltrations: (1) Their circumscribed character and situation in the adrenal cortex; and (2) the fact that they may occur *before*

any clinical evidences of scurvy are observed, and even before any notable scorbutic changes are to be found at autopsy between cartilage and rib.

The circumscribed character of the hæmorrhagic infiltrations and their situation in the adrenal cortex are shown in Fig. 70. A higher magnification of a similar section is shown in Fig. 72. The hæmorrhagic areas are of varying sizes; their more or less uniform distribution around the periphery of the cortex is their characteristic feature. I have not observed this curious distribution of hæmorrhages in the adrenal glands of guinea-pigs dying of infectious diseases in which both cortex and medulla are often extensively congested. In three cases the hæmorrhagic areas were distributed more or less uniformly around the periphery of the cortex; in one they were present on only one side; in the fifth case they were absent, a moderate degree of generalized hæmorrhagic infiltration of the cortex alone being present.

The changes in the cortical cells consist in (*a*) loss of their tessellated appearance; (*b*) vacuolation and disintegration of cells; and (*c*) disappearance or loss of staining reactions of a proportion of their nuclei. These changes are well seen in the photo-micrographs (Figs. 71 and 72); they call for no further description.

The medulla is much disorganized, and shows cellular disintegration with scattered blood-cells lying throughout its substance. Usually it is possible to detect in healthy glands the chrome-staining granules of the medullary cells. In the case of guinea-pigs fed on the scorbutic dietary these granules are few or altogether wanting.

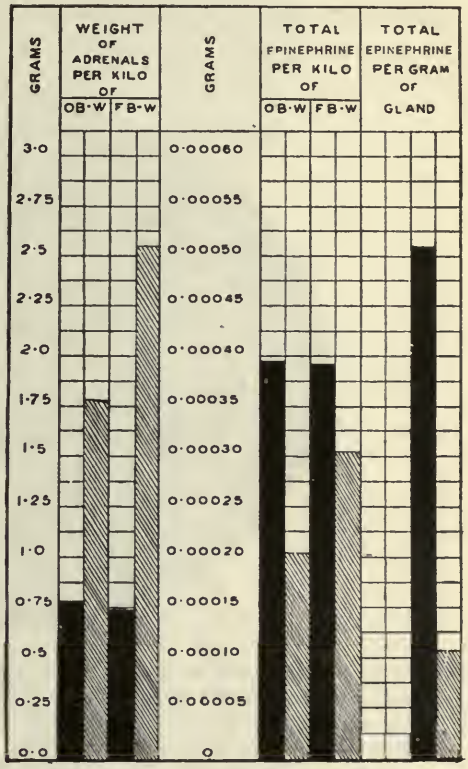

FIG. 69.—Showing weight of adrenals and total epinephrine per kilogram of original (OB-W) and of final (FB-W) body-weight, also total epinephrine per gram of gland in (*a*) healthy guinea-pigs (black columns) and in (*b*) guinea-pigs fed on a scorbutic diet (shaded columns).

I have been much impressed by finding that the histo-pathological changes I have described were present in the adrenals of guinea-pigs, fed on the scorbutic dietary, which exhibited during life no clinical evidences of scurvy. Depression of adrenal function may, therefore, be regarded as a pre-scorbutic manifestation of a dietary deficient in accessory food factors of the "C" class. Having regard to the fact that a form of purpura is due to acute adrenal deficiency, it becomes a question for consideration whether the acute

adrenal deficiency produced by want of vitamin C is not the essential pathological factor in scurvy.

Summarizing the results observed in guinea-pigs, it may be said that a scorbutic diet gives rise to (1) an increase in size and in weight of the adrenal glands; (2) a marked diminution in the epinephrine-content of these organs; (3) hæmorrhagic infiltration of the adrenal glands, usually circumscribed in extent and situated around the periphery of the adrenal cortex; and (4) to degenerative changes in the cellular elements of the adrenal cortex and medulla.

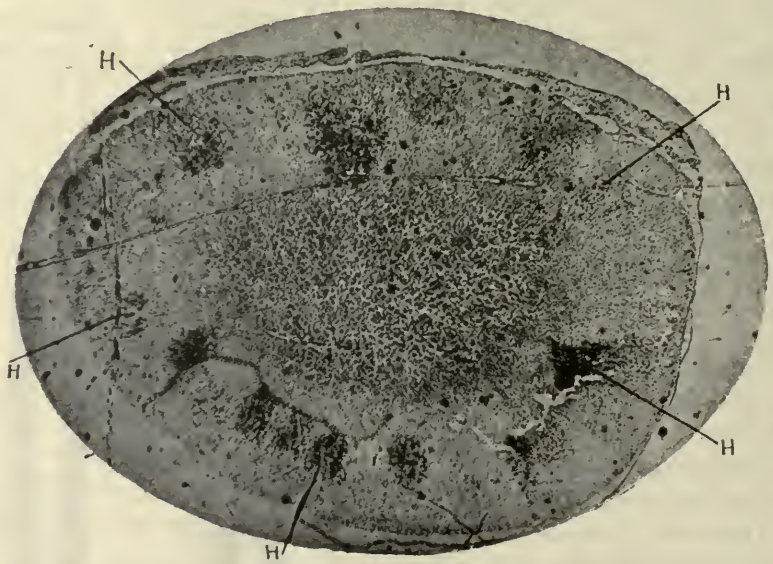

FIG. 70.—Photograph of section of adrenal gland from a guinea-pig fed on a scorbutic diet of crushed oats and autoclaved milk. Note: fourteen circumscribed areas of hæmorrhage distributed throughout the cortex. Some of these are indicated by the letter H; the others are unmarked. The photograph was taken by interposing a lens between the bellows of the camera and the object. The magnification is roughly 20 to 30 diameters. The slide to which the specimen was fixed was much scratched, the scratches showing in the photograph.

These changes indicate that—

1. A scorbutic diet causes pronounced depreciation in functional capacity of the adrenal glands.

2. The impairment of adrenal function may occur before clinical evidences of scurvy manifest themselves.

3. Acute adrenal deficiency may be brought about by deprivation of vitamin C.

These observations in guinea-pigs have been confirmed by Bassett-Smith,[1] and more recently by La Mer and Campbell.[2] The last observers have found

[1] *Proc. Roy. Soc. Med.*, London, 1920 (July), XIII, No. 9 (War Section), p. 51.
[2] *Proc. Soc. Exp. Biol. and Med.*, 1920.

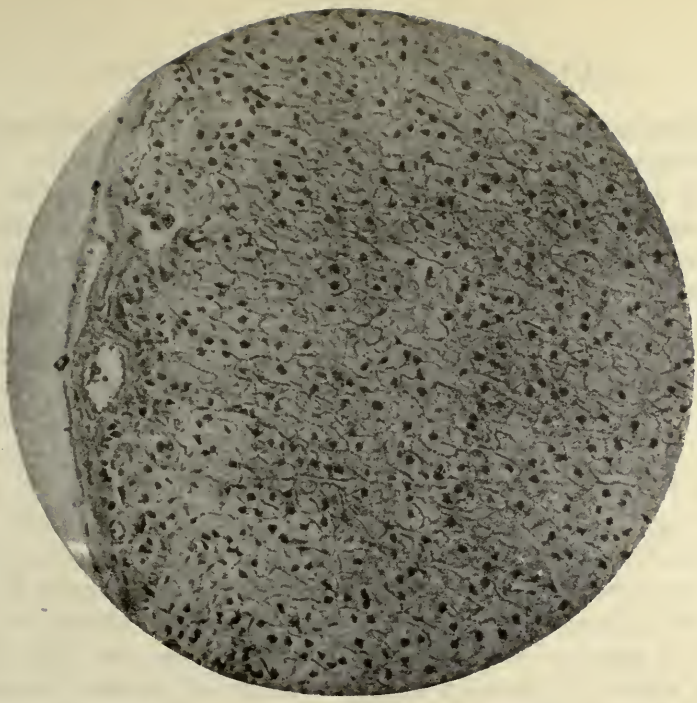

FIG. 71.—Section of adrenal cortex from a healthy guinea-pig, × 105. Note tessellated appearance of cortical cells and their darkly-staining nuclei.

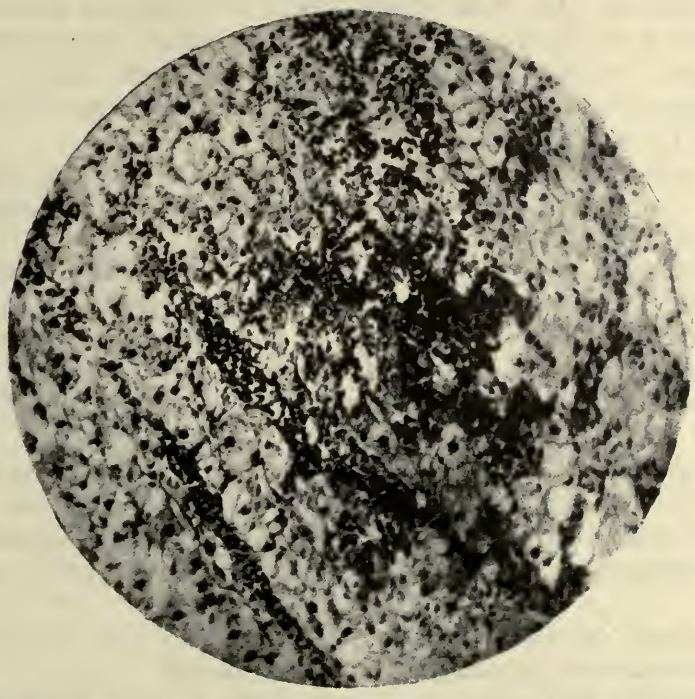

FIG. 72.—Section of adrenal cortex from a guinea-pig dying in consequence of a scorbutic diet of crushed oats and autoclaved milk, × 105. The animal showed prior to its death none of the clinical evidences of scurvy, although at autopsy it presented numerous hæmorrhages into the tissues. Note loss of tessellated structure, marked vacuolation of cells, disappearance of nuclei, pronounced hæmorrhagic infiltration.

that the increase in weight of the suprarenal glands is directly proportional to the time during which the animals have been fed on the scorbutic diet. It is most pronounced in those whose life has been prolonged by the partial protection afforded by small but insufficient quantities of tomato juice. Rondoni [1] also, in 1915, noted an increase in size and hyperæmia of the suprarenals in guinea-pigs fed exclusively on cereals. My observations dealing with the effects of complete avitaminosis on pigeons and monkeys have been confirmed by Cramer,[2] who, experimenting with mice and rats fed on a synthetic dietary (consisting of purified casein, starch, inorganic salts, and olive oil) found that the characteristic picture of an adrenal in complete avitaminosis is a full load of epinephrine in the medulla, and an almost complete disappearance of lipoid from the cortex. More recently further confirmation has been provided by Kellaway,[3] who undertook a study of the effects of certain dietary deficiencies on the suprarenal glands for the purpose of throwing further light on my observation as to the increase in size and in content of epinephrine of these organs in pigeons, in consequence of avitaminosis. He observed that " these changes in the suprarenal glands of pigeons were found constantly when the diet consisted of polished rice alone, or when an adequate ration of protein (casein rendered free from fat and from accessory food factors by repeated extraction with alcohol and ether) or fat was added to the dietary, and was associated with the appearance of polyneuritis. The daily administration of a sufficient amount of ' marmite ' to the diet of polished rice prevented these changes from occurring."

Summary.—The data afforded in this chapter indicate that—

(1) The adrenal glands enlarge in consequence of all classes of deficient food employed in the experiments.

(2) This enlargement is the result either of acute inanition consequent on deprivation of all food, of proximate principles, or of the more chronic inanition which results from deprivation of vitamins.

(3) The enlargement tends to be less marked when the food is more perfectly balanced with respect to proximate principles, and tends to be more marked when the food is disproportionately rich in energy-bearing constituents.

(4) The enlargement is associated with a full load of adrenalin in the presence of complete avitaminosis, and with an almost complete absence of lipoids from the cortex.

(5) The addition of butter to the dietary of autoclaved rice gives rise to a reduction in the epinephrine-content of the enlarged organs, and appears to increase the congestive changes in the medulla. In these circumstances the amount of epinephrine is, per gram of gland, approximately one-half that of health.

(6) Concurrent infections in cases of polyneuritis columbarum cause the epinephrine-content of the enlarged adrenals to be low.

(7) A scorbutic diet gives rise in guinea-pigs to great enlargement of the

[1] *Brit. Med. Jour.*, 1919, I. 542.
[2] Loc. cit. [3] Loc. cit.

adrenal glands with great reduction in their epinephrine-content; the enlargement is associated with degenerative and hæmorrhagic changes in the organ. Impairment of functional capacity of the adrenal glands occurs before evidences of scurvy manifest themselves clinically. It is one of the most pre-eminent pathological features of experimentally-produced scurvy in guinea-pigs.

(8) The functional perfection of the adrenal glands is dependent on the quality of the food.

CHAPTER XVIII

THE ADRENAL GLANDS AND MALNUTRITIONAL ŒDEMA

Malnutritional Œdema.—My observations with regard to malnutritional œdema were made in pigeons. They are included with those relating to the adrenal glands, because of the intimate association which has been found to exist in pigeons between enlargement of these organs and the presence of œdema.

The evidences of œdema met with in pigeons in my experiments comprised: (1) Œdematous degeneration of the auriculo-ventricular band of fat, which was very frequently encountered; (2) hydropericardium, also of frequent occurrence; (3) ascites, œdema of lungs, œdema of muscles, and much less commonly subcutaneous œdema. The effusion into the pericardial sac varied from a few drops of clear amber-coloured fluid, without sign of turbidity, and sterile on bacteriological examination, to as much as 13·5 c.c. (Fig. 73). Very rarely the fluid was blood-stained; in this event an organism very virulent for pigeons, and causing hæmorrhages into the heart's muscle and into other organs and tissues of the body, was usually associated with the hæmopericardium. This organism was of peculiar interest in that it produced lesions, on subcutaneous inoculations into healthy pigeons, closely resembling those found in scurvy, including great enlargement and disintegration of the adrenals, with great diminution of their epinephrine-content. Infection by this organism is referred to in the three largest adrenals mentioned on p. 166, Chapter XVII. In fowls, also, hydropericardium has frequently been encountered. Shiga and Kasama [1] have reported the occurrence of œdema in pigeons and fowls fed on polished rice, as did Eijkman. It is of much interest, therefore, to find that Vedder and Clark [1] "did not find œdema or pericardial effusions in any of the fowls autopsied"; while Kellaway [2] reports that œdema is of infrequent occurrence in pigeons fed on polished rice. Seeking for an explanation of these apparently conflicting reports, I find it in differences in the rices used by workers in the East and those in the West. The rice in Europe is very highly polished, and causes death from polyneuritis much more rapidly than the rices in common use in the East. Hydropericardium is rarely met with in pigeons fed on the commercial rices of India before the twenty-fourth day; it seems likely, therefore, that in pigeons fed on highly-polished rice, which die as a rule in periods ranging from

[1] Vedder, *Beri-beri*, London, 1913.
[2] *Proc. Roy. Soc.*, Series B, XC, B642, p. 6.

15 to 25 days, œdema will be much less frequently encountered than in birds which survive on Indian rices for an average period of 45 days. It is to be remembered that it is on the rices in common use in the East that wet beri-beri develops. If this explanation be correct, the point is one of importance, since it indicates that inanition, the fundamental factor in the production of œdema, must have reached a certain stage before œdema can occur. It means, in short, that an absolute avitaminosis may cause the birds to die of nervous lesions before the degree of inanition necessary for the development of œdema has been reached. Serous or mucoid degeneration of the auriculo-ventricular band of fat, some drops of fluid in the pericardial sac, some œdema of the lungs and slight œdema of the groins were the evidences of œdema met with in pigeons starved to death. Inanition is, therefore, capable in itself of causing œdema, as, indeed, the conditions known as "epidemic dropsy," "hunger œdema" or "war œdema" abundantly show. At a time when so much interest attaches to the causation of these œdemas, is may be well to point out that so long ago as 1877–8 it was recognized by Cornish and Porter in India[1] that "famine œdema" was due to food deficient in total calories, and especially in protein; a truth which was further proven by the work of Greig[2] on "Epidemic Dropsy" several years before the outbreak of war. Kohman,[1] by her experimental work on rats, has more recently added further proof of the accuracy of Cornish and Porter's conclusions.

FIG. 73.—Hydropericardium containing 13·5 c.c. of fluid occurring in pigeon fed exclusively on milled and autoclaved rice.

My own observations have been made on large numbers of pigeons fed (1) exclusively on autoclaved rice; (2) on autoclaved rice with fresh butter derived from cows variously fed; (3) on autoclaved rice with butter and onions; (4) on autoclaved rice with coconut oil. The method of observation followed was to ascertain the weights of the adrenal glands per kilogram of original body-weight of the birds, to determine, by the method of Folin, Cannon, and Dennis,[3] the epinephrine-content of the enlarged organs; and, finally, to contrast the results thus reached with the incidence of œdema. Full details of these observations are given in tabular form in Appendix I to this monograph. In preparing these tables, I have included as hydropericardium all cases in which fluid could be pipetted off from the pericardial sac, even in amounts not exceeding two drops, since among the large number of healthy control pigeons I have employed, no appre-

[1] Various Reports relative to the Indian Famine of 1877.
[2] *Scientf. Mem. Govt. of India*, 1911, No. 45, and 1912, No. 49.
[3] *Jour. Biol. Chem.*, 1912–13, XIII. 477.

ciable amount of fluid was ever present in this situation. I have considered, therefore, that even small amounts of fluid represent early stages in the process of effusion.

1. Incidence of Œdema with Special Reference to the Weight of the Adrenal Glands in Pigeons fed on Milled and Autoclaved Rice (Table I, Appendix I).—The birds in this series were adults—18 males and 13 females.

They were fed for the first 40 days of the experiment on milled Rangoon rice, and thereafter on the same rice autoclaved at a temperature of 130° C. for three-quarters of an hour. Polyneuritis columbarum made its appearance in periods ranging from 30 to 100 days; the average depletion period being 67·1 days. Sterility of the blood was demonstrated in all cases.[1]

Five among males showed evidences of œdema at autopsy; four among females. The sex incidence was thus very slightly higher in females than in males; being 30 per cent. in the former, 28 per cent. in the latter. Among males the first case of œdema was encountered at autopsy on the forty-ninth day of the experiment; among females on the seventy-seventh day. Males are therefore affected earlier than females; an observation in conformity with the sex-incidence of "wet beri-beri," "hunger œdema," and "epidemic dropsy." The incidence of œdema among the 31 adult birds was 29 per cent.; there being nine cases with œdema and 22 cases without œdema.

The average weight of the adrenal glands per kilogram of body-weight in 35 pigeons fed on mixed grains and grit, which acted as controls in this experiment, was 95 mgrms. The average weight of the adrenals in 22 cases of polyneuritis without œdema was 127 milligrams per kilogram of original body-weight; in 9 cases with œdema, 196 milligrams. The weight of the adrenals was thus greater on the average in cases of *dry* polyneuritis than in health, and much greater in cases of *wet* polyneuritis. The minimum weight of the adrenal glands in any case of *wet* polyneuritis was 147 milligrams per kilogram of original body-weight. The total number of cases of polyneuritis having adrenals weighing 147 milligrams or over was 13; of these 9, or 70 per cent., had evidences of œdema, and 4, or 30 per cent., had no evidence of œdema.

There was a marked tendency to the occurrence of œdema in deficiently-fed adult pigeons, whose adrenal glands weighed 147 milligrams per kilogram of original body-weight or over. In all cases presenting evidence of œdema, or 100 per cent., the adrenals equalled or exceeded this weight.

2. Incidence of Œdema with Special Reference to the Weight of the Adrenal Clands in Young and Growing Pigeons fed Exclusively on Autoclaved Rice (Table II, Appendix I).—The birds in this series were adolescents—14 males and 15 females. Their average age was 6 to 9 months.

They were fed throughout the course of the experiment on autoclaved rice. Polyneuritis columbarum made its appearance in periods ranging from 27 to 94 days; the average depletion period was 43·5 days. Sterility of the blood was demonstrated in all cases.

[1] "Sterility of the blood" refers to bacterial organisms. It has been pointed out that practically every pigeon was infected with Halteridium.

Eight among males showed evidences of œdema at autopsy; nine among females. The sex incidence was thus slightly higher in females than in males; being 60 per cent. in the former, and 57 per cent. in the latter. In both sexes it was twice as high in young birds as in adults. Among males the first case of œdema was encountered at autopsy on the twenty-fourth day of the experiment; among females on the sixtieth day. Males are, therefore, affected earlier than females. The incidence of œdema among the 29 young birds was 58 per cent.; there being 17 cases with œdema and 12 cases without œdema.

Taking the average weight of the adrenal glands per kilogram of body-weight in young control birds as 100 milligrams, it was found that the average weight of these organs in 12 cases of polyneuritis without œdema was 157·4 milligrams; in 17 cases with œdema, 249·4 milligrams. The weight of the adrenal glands was thus greater on the average in cases of *dry* polyneuritis than in health, and much greater in cases of *wet* polyneuritis. The response of these organs to the food deficiency was also much more marked than in the case of adult pigeons, and this greater response was associated with a higher incidence of œdema. The minimum weight of the adrenal glands in any case of *wet* polyneuritis was 180 milligrams per kilogram of original body-weight. The total number of cases of polyneuritis having adrenals weighing 180 milligrams, or over, was 19; of these 17, or 89·4 per cent., had evidence of œdema, and 2, or 10·6 per cent., had no evidence of œdema.

There was a very marked tendency to the occurrence of œdema in deficiently-fed young birds whose adrenal glands weighed 180 milligrams per kilogram of original body-weight or over. In all cases presenting evidence of œdema, or 100 per cent., the adrenals equalled or exceeded this weight.

3. **Chemical Estimation of Epinephrine in the Adrenal Glands of Control Pigeons and of Cases of Polyneuritis Columbarum fed Exclusively on Autoclaved Rice (Tables III, IV, V, and VI, Appendix I).**—Kymographic observations had already demonstrated an increase of the epinephrine-content proportionate to the increase in size of the glands in cases of polyneuritis. Chemical estimations of epinephrine were made in 22 further cases of polyneuritis—12 cases without œdema and 10 cases with œdema—and in 10 healthy control pigeons. With one exception the heart's blood was sterile at autopsy. All estimations were made immediately after the removal of the adrenal glands, and each was controlled by estimating at the same time the epinephrine-content of the organs from a healthy control pigeon. It usually happened that one, two, or more estimations in respect to diseased birds were made at the same time as one estimation in respect to a control bird.

Among the 10 controls the weight of the adrenals ranged between 75 and 114 milligrams, in cases of *dry* polyneuritis, between 85 and 275 milligrams; in cases of *wet* polyneuritis, between 145 and 478 milligrams per kilogram of original body-weight. The total amount of epinephrine in the healthy glands ranged between 0·045 and 0·090 milligrams; in cases of *dry* polyneuritis, between 0·045 and 0·138 milligrams; in cases of *wet* polyneuritis, between 0·090 and 0·165 milligrams. In 10 out of 12 cases of *dry* polyneuritis the total amount of epinephrine was within the limits of health, but on a higher average level. In no case of *wet* polyneuritis was the epinephrine-content within the limits of health, although in

one case (No. 244, Table V, Appendix I) it was as low as the maximum limit found among 10 healthy birds.

The average epinephrine-content *per gram of gland* in 10 *healthy* pigeons was 0·0023 gram; in 12 cases of *dry* polyneuritis, 0·0021 gram; in 10 cases of *wet* polyneuritis, 0·0018 gram. Thus per gram of gland the average epinephrine-content was, in cases of

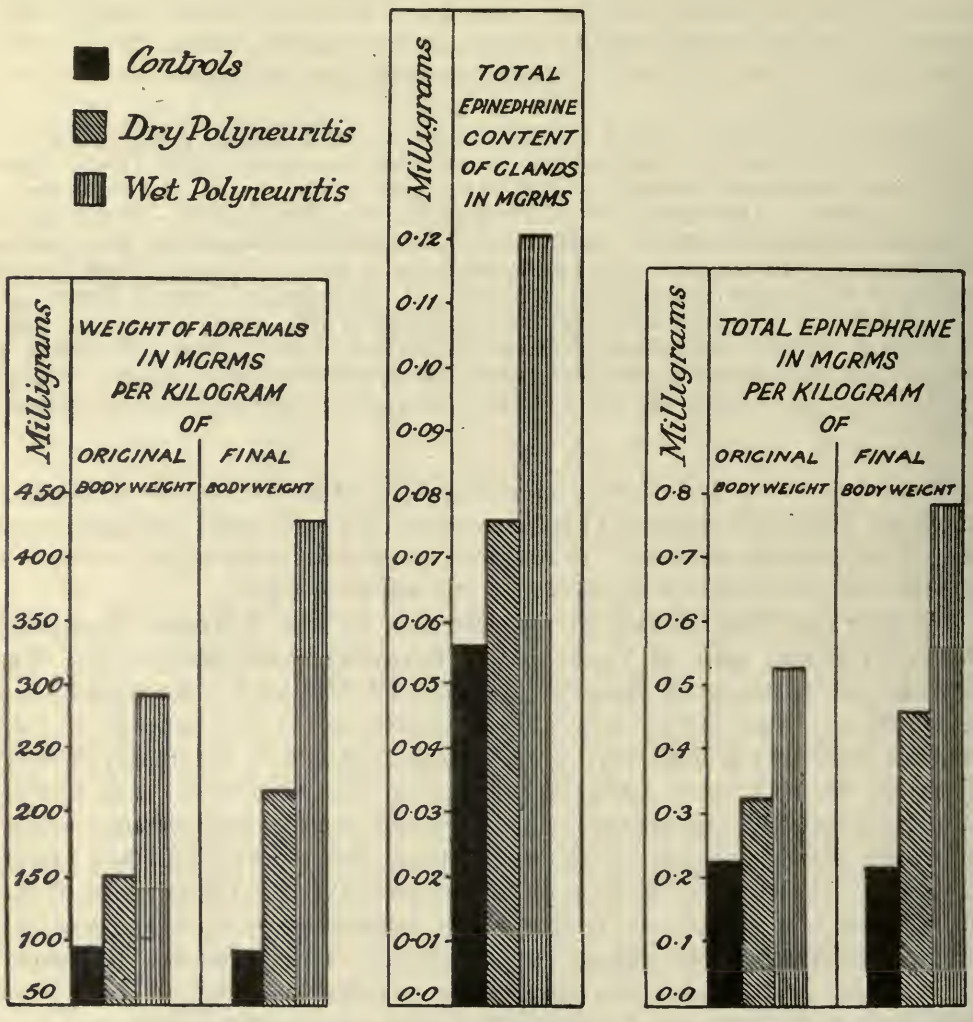

FIG. 74.—Showing epinephrine-content of the adrenal glands in healthy pigeons and in cases of *dry* and *wet* polyneuritis columbarum.

dry polyneuritis, approximately the same as in health, in cases of *wet* polyneuritis slightly below that of health.

The total amount of epinephrine per kilogram of original body-weight ranged in 10 *healthy* controls between 0·187 and 0·257 milligram; in cases of *dry* polyneuritis, between 0·173 and 0·552 milligram; in cases of *wet* polyneuritis, between 0·408 and 0·750 milligram. Thus while in *dry* polyneuritis the total amount of epinephrine in the body (as estimated by that found in the adrenal glands) was within the limits of health

in five cases, and above the limits of health in seven cases (Tables III, IV, V, Appendix I), it was in all cases of *wet* polyneuritis well above the limits of health.

These results are represented graphically in Fig. 74.

Summary.—The results so far reached may be summarized as follows:

(1) Young and growing birds are more prone to develop œdema than adults.

(2) The incidence of œdema differs little in the two sexes; males are, however, affected earlier than females.

(3) Œdema is constantly associated with great enlargement of the adrenal glands.

(4) Great enlargement of the adrenal glands is, *per contra*, not always associated with œdema; the frequency of this association is dependent in considerable measure on the age of the birds; 70 per cent. of cases of polyneuritis among adult pigeons in which there is great enlargement of the adrenal glands have œdema; 90 per cent. among young birds having great enlargement of the adrenal glands have œdema.

(5) The response of the adrenal glands to food deficiency is much greater in young birds than in adult birds; this greater response is associated with a greater incidence of œdema.

(6) The average epinephrine-content *per gram of gland* is approximately the same as in health in cases of *dry* polyneuritis, and rather less than in health in the greatly enlarged adrenals from cases of *wet* polyneuritis.

(7) The weight of the adrenal glands, their epinephrine-content, and the total amount of epinephrine per kilogram of body-weight, are on the average greater in *dry* polyneuritis than in health, and much greater in *wet* polyneuritis than in either.

CHAPTER XIX

THE ADRENAL GLANDS AND MALNUTRITIONAL ŒDEMA (*continued*)

HAVING determined thus far the extent of the association between adrenal enlargement and œdema in pigeons fed exclusively on rice, it is now necessary to examine how far this association is effected by the addition of other food substances to the basal diet of autoclaved rice.

1. Incidence of Œdema with Special Reference to the Adrenal Glands in Pigeons fed on a Dietary of Autoclaved Rice, Fresh Butter, and Fresh Onions.—The object of these additions to the dietary of autoclaved rice was to provide an abundance of vitamin A and of vitamin C, while leaving the food mixture deficient in vitamin B. The dietary was thereby rendered richer in salts, slightly richer in protein, and excessively rich in fats as well as in starch. The pigeons in this series were young birds, aged approximately 9 to 12 months. Fourteen were females and six were males.

Details of the experiment are given in Chapter III. Polyneuritis columbarum made its appearance in periods ranging from 21 to 36 days; the average being 29 days. Sterility of the blood was demonstrated in all cases.

One among 6 males, and one among 14 females, showed evidence of the œdema at autopsy; the former on the twenty-first day of the experiment, the latter on the twenty-seventh. The incidence of œdema among these 20 cases of polyneuritis was 10 per cent.; there being 2 with œdema and 18 without œdema (Table VII, Appendix I).

The average weight of the adrenal glands per kilogram of body-weight in 20 healthy control pigeons receiving butter and onions with their natural food of mixed grains, in proportions identical with those in the deficient food mixture, was 68·3 milligrams; that of the adrenals in 18 cases of *dry* polyneuritis, 155 milligrams; and in 2 cases of *wet* polyneuritis, 214 milligrams. The weight of the glands was thus much greater in *dry* polyneuritis than in health, and still greater in *wet* polyneuritis. The minimum weight of the adrenal glands in any case of *wet* polyneuritis was 203 milligrams per kilogram of original body-weight. The total number of cases of polyneuritis having adrenal glands weighing 203 milligrams, or over, was 3; of these 2 had evidence of œdema and 1 had not.

When these results are contrasted with those in 82 cases of polyneuritis columbarum resulting from an exclusive diet of milled and autoclaved rice, it

is found that the addition of the butter and onions caused the incidence of œdema to drop from 43·9 per cent. to 10 per cent. This may have been due in some measure to the more rapid production of the disease, and the more rapid death of the birds receiving the butter and the onions. This point will be dealt with presently. A more significant finding, however, relates to the epinephrine-content of the enlarged adrenals. From among these 20 cases, 7 were taken at random in order to determine by physiological methods the amount of epinephrine in the enlarged glands. It was found, as has been recorded in a preceding chapter (Fig. 64), that the epinephrine-content was not increased, and did not, in fact, amount to more than one-half that of health. This result was obviously due either to the butter or to the onions, or to both. The point was consequently investigated further.

2. Influence of Butter on the Adrenal Glands.—It has already been pointed out that the addition of butter to the natural food of pigeons causes the adrenal glands to be smaller, on the average, than in birds receiving no butter; 68·3 milligrams per kilogram of body-weight in the former as compared with 95 milligrams in the latter.

Among the 82 cases of polyneuritis so far dealt with, and resulting from an exclusive diet of rice, 31 had been fed for the first 40 days of the experiment on raw rice, and thereafter on autoclaved rice, and 12 had been fed on rice autoclaved for one and a half hours—that is to say, for a longer period than usual. As these differences might have been of some importance in confusing the present issue , the 43 birds so fed are excluded, and the remaining 39 used for comparison with cases of polyneuritis induced by a dietary of rice, autoclaved at 130° C. for three-quarters of an hour, to which butter made from the milk of cows fed on *green* fodder was added. With the exception of the butter, which was added in the proportion of one-sixth of an ounce per bird per diem, the experiments were identical; the birds used being of approximately the same age in the two cases. Details are given in Tables VIII and IX, Appendix I. In these tables the cases are arranged in the order of the death of the birds. When the results are contrasted it is found:

(1) That pigeons, to whose dietary of autoclaved rice butter was added, died or were killed at the point of death in periods ranging from 20 to 45 days, with an average of 33·9 days; as compared with a range of 24 to 95 days, and an average of 50·7 days, in those receiving no butter. The added butter thus caused them to die much more rapidly; a conclusion already reached from previous experiments in both pigeons and monkeys.

(2) All cases of œdema in butter-fed pigeons were encountered at autopsy within the last nine days of the experiment (thirty-seventh to forty-fifth day). No case presented evidence of œdema out of 19 dying of polyneuritis before the thirty-seventh day. On the other hand, in pigeons fed exclusively on autoclaved rice, cases of œdema were encountered at irregular intervals between the twenty-fourth and the ninety-fifth day of the experiment; 8 cases out of 13, dying before the thirty-seventh day, presented evidence of œdema.

(3) Three cases exhibiting serous degeneration of the auriculo-ventricular band of fat without other evidence of œdema occurred among butter-fed pigeons, whereas, in pigeons fed exclusively on autoclaved rice, such serous degeneration of the band was accompanied with other evidence of œdema in all cases except one.

(4) The percentage number of cases exhibiting evidence of œdema among 29 butter-fed pigeons was 24·1, as compared with 56·4 among those receiving no butter. Clearly, then, the butter afforded the birds complete protection against œdema up to approximately the thirty-seventh day, after which no protection was afforded.

It is evident from these results that there exists in butter, made from the milk of cows fed on *green* fodder, some substance which has a marked influence in reducing the incidence, and in delaying the onset, of œdema in pigeons fed on autoclaved rice. It is evident, also, that the protection afforded against œdema by the butter is not to be accounted for, in general, by the more rapid onset of symptoms and the more rapid death of the birds receiving it. To what, then, is it due ? Evidence on this point is available from comparative chemical estimations of epinephrine-content of the adrenal glands in butter-fed and in non-butter-fed pigeons as well as from further experiments.

3. Chemical Estimations of Epinephrine in 20 Control Pigeons, in 20 Cases of Polyneuritis resulting from a Diet of Autoclaved Rice and Butter, and in 8 Cases of Polyneuritis resulting from an Exclusive Diet of Autoclaved Rice (Tables IX, X, XI, and XII, Appendix I).—The results of epinephrine estimations in 20 healthy control pigeons are shown in Table X of the appendix ; those in 20 cases of polyneuritis resulting from a diet of autoclaved rice and butter in Table IX ; those of 8 cases resulting from an exclusive diet of autoclaved rice in Table XI. These results are contrasted in Table XII. From the data afforded by these tables the following facts emerge : (1) Whereas cases of *dry* polyneuritis, resulting from an exclusive diet of autoclaved rice, had a total epinephrine-content of the adrenal glands markedly in excess of health, cases of *dry* polyneuritis, resulting from a diet of autoclaved rice *plus butter*, had a total epinephrine-content rather less than that of health ; thus confirming the result reached by physiological methods of estimation. (2) Cases of *wet* polyneuritis, whether resulting from an exclusive diet of autoclaved rice or from a diet of autoclaved rice *plus butter*, had an epinephrine-content of the adrenal glands greatly in excess of that of health. (3) In cases of polyneuritis in which the only evidence of œdema was serous degeneration of the band of fat at the auriculo-ventricular junction of the heart, the epinephrine-content of the adrenal glands was high in non-butter-fed pigeons and low in butter-fed pigeons. This result appears to indicate that the serous or mucoid degeneration is due rather to inanition than to the absence of any hypothetical anti-œdema substance, since it is not appreciably affected by the addition of butter to the deficient food. Leaving these out of our reckoning, the results indicate that the protection afforded against serous effusions by butter,

made from the milk of cows fed on *green* fodder, is associated with an epinephrine-content of the adrenal glands which does not exceed, but is rather less than, that of health.

Returning now to a comparison of Tables IX and XI, it will be noted that, in cases among butter-fed pigeons dying prior to the thirty-seventh day, the epinephrine-content of their adrenal glands reached the average of health (0·255 milligram per kilogram of body-weight) in three cases only; in no case did it exceed the maximum limit of health (0·430 milligram, Table X). On the other hand, in non-butter-fed cases (Table XI, Appendix I) of polyneuritis dying before the thirty-seventh day, the epinephrine-content of the glands greatly exceeded the maximum limits of health in all cases, and œdema was present in two of them. In the comparisons here instituted I have included only epinephrine estimations which were made in birds subjected to experimentation at the same time; were the results of the estimations detailed in Tables IV and V (Appendix I) included also, the difference in the reaction of the adrenal glands to butter in the presence of a dietary of autoclaved rice would be all the more marked. I have refrained from including them for the reasons that the experiments referred to in Tables IV and V were carried out at a different season of the year, and with a different stock of reagents which gave slightly higher results in the second series than in the first. It may be said, however, with regard to the data afforded in Tables IV and V, that these also showed in birds, dying prior to the thirty-seventh day of experiment, an epinephrine-content of the adrenal glands greatly in excess of that of health, and that among them a high proportion presented evidence of œdema. The conclusion is thus justified that the protection against serous effusions afforded by the butter for the first thirty-six days of the experiment was associated with an epinephrine-content of the adrenal glands which was not proportionate to their increase in size, and was therefore within the limits of health, or slightly below these limits. On the other hand, in birds receiving no butter, the lack of protection against serous effusion, during the same period of 36 days, was associated with an epinephrine-content of the adrenal glands which was approximately proportionate to their increase in size, and was therefore in excess of that of health.

From the thirty-seventh day of the experiment onwards, pigeons receiving butter in addition to the autoclaved rice showed a case incidence of *wet* polyneuritis, an hypertrophy of the adrenal glands, and an epinephrine-content of these organs as great or greater than those receiving no butter. In these circumstances pigeons exhibiting serous effusions conformed to the rule that *wet* polyneuritis is invariably associated with an epinephrine-content of the adrenal glands approximately proportionate to their increase in size. To this rule my results have provided no exception.

Further, it will be observed from Table IX that, among pigeons which survived the dietary of autoclaved rice *plus butter* for longer than 37 days, the minority, which exhibited no evidence of serous effusion, had an epinephrine-content of the adrenal glands no greater than that found in health, and usually considerably

less; the majority, on the other hand, whose enlarged adrenals exhibited a high epinephrine-content, invariably presented evidence of œdema.

4. Histological Observations.—These did not differ appreciably from those described in Chapter XVII. Congestion of the medullary areas of the organ, sometimes so extensive as to have destroyed them in large part, was the chief histological feature (Figs. 66, 67). The number of chrome-staining granules in non-congested portions of the medulla was smaller than that usually encountered in health. No study of the cortical lipoid could be made, nor of the adrenals from cases of *wet* polyneuritis resulting from the dietary of autoclaved rice plus butter. Such a study will reveal most interesting information.

5. The Effects of Coconut Oil on the Incidence of Œdema.—Ten pigeons were fed on autoclaved rice to which coconut oil was added in the proportion of one-sixth of an ounce per bird per diem. All ten developed polyneuritis columbarum; five presented evidence of œdema and five did not. The incidence of œdema, 50 per cent., was thus as high as in pigeons fed exclusively on autoclaved rice. No protection against œdema is afforded by coconut oil. The adrenal medulla was invariably much congested, suggesting that the fat component of the food is responsible for this congestion both in birds receiving coconut oil and in those receiving butter.

6. To what is the Protection due which Butter affords against Serous Effusion?—An exclusive diet of autoclaved rice, in addition to its total lack of all three classes of vitamins, is deficient in protein, in fats, and in salts, and excessively rich in carbohydrates. In birds receiving butter in addition to the rice the deficiency of vitamin A is made good. The slight casein-content of the butter reduces the deficiency of protein, the excess of starch remains the same, while the excess of fats adds to the burden on the oxidative resources of the body. It may be, therefore, that the added casein is responsible for the relative freedom of butter-fed pigeons from œdema. On the other hand, butter may contribute to the deficient dietary some substance of a vitaminic nature which is the responsible factor, or both protein and vitamin may be concerned in the protection which the butter affords. Fat *per se* does not appear to possess a favourable influence in this regard, since an equal amount of coconut oil afforded the birds no protection. The experiments now to be detailed provide some additional evidence on these points.

7. Butter varies in its Capacity to Protect against Œdema.—(*a*) In Table VII, Appendix I, the results of an experiment are given in which twenty cases of polyneuritis columbarum were produced as a result of a food mixture of autoclaved rice plus fresh butter and onions. The butter used was made from the milk of cows fed on *green* fodder. It was added to the autoclaved rice in the proportion of one-twelfth of an ounce per bird per diem. Two cases, or 10 per cent., presented serous effusion at autopsy.

(*b*) During the dry months of the year in the part of the Nilgiris Hills where my laboratory was situated, the local cows were dependent for food on what they could pick up from the hill-sides. Fodder was not only scanty, but such

as was available was dried up by the heat and drought. During these months I placed twenty pigeons on a deficient food mixture consisting of autoclaved rice plus butter and fresh onions. The butter was made from the milk of cows fed on the dry parched fodder; it was added to the rice in the same proportion as in the foregoing experiment—one-twelfth of an ounce per bird per diem. The onions also were added in the same amount as in the previous experiment. Seven pigeons, out of twenty developing polyneuritis in consequence of this dietary, were found to present evidence of œdema at autopsy. Thus 35 per cent. of pigeons receiving the butter made from the milk of the cows fed on *dry* fodder developed œdema, as compared with 10 per cent. in the case of pigeons receiving the butter made from the milk of cows fed on *green* fodder.

In these two experiments the composition of the deficient food mixture was to all appearances the same; the rice was autoclaved at the same temperature and for the same period, the onions and butter were provided in like quantity. Thus any influence in inhibiting the assimilation of protein, or in promoting the retention of water in the tissues, which may have been exercised by the excessive starchy component of the food, was exercised in equal degree in both experiments. Similarly, any protective action on the part of the small casein-content of the butter, and any influence exerted by the vitamin-content of the onions, was, so far as one can say, exercised in equal measure in both experiments. The conclusion thus appears to emerge that the greater incidence of œdema in the one case was due to the lesser content, in the butter from *dry*-fodder-fed cows, of some substance other than protein or fat; a substance which was present in considerably higher proportion in butter from *green*-fodder-fed cows. Suspicion at once falls on lipochromes, or on substances associated with lipochromes, since the *dry*-fodder butter was noticeably deficient in these pigments; that is to say, on vitamin A or on a substance allied to it.

(*c*) Further evidence is provided by a pigeon cured of polyneuritis by the injection into the crop, at the height of the disease, of a vitamin extract made by extracting the yolks of four eggs with acidulated alcohol. The bird had suffered from the cerebellar type of the disease in its most typical form, and from profuse diarrhœa. Within twenty-four hours of receiving the extract it was relieved of the diarrhœa and of all acute nervous symptoms, with the exception of slight residual paralysis. The autoclaved rice diet was continued, and the bird remained for four days in apparently restored health. It then died suddenly. At autopsy it was found to have suffered from an extensive hydropericardium; the pericardial sac wall was quite opaque, and collapsed, like a half-empty bag, over the atrophied heart. The sac still held 1 c.c. of clear fluid, but it was obvious that it must have held, as my extensive experience of such cases justifies me in saying, at least 5 c.c. of fluid at the time the vitamin extract was administered. The adrenal glands appeared normal, and weighed only 25 milligrams, a circumstance so exceptional in cases of hydropericardium that I am satisfied not only had the vitamin extract caused the hydropericardium to disappear in major part, but it had caused the adrenals also to diminish in size to within normal

limits. Such an isolated observation is not in itself conclusive, but, taken in conjunction with other data, it is evidence to which due importance must be attached.

Beyond this point my own investigations do not go. They admit of this conclusion, namely: there exists in butter some substance, possibly vitamin A, or a substance closely related to it, which is capable of affording a certain degree of protection against œdema in pigeons fed on autoclaved rice. It cannot wholly protect against œdema, as vitamin B would appear to protect against alimentary polyneuritis; but there can, I think, be no doubt that its absence favours the production of œdema resulting from acute inanition or from chronic inanition, consequent on protein shortage and deficiency of vitamin B.

(*d*) The conclusion thus reached is in conformity with the therapeutic observations of Vedder,[1] which led him to believe that his extract of rice polishings contains two specific vitamins: "one which cures *wet* beri-beri, and one which cures *dry* beri-beri."

(*e*) The data so far brought forward have provided no positive information as to the effects of the absence of a hypothetical "anti-œdema" substance from a food otherwise well balanced. Negative evidence is afforded by the monkeys, fed on autoclaved food and onion, which did not develop œdema. In consequence of this negative result one is led to expect that, as in the case of all vitamins, a well-balanced dietary will delay markedly the onset of symptoms due to want of a hypothetical anti-œdema substance. Evidence in this connexion is available from the literature. Harden and Zilva[2] report that they observed œdema in one of three monkeys fed on a diet deficient in vitamin A, but considered to be complete in other respects with the exception of a low fat content. The diet consisted of a daily ration of 250 to 300 grams of boiled polished rice, 10 grams of marmite, 2 grams of salt mixture and 4 c·cm. of lemon juice; it was thus somewhat rich in starch as well as deficient in fat and in vitamin A. This observation carries the inquiry a stage further, and provides additional evidence that vitamin A is the possible "anti-œdema factor" above referred to. It shows that, when this vitamin is absent from a dietary that contains a sufficiency of vitamin B but is rich in starch and deficient in fat œdema may occur.

(*f*) Further evidence from the literature relates to "war or hunger œdema." Menzies[3] found that "hunger œdema" was present in English poor-law and insane institutions during the winter of 1917–18. He reports that "calories were sufficient to sustain life, but the food had to be presented in the form of well-cooked soups, stews, or puddings, while fresh milk was in great deficiency. The cases were relieved when the spring vegetables came into season, and definitely abolished later in the year by the fortunate purchase of 50 gallons of cod-liver oil, then almost unprocurable, and later on by the release of a special cheese ration by the Central Food Control." Here the deficiency of vitamin A, together with a high fluid intake, were the responsible factors in the production

[1] *Beri-beri*, London, 1913.
[2] *Lancet*, London, 1919 (Nov. 1), No. 2, p. 780.
[3] *Lancet*, 1920 (Feb. 7), p. 350.

of the œdema. Beyermann [1] also reports that, in twelve cases among the insane, the addition of fresh vegetables to the ordinary diet caused the disappearance of malnutritional œdema.

(*g*) Kohman [2] has brought forward evidence to show the importance of deficiency of protein in the causation of œdema. She found, when rats were fed on a diet of carrots, which is deficient in suitable protein although rich in vitamin A, that œdema is prone to occur. Indeed, all the available evidence, provided either by experiment or by clinical study of such malnutritional œdemas as " famine dropsy," " epidemic dropsy," " war œdema," or " hunger œdema," go to prove the high importance of Cornish's [3] conclusion, emphasizing the predominant importance of food deficient in protein in the causation of such œdemas. Throughout this volume, if one fact more than another be pre-eminent, it is the interdependence of vitamins and of proximate principles of the food on each other. So it seems to me to be with the anti-œdema factor: its action is more pronounced in the presence of an ill-balanced food; less so in the presence of a well-balanced food. A sufficiency of protein, in the absence of vitamin A, does not render a food safe in so far as œdema-production is concerned, nor does a sufficiency of vitamin A in the absence of a sufficiency of protein. In the present state of knowledge it would be as unwise to ignore a vitaminic influence in the production of œdema as to ignore the influence of other substances requisite for perfect nutrition.

Rôle of the Adrenals in Œdema-production.—The question now arises: Does great enlargement of the adrenal glands, with great increase in their epinephrine-content, play a part in œdema-production or is the œdema the cause of these adrenal changes? I shall not attempt to answer it, but confine myself to summarizing the existing evidence: (1) In the absence of an anti-œdema substance from a dietary disproportionately rich in starch and deficient in vitamin B, great enlargement of the adrenal glands, with an increase in their epinephrine-content, corresponding approximately to their increase in size, occurs in pigeons at a time when all other organs—the pituitary body excepted—undergo atrophy. (2) In these circumstances about 85 per cent. of pigeons whose adrenal glands showed these changes had evidence of œdema, and all cases having evidence of œdema showed these changes. (3) When this anti-œdema substance was provided in the deficient food, the enlargement of the adrenal glands also occurred, but it was not then associated, as a rule, with an increase in their epinephrine-content; coincidentally there was a marked drop in the incidence of œdema. (4) In exceptional cases, in these circumstances, when the enlargement of the adrenal glands was associated with an increase in their epinephrine-content corresponding approximately to their increase in size, œdema did occur despite the presence of the anti-œdema substance in the dietary. It seems probable that in these cases the protective substance was not assimilated,

[1] *Nederlandsch. Tijdschr. v. Geneesk. I*, 1919 (June 28), p. 2265.
[2] *Amer. Jour. Physiol.* (Baltimore), 1920, LI, No. 2, p. 378.
[3] Cornish, R.W., Reports *re* Indian Famine, 1877–8.

owing either to almost complete loss of appetite and abstinence from food, or to changes in the gastro-intestinal tract interfering with its adequate absorption. (5) Vitamin extracts of egg-yolk or of rice-polishings contain a substance which dispels the œdema, and this substance appears to restore simultaneously the adrenal glands to a normal size. (6) Medullary hypertrophy of the suprarenal glands, and increase in their epinephrine-content, occurs in beri-beri (Ohno).[1] It is obvious from these facts that a very intimate relation exists between the presence of œdema and an abnormally high content of epinephrine in the adrenal medulla, when associated with malnutrition of the tissues.

There are other facts of interest in this connexion relating to the adrenal cortex. Avitaminosis causes an almost complete disappearance of lipoids from the cortex of the adrenal glands (Cramer),[2] and it seems probable that in pigeons the addition of butter to the deficient dietary of autoclaved rice prevented, to a considerable extent, this disappearance. That this view is correct is shown by recent observations of Cramer,[3] who finds an extensive depletion of lipoids from both the adrenal cortex and glandular adipose tissue when there is deficiency of vitamin A. With deficiency of vitamin B this severe depletion does not occur, although the distribution of lipoids in the adrenal cortex becomes irregular; in these circumstances the glandular adipose tissue continues to hold a fair load of lipoid. On the other hand, when both vitamin A and vitamin B are deficient there is a great disappearance of lipoid from both the adrenal cortex and the glandular adipose tissue. When Cramer's observations are taken in conjunction with my own, they appear to indicate that the occurrence of œdema is associated with a dispersal of lipoid from the adrenal cortex and with an accumulation of epinephrine in the medulla. That is to say, œdema-production is associated with profound disturbance of lipoid metabolism as well as with profound disturbance in function of the adrenal cortex. Other evidence pointing to disturbance of lipoid metabolism is to be found in the great reduction of the lipoid-content of the blood which occurs in "war œdema" (Maase and Zondek[4]; Knack and Neumann[5]) and in beri-beri (de Langen and Schut[6]). These are among the points which come up for consideration in attempting to interpret the significance of the adrenal changes associated with œdema. They represent, however, but one aspect of a vaster problem which concerns the metabolic functions of the adrenal glands in general. In what way, for instance, are these organs concerned in the metabolism of protein and in the metabolism of fat? Is the high content of epinephrine, consequent on avitaminosis, related to the dispersal of lipoid from the cortex, or to failure of protein metabolism? Is epinephrine the ash from the cortical fire? Is it a mere excretion, as suggested

[1] Ohno, *Tokyo Igakukac Zasshi* (*Mitteil. d. Med. Gesellsch. z. Tokyo*), 1917, XXXI. 5; Shimbo, *Verhandl. der Japan. Path. Gesellsch. Tokyo*, 1918, VIII. 194.

[2] *Brit. Jour. Exp. Path.*, 1920, I, No. 4, pp. 1–13.

[3] Private Communication to Author, 1920 (Nov. 9).

[4] *Das Hunger-ödem*, Leipzig, 1920.

[5] *Deutsch. Med. Woch.*, 1917 (July 19), p. 901.

[6] *Med. Geneesk Lab. Weltevreden*, 1919, 3rd Series, A, Nos. 2–3, pp. 44–67.

by Gley,[1] or is it a powerful hormone concerned in the control of metabolic processes? A definite answer to these questions is necessary before the true significance of the association of adrenal derangement and œdema can be appraised and, indeed, before the rôle of the adrenal glands in the human economy can be truly evaluated. In the meantime we can conclude that—

In the presence of a diet deficient in vitamins A and B, in protein, and excessively rich in starch, œdema-production is associated with derangement of adrenal function both as to its cortex and as to its medulla. This disturbance of function is evidenced by great enlargement of the glands, dispersal of lipoids from the cortex, and an increased epinephrine-content of the medulla.

Two main facts have emerged from the studies in this and the two preceding chapters:

1. The functional perfection of the adrenal glands is dependent upon the balance of the food and upon the quality and quantity of its vitamins.

2. An intimate relationship exists between the adrenal glands and the metabolic processes of the animal organism.

[1] Gley, E., *Quatre leçons sur les sécrétions internes*, Paris, 1920.

CHAPTER XX

THE HEART AND BLOOD-VESSELS

CARDIAC atrophy is a conspicuous feature of the morbid states resulting from a diet of milled rice (Figs. 13 and 16). This is all the more remarkable since hypertrophy of the heart is the rule in human beri-beri. Thus Ellis (1898) found the average weight of the heart in 125 cases of beri-beri to be 13·37 ounces, while in 204 cases dying from other diseases the average weight was just under 9 ounces.

In " war œdema," on the other hand, the weight of the heart may be as low as 180 grams as compared with 250–320 grams in health (Oberndorfer).

The size of the heart varies considerably *in pigeons* of approximately the same weight and age. In healthy males its weight ranged in a series of 20 birds between 2·4 grams and 3·8 grams, the average being 3 grams. In 15 healthy females the range lay between 1·8 and 3·9 grams, with an average of 2·7 grams. When the weight of the heart is calculated against the body-weight of the birds, it is found to be approximately the same, on the average, in the two sexes: 10·5 grams per kilogram in males, and 10·2 grams per kilogram in females. In cases of polyneuritis columbarum the same wide variations are found, but on a lower level. Thus in males the weight ranges between 1·6 and 3 grams, with an average of 2·25 grams; in females between 1·4 and 3·5 grams, with an average of 2·1 grams. Per kilogram of original body-weight the figure for males is 7·6 grams, and for females 7·6 grams, or the same in both sexes.

Five features strike one in examining the hearts of polyneuritic birds: their small size as compared with those of healthy birds; the frequency of dilatation of the auricles and the right heart; the frequent lack of firmness of the heart's musculature; the degenerated appearance, especially of the auricles; and the comparatively frequent presence of a band of œdema replacing the auriculo-ventricular band of fat. All these are not usually present in the same organ; as a rule its small size is the only conspicuous feature, the auricles dilated with clot being seated like a cap on the atrophic ventricles. It is not uncommon, when hydropericardium is present or when the right heart is much dilated, to find several of these features occurring together. Then, on severing the heart from the great vessels and throwing it into a basin of saline, it may be seen to collapse like an empty bag. Dilatation of the right heart has been almost constantly present with hydropericardium; but there have been a sufficient number of exceptions to make the absence of dilatation a notable feature. Degenerative changes in the heart's muscle are evidenced by the pale colour of its fibres, usually in limited areas, but occasionally throughout its whole extent.

The auricle walls are often very thin, sometimes even transparent in parts. One curious feature which has been observed in many of these hearts, as well as in 50 per cent. of cases dying of inanition, is œdema of the heart's musculature. This is usually confined to the area formerly occupied by the auriculo-ventricular band of fat. The band of œdema may extend round the heart at this point or be confined to certain areas. It is usually associated with great thinning of the auricle walls. In one remarkable case the whole cardiac musculature was œdematous; the surface of the organ was covered with a transparent layer of clear albuminous material, especially well marked at the auriculo-ventricular junction, extending downwards over the anterior surface of the ventricles. In two cases subserous ecchymoses were widely distributed over the ventricular surfaces, the effusion being blood-stained. In both of these an organism, highly virulent for healthy pigeons, and causing, on subcutaneous injection, extensive hæmorrhage into the cardiac muscle and other tissues, was isolated from the heart's blood. Another curious feature found in some cases was the persistent beating of the auricles after the ventricles had ceased to act. This phenomenon is not unusual among laboratory animals, however fed, which have been killed for experimental purposes, but it was more frequently encountered among cases of polyneuritis than among control pigeons killed at the same time. In connexion with the ventricular atrophy in cases of polyneuritis columbarum, as contrasted with the hypertrophy in human beri-beri, the difference in nervous control of the heart in the two species is of interest. In mammals the augmentor nerves act both upon the ventricles and the auricles, whereas in birds they act on the auricles only. The action of epinephrine differs in the two species: it causes the ventricular contraction to be distinctly increased in mammals, and to be distinctly decreased in birds.[1] In the latter the increased arterial pressure caused by the epinephrine is not compensated by the stimulation of an augmentor mechanism in the ventricles.[1] The adrenal hypertrophy occurring in polyneuritis columbarum may be of some significance in this connexion.

It is remarkable that in no case was hypertrophy of the heart, comparable to that found in human beri-beri, observed *in monkeys*. In all categories atrophy was pronounced, being most marked in animals fed on autoclaved food and onions (Fig. 16).

The weight of the heart in control monkeys ranged between 9·37 grams and 14·55 grams, with an average weight, per kilogram of original body-weight, of 4·47 grams. In monkeys fed exclusively on autoclaved rice (adolescent animals) the range of weight was narrow, being from 5·25 grams to 7·3 grams, with an average weight, per kilogram of original body-weight, of 3·53 grams. In those fed on autoclaved rice and butter (adult animals) the weight of the heart ranged between 6·7 grams and 8·82 grams, with an average, per kilogram of original body-weight, of 3·44 grams. In no case did the weight of the heart equal the minimum encountered in controls. Again, in animals fed on autoclaved food plus onion, the weight of the heart ranged between 3·27 and 4·5 grams in baby monkeys, and between 5·8 and 7·8 grams in adult animals; the average weight per kilogram of original body-weight being, in the six animals, 3·03 grams. Only

[1] Paton, N., *Regulators of Metabolism*, 1913.

in monkeys fed on autoclaved food, butter, and onions did the weight of the heart equal in any case the minimum encountered in controls; indeed, no less than three were within the limits of health, being 9·65, 9·88, and 11·57 grams respectively. The remaining two, however, fell far short of the minimum of health, being but 7·4 and 7·5 grams respectively.

Œdema of the auriculo-ventricular junction of the heart, so common in pigeons fed on autoclaved rice, was not encountered in monkeys. Perhaps the most notable observation with regard to the heart in these animals, apart from its atrophy in all categories, was the occurrence in two, fed on autoclaved food and onion, of ecchymoses under its serous surface. In one of these both auricles and ventricles were so affected, in the other the right ventricle only. The former case had four drops of fluid in tne pericardium. This appearance was not found in monkeys other than those fed on autoclaved food and onion. Dilatation of the right heart was not infrequent.

The small size of the heart and the pronounced ventricular atrophy are frequently commented upon in post-mortem records of cases of " war œdema." Among prisoners of war suffering from this malady, the heart, according to Enright,[1] usually weighed from 3 to 5 ounces, as compared with about 9 ounces in health. The small size of the heart in " war œdema " is one of the outstanding differences between this condition and wet beri-beri, as it is between polyneuritis columbarum and beri-beri. It is notable that the cardiac atrophy is much more marked when the food is deficient in both vitamin A and vitamin B. For this reason I am led to suspect that vitamin A has a specific effect on the nutrition of heart muscle (Fig. 16). Œdema of the auriculo-ventricular junction was, according to Menzies,[2] almost universal in cases of " hunger œdema " among the insane. Park [3] also comments on its great frequency in " war œdema."

The Vessels.—Venous engorgement is common, and the great veins are often found at autopsy to be filled with clot. In some cases the intravenous clotting extended into the femoral veins. Changes in the arteries were confined to those already described in the spleen of polyneuritic pigeons. Yamagiwa [4] lays great stress on a state of tonic contraction of the arterioles, which he considers is the determining pathological factor in the production of beri-beri. I have found no confirmation of his observation in the literature, but if it be correct, it is of peculiar interest in connexion with the hypertrophy of the adrenal medulla.

Summary.—The observations recorded in this chapter have a distinct interest for cardiologists, for in view of the high incidence, at the present day, of cardiac disorders which are not always definitely traceable to bacterial agencies, a study of cardiac derangements from the point of view of nutrition seems likely to open up new avenues of knowledge. One important result emerges from these observations, namely: that an adequate supply of vitamin A and vitamin B is essential to the perfect nutrition of the heart. They appear also to have a pointed signifi-

[1] *Lancet*, London, 1920 (Feb. 7), p. 314. [2] Ibid., p. 350.
[3] *Jour. Amer. Med. Assoc.*, 1918 (June 18), LXX, No. 24, p. 1826.
[4] Vedder, *Beri-beri*, London, 1913.

cance in connexion with the cardiac disorder known as "effort syndrome" and with the rheumatic heart of childhood. The former condition is not infrequently associated with faulty feeding, especially in schoolboys, undergraduates, and young soldiers, who indulge in much violent exercise; the latter is more common in the poor than the rich, and develops more frequently in winter than in summer (Poynton).[1] The circumstances under which these cardiac disorders arise suggest that malnutrition, and especially vitamin-deficiency, may play a determining part in their production.

[1] *Brit. Med. Jour.*, 1920 (Dec. 11), p. 882.

CHAPTER XXI

THE KIDNEYS AND BLADDER

The Kidneys in Pigeons.—The kidneys showed but a slight degree of atrophy, as indicated by weight, in consequence of the deficient foods. Macroscopically they appeared to differ little, in the majority of cases, from those of healthy birds. In about 20 per cent. they were congested. Great variation in the weight of the organs was found in both healthy and diseased birds; there was no constant relationship between their weight and the body-weight.

In healthy males their weight ranged between 1·2 and 2·4 grams, with an average of 1·6 grams; in healthy females between 1·2 and 1·9 grams, with an average of 1·48 grams. Their average weight per kilogram of body-weight was 5·4 grams in healthy males, 5·5 grams in healthy females. In cases of polyneuritis columbarum the same wide variations were found. In males the range lay between 1·3 and 1·8 grams, with an average of 1·5 grams; in females between 1·1 and 2·4 grams, with an average of 1·5 grams. Per kilogram of original body-weight, the figure for males was 5·3 grams, for females 5·5 grams.

The largest kidneys were usually those showing most evidences of congestion. No connexion could, however, be established between the state of the kidneys and the presence of œdema, for while the largest and most congested kidneys were often found in birds with the largest adrenals, and therefore with evidence of œdema, large and congested kidneys were equally common in birds with small adrenals and no evidence of œdema. The histological changes consisted in congestion, and less commonly mild degrees of cellular degeneration. Some degree of congestion was, on histological examination, an almost constant feature. It was sometimes slight and confined to engorgement of the vessels, but more often it involved the glomerular tufts, or gave rise to hæmorrhagic extravasations of greater or lesser degree between the tubules (Fig. 75). The secretory epithelium often presented little or no change, or but slight degrees of cloudy swelling. Occasionally specimens were encountered in which the cells had undergone extensive necrosis. Cases presenting evidences of œdema did not differ materially from those without œdema. In general the pathological changes were not so severe as to impair appreciably the functional capacity of the organ; there were, however, exceptions to this rule.

The Kidneys in Monkeys.—The gravimetric observations with regard to the kidneys of these animals are peculiar (Fig. 16). In those fed on autoclaved

rice dietaries the average weight was greater than in health; in those fed on autoclaved food dietaries it was less than in health. Among the latter the atrophy was most marked in animals deprived of both vitamin A and vitamin B. The urine was examined in a number of cases, but with negative results, both as regards albumen and sugar. The naked-eye appearance of the kidneys presented no noteworthy features; in a few they appeared to be anæmic. No histological examinations could be undertaken.

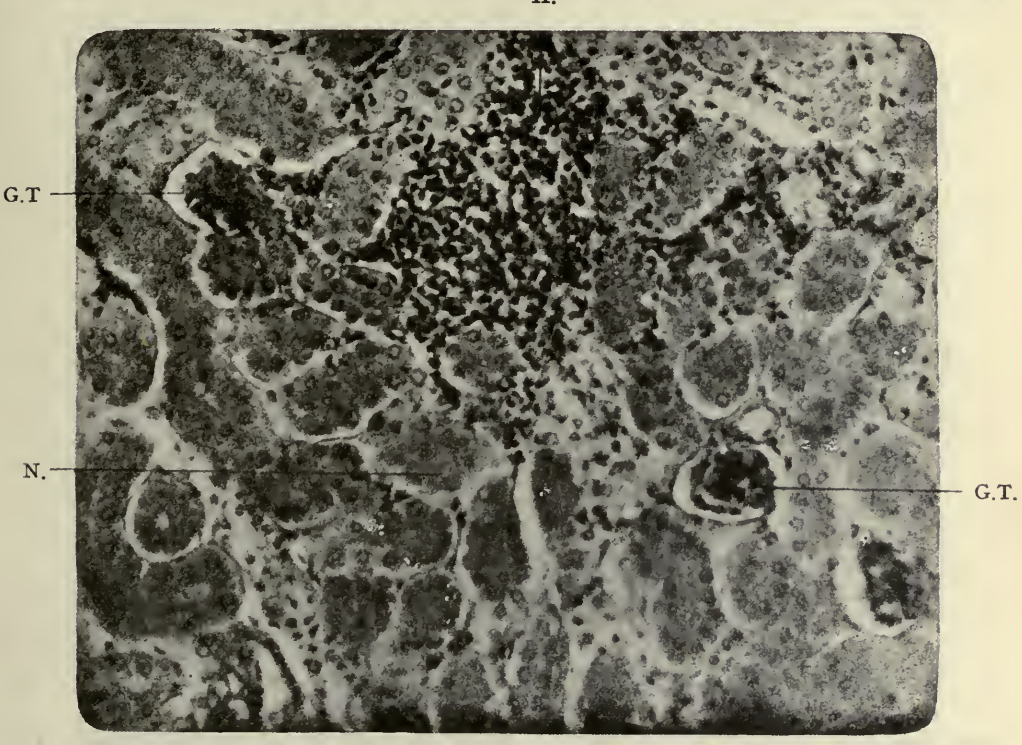

FIG. 75.—Section of kidney from a case of experimentally-produced polyneuritis columbarum, × 165. Note marked congestion and hæmorrhage (H), engorgement of glomerular tufts (G.T.), necrobiosis of a small proportion of cells (N), slight cloudiness of tubular cells.

Summary.—These observations with regard to the kidneys, although incomplete, provide sufficient evidence that the organs are not greatly deranged in consequence of food deficiency, and that malnutritional œdema is not due to organic renal change. The rarity of the occurrence of albuminuria in wet beri-beri and in "war œdema" is further proof of this fact. How far the œdema may be due to inhibition of renal function consequent on deranged endocrine action is a matter that requires investigation.

It would appear, from experiments carried out by Gaglio,[1] that vitamins are present in healthy urine. He found that the administration of 3 to 4 c.c. of

[1] *Il Policlinico*, Sez. Prat., 1919 (Nov. 23).

human urine had a rapidly curative effect on the polyneuritis of pigeons. When the urine was given two or three times a day the birds showed a remarkable improvement, and the following day were quite cured. The nervous symptoms, however, reappeared later in an attenuated form if the polished rice was persisted with.

The Bladder.—The effects of a scorbutic diet on the bladder were studied in five guinea-pigs. The animals were fed on crushed oats and autoclaved milk. The appearances presented by the bladder were contrasted with those in healthy

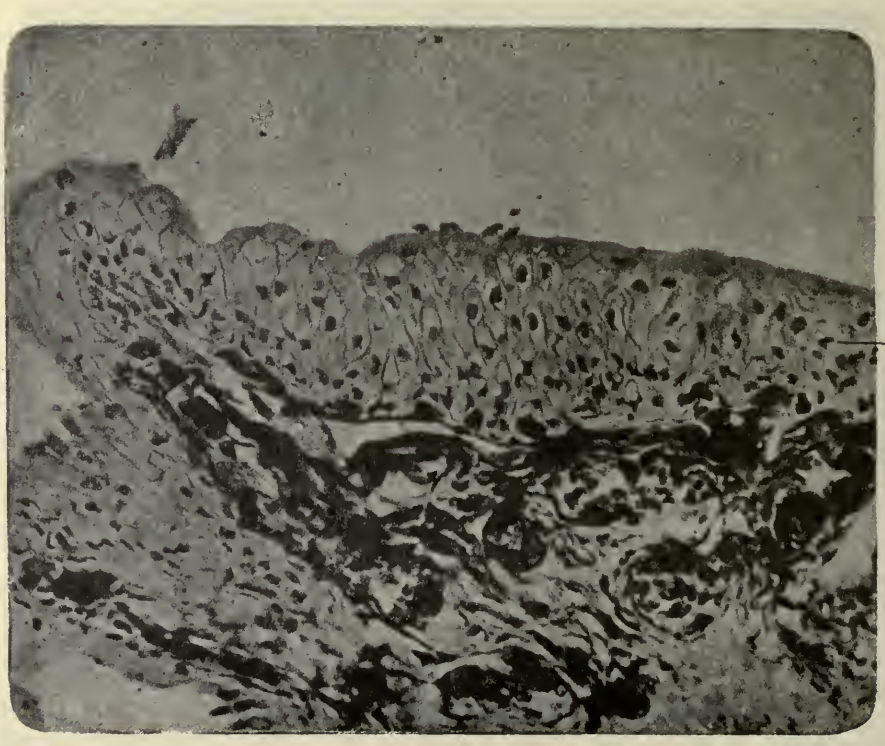

FIG. 76.—Section of mucous membrane of bladder from a healthy guinea-pig, × 165. Note normal tessellated appearance of epithelial lining (E) and darkly-staining nuclei of cells. Specimen stained with iron hæmatoxylin.

guinea-pigs fed on crushed oats, autoclaved milk, and abundance of green vegetables. The changes observed in the bladder of animals receiving no vegetables were, therefore, due to the want of these in the food; that is to say, to the want of vitamin C, of inorganic salts, and possibly of other substances requisite for the maintenance of perfect health.

The animals fed on the scorbutic diet died within periods varying from 19 to 29 days. Their average initial weight was 532 grams; the average loss of weight amounted to 152 grams. Only one developed clinical signs of scurvy; this animal had survived the deficient dietary for 29 days. In two only were naked-eye evidences of a scorbutic state obvious at autopsy; one of these survived the deficient dietary for 29 days, the

other for 25 days. In all hæmorrhagic infiltration of the organs—the adrenals, the kidneys, the liver, the intestines—was present in greater or lesser degree on histological examination. The heart's blood of the guinea-pig, which exhibited clinical evidences of scurvy, yielded on culture at autopsy a coliform organism. The epinephrine-content of the suprarenal glands in this animal was very low.

Clinical Evidences of Derangement of the Bladder.—Hæmaturia was observed in one animal only; in this the clinical evidences of experimental

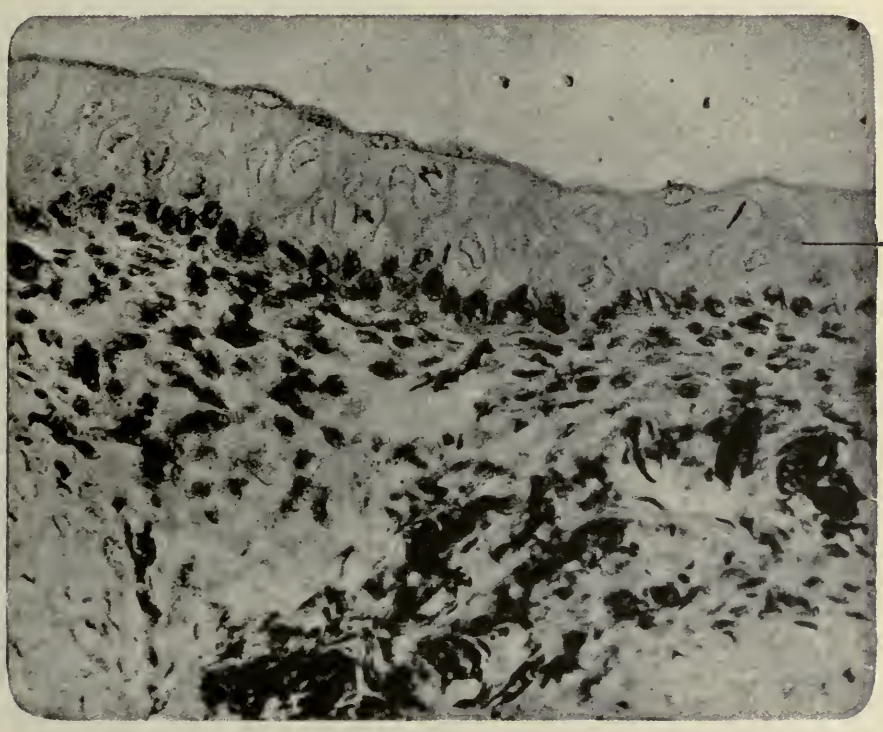

FIG. 77.—Section of mucous membrane of bladder from a guinea-pig fed on a scorbutic diet of crushed oats and autoclaved milk, × 165. Note loss of tessellated appearance of epitheliai cells (E), swelling of cells and nuclei, loss of staining characters—due to disappearance of nuclear chromatin—vacuolation of cells around the nuclei. Specimen taken from a non-infiltrated area of the mucous membrane. Stained with iron hæmatoxylin.

scurvy were well marked. In the four remaining animals hæmaturia was not observed. The urine was not examined microscopically; it seems probable, therefore, that a slight degree of hæmaturia may have occurred in one other case, although not detected clinically.

Naked-eye Evidences of Derangement of the Bladder.—At autopsy the bladder was empty and tightly contracted in all cases. In two it resembled an acorn set in a thick-lipped cup. This appearance was due to œdematous swelling of the tissues around the neck of the bladder.

Engorgement of the vessels with subperitoneal ecchymoses was a prominent

feature in four cases. In some the congestion was more marked at the apex, in others at the base. On opening the bladder and examining the mucous surface with the hand-lens, congestion of its mucous membrane, with patchy ecchymoses at various points, was present in greater or lesser degree in all cases. The congested and ecchymotic areas were of unequal distribution and of varying extent in different animals.

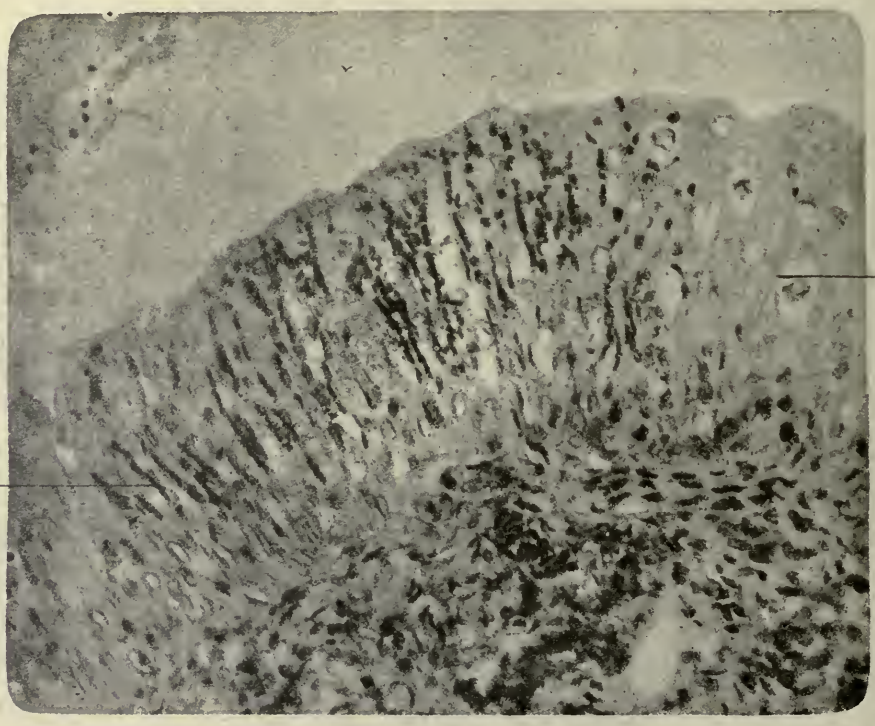

FIG. 78.—Section of mucous membrane of bladder from a guinea-pig fed on a scorbutic diet of crushed oats and autoclaved milk, × 165. Note loss of tessellated appearance of epithelial cells (E), swelling of cells, vacuolation around nuclei, loss of staining characters of nuclei, complete disappearance of nuclei from certain cells, and linear distribution of hæmorrhagic infiltration (H.I.) between the epithelial cells. The epithelial covering is considerably thicker than in health, due to the swelling of the cells and to hæmorrhagic infiltration between them. The specimen represents the appearance seen in several areas of the epithelial lining in two out of five animals. A third animal showed the same changes in lesser degree. All three animals exhibited no *clinical* evidences of scurvy and no hæmaturia. Specimen stained with iron hæmatoxylin.

Histological Evidences of Derangement of the Bladder.—The histological changes consisted in (1) congestion of all coats, with hæmorrhagic infiltration of the mucous membrane; and (2) degenerative changes in the epithelium of the mucous membrane.

The vessels of the bladder walls were intensely engorged in four cases. Extravasation of blood-corpuscles into the submucous and muscular coats, and between the epithelial cells of the mucous membrane, was an almost constant feature

(compare Figs. 76, 77, 78, and 79). This extravasation was of varying degrees of intensity in different animals and at different parts of the bladder wall; it was not present at every area of the mucous surface, but was confined to certain points, the intervening areas showing little or none (Fig. 77). In one animal hæmorrhagic infiltration was found at only two points, and was of lesser degree than that seen in Fig. 78. This figure typifies the appearances seen at several

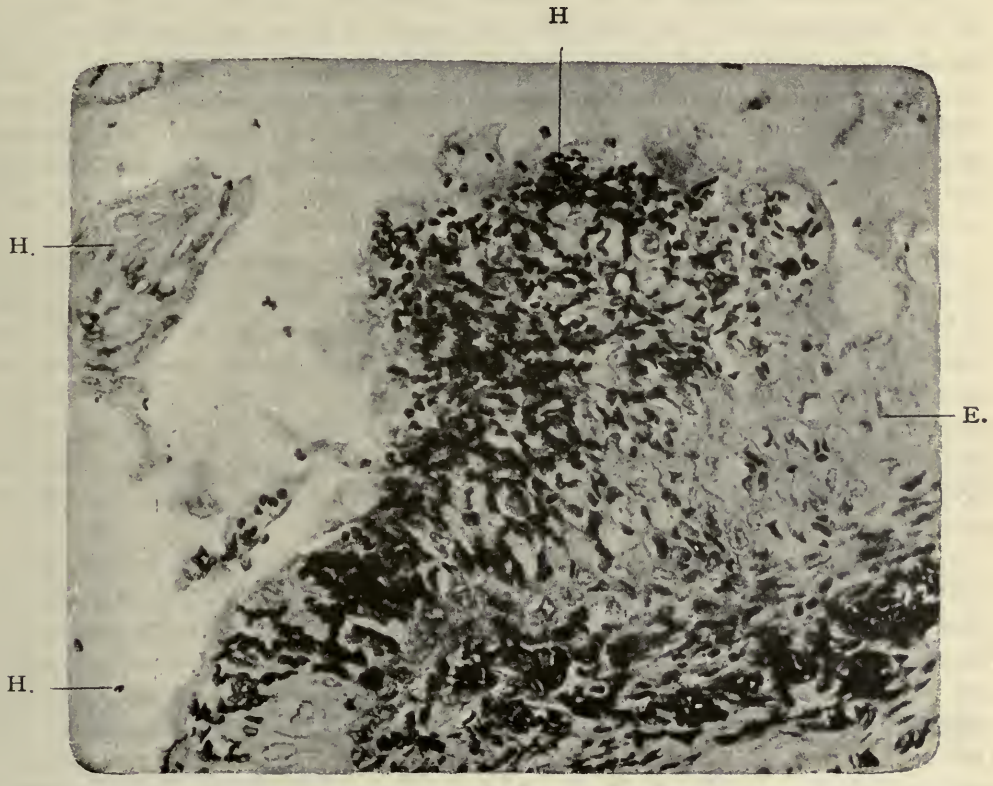

Fig. 79.—Section of mucous membrane of bladder from a fourth guinea-pig fed on the same scorbutic diet, × 165. Note same general appearances as in Fig. 78, but in more marked degree. Hæmaturia was not observed during life, but may have been missed as the urine was not examined microscopically. This animal exhibited no clinical signs of scurvy, although at autopsy *naked-eye* evidences of this state were present. Specimen stained with iron hæmatoxylin.

points of the lining epithelium in two other animals. Fig. 79 illustrates the degree of hæmorrhagic infiltration in a fourth and fifth; in one of these hæmaturia was a clinical feature of the case. In animals showing the lesser degrees of hæmorrhagic infiltration, the infiltrating corpuscles either did not reach the marginal layer of epithelial cells, or, having reached it, were extruded into the lumen of the viscus in but small numbers. In the more pronounced degrees of hæmorrhagic infiltration, blood-corpuscles were extruded into the cavity of the bladder in larger numbers, or in such quantity as to constitute actual hæmorrhages

(Fig. 79). It will be noted that the hæmorrhagic infiltration often caused the epithelial lining to bulge into the cavity of the bladder at the points where it occurred (Fig. 79). The various stages in the hæmorrhagic process are well shown in the photo-micrographs and call for no further description. Congestion of the submucous and muscular coats was present in greater or lesser degree in all cases.

Degenerative changes in the bladder epithelium consisted in (1) swelling of the epithelial cells; (2) swelling of the nuclei of these cells and loss of their staining characters; and (3) desquamation of degenerated epithelial cells. These changes are sufficiently well illustrated by the photo-micrographs; they require no further description. Fig. 77 is introduced to illustrate an area of the bladder mucous membrane where no hæmorrhagic infiltration of the epithelial covering was present. In this the degenerative changes in the epithelial cells are well seen.

Summary.—Considered from the clinical point of view, these observations afford an explanation of the comparatively frequent occurrence of hæmaturia in human scurvy. They indicate that this symptom, which is usually a late manifestation of the scorbutic state in man, is sometimes the result of an extreme degree of congestive and degenerative change in the mucous coat and epithelial lining of the bladder. They indicate also that congestive states of the bladder may occur in guinea-pigs, fed on a scorbutic diet, which exhibit no obvious clinical evidences of scurvy during life, and little or no naked-eye pathological evidences of this malady after death.

Congestion of the bladder without clinical evidences of hæmaturia may, then, be regarded as a pre-scorbutic process in guinea-pigs. This being so, a point of practical importance to the physician is to ascertain, by clinical and therapeutical observation, whether congestion of the bladder may not be so produced in man, and if so, whether certain abnormalities of micturition may not sometimes be evidences of a pre-scorbutic state in human beings, especially in children. In this connexion it is of great interest to note that enuresis nocturna became more prevalent—according to Pese [1]—during the war. He found that 30 per cent. of all the small children and 10 per cent. of the older children suffered from it in the children's asylum at Breslau. Rubner [2] also comments on the tendency to polyuria noted in the German population in consequence of substandard diet. Interesting also in this connexion is the study of enuresis by Grover,[3] who found that the underlying cause of enuresis is neuro-muscular fatigue—which is itself one of the cardinal effects of food deficiency.

[1] *Jahrbuch für Kinderheilkunde*, Berlin, 1920, XCI, No. 5, p. 357.
[2] *Jour. Amer. Med. Assoc.*, 1919, CXXIII, No. 3, p. 168.
[3] Grover, J. I., *Jour. Am. Med. Assoc.*, 1918 (Aug. 24), LXXI, No. 8, p. 626.

CHAPTER XXII

THE NERVOUS SYSTEM

The Brain.—*In pigeons* a slight loss of weight of this organ occurs in both males and females in consequence of an exclusive diet of rice.

In healthy pigeons the weight of the brain ranges in males between 1·7 and 2·08 grams, the average being 2 grams; in healthy females between 1·6 and 1·9 grams, the average being 1·8 grams. When calculated against the body-weight of the birds, the weight of the brain per kilogram is approximately the same in both sexes: 6·9 grams in males and 7 grams in females.

In cases of polyneuritis columbarum resulting from an exclusive diet of rice, the same variations in the weight of this organ are observed as in health. In males the range lies between 1·8 and 2·09 grams, with an average of 1·9 grams; in females between 1·5 and 1·9 grams, with an average of 1·8 grams. The weight of the organ per kilogram of original body-weight is 6·8 grams in male polyneuritic pigeons, 6·6 grams in female polyneuritic pigeons.

In cases of polyneuritis resulting from a dietary of rice, butter, and onions, the average weight of the brain per kilogram of original body-weight is greater than in health, or in birds fed exclusively on autoclaved rice, being 7·2 grams as compared with 6·9 grams in health, and 6·7 grams in pigeons fed exclusively on rice. When, on the other hand, butter is added to the natural food of healthy birds, the weight of the brain is less than in healthy birds receiving no butter, and markedly less than that of pigeons receiving butter with the deficient food, being but 6·2 grams per kilogram of body-weight. This remarkable effect of butter on the weight of the brain has been found also in monkeys.

The macroscopical appearances of the brain and its membranes as seen in polyneuritic pigeons are by no means constant. Hyperæmia of the meninges is occasionally present, more rarely the hyperæmia also affects the brain substance. On the other hand, the brain and its membranes may present quite normal appearances, or the brain substance may be of a peculiar whiteness similar to that so constantly seen in inanition, and indicative of pronounced anæmia. Perhaps the most frequent evidence of disease is softening. This increased diffluence has been observed in a considerable proportion of cases. I was unable to find, from macroscopical examination, any constant gross anatomical appearances peculiar to those cases in which brain symptoms were marked. Anæmia and softening have been as frequent features as hyperæmia.

Points of difference in symptomatology between experimentally-produced polyneuritis and human beri-beri are the convulsive seizures and the pronounced inco-ordination which characterize the avian form of the malady.

The limitation of these symptoms to birds has led many to doubt the fundamental identity of the morbid state in Aves and in Man. Richter has investigated these points, and found changes indicative of progressive degeneration of nerve-cells, especially in groups of cells in the corpus bigeminum (optic lobe) on both sides, the large cells being swollen and vacuolated. He came to the conclusion that in pigeons the clinical picture is that of a severe disturbance of the centre of gravity, due to derangement of function of groups of cells within the sphere of influence of the cerebellum.

In monkeys the gravimetric method of observation followed in these studies has yielded remarkable results in the case of the brain (Fig. 17). The weight of the organ is not strictly comparable in all four classes of deficient dietaries: it varies widely at different age-periods in man, and no doubt varies in like manner in monkeys. The controls are, however, comparable with animals fed on autoclaved rice and butter, and with those fed on autoclaved food, butter, and onion; the age of the animals in these three categories being approximately the same. In monkeys which received butter with the deficient food, in an amount equal to that added to the food of controls, the weight of the brain per kilogram of original body-weight was considerably greater than in controls, being markedly so when the deficient food was excessively rich in starch, an observation which confirms that already recorded in pigeons. We have seen that, when control pigeons received butter in addition to their natural food, the average weight of the brain was 6·2 grams per kilogram of body-weight, and that, when butter was added in the same proportion to a dietary of autoclaved rice, the corresponding figure was 7·2 grams, or an increase in weight amounting to about one-seventh part of the weight of the organ. In monkeys the corresponding weights are, for healthy animals, 28·8 grams, and for those fed on autoclaved rice and butter, 32·4 grams; or, again, an increase of approximately one-seventh part of the organ's weight. It appears to be more than a coincidence that in both species an excess of fats should, in the absence of vitamin B when associated with deficient protein intake and excess starch, cause a similar increase in weight of the brain. It may, then, be taken as established that the weight of the brain tends to be increased in consequence of a dietary which possesses these faults. This result indicates that the brain is capable of considerable variations in weight, and, it may be presumed, in size, dependent on the composition of the food. The importance of this observation with respect to the occurrence of headaches, mental confusion, lack of concentration, and other evidences of mental disorder would appear to be considerable. The influence of diet on the causation of mental disorder has been emphasized by Mercier,[1] and the observations here recorded appear to provide the experimental proof of his contentions. He found that headache, lack of power of concentration, and impairment of memory were frequent consequences of a dietary excessively rich in fats and carbohydrates; and that deficiency of meat was a potent cause of mental confusion. He records a recovery or amelioration rate in such cases of about 94 to 95 per cent.

[1] *Lancet*, London, 1916, March 4, pp. 510–13, and March 11, pp. 561–5.

following on the correction of the dietetic faults. The observations of Blanton[1] among schoolchildren suffering from malnutrition due to war conditions are equally instructive. In addition to lack of nervous and physical energy, he found them to be inattentive, to exhibit poor or slow comprehension for school-work, to have poor memories, and to present a state of general nervous restlessness. There was also a marked increase in poor, lisping, slurring speech due to retardation or interference of the time co-ordination necessary for good speech.

It seems, then, that the weight of the brain is largely dependent on the quality of the food, and that when protein and accessory food factors of the "B" class are deficient, and carbohydrates and fats are in excess, the brain-weight, and presumably also its bulk, is increased. This change is attributable to alterations in the composition of the blood. Weed and McKibben have recently demonstrated that pronounced changes in the brain-volume can be produced by alterations in the osmotic pressure of the blood.[2] Such alterations were brought about by the intravenous injection of hypotonic and hypertonic solutions. Amongst the factors in the deficient dietaries, employed in these experiments, which are likely to bring about such alterations in osmotic pressure, lack of protein is one. It has been shown (Chapter VIII, Table VIII) that in pigeons fed exclusively on rice polishings, which contain an abundance of vitamin B but are deficient in proteins and calories, an increase in weight of the brain occurs equal to that resulting from a diet deficient in vitamin B and excessively rich in starch and fats. In both instances the chief factor responsible for this change is probably the inadequate assimilation of protein, brought about in the one case by its deficiency in the food and in the other by deficiency of vitamin B and excess of energy-bearing constituents, which interfere with its adequate utilization.

The practical outcome of these observations is the necessity for adjusting the vitamin, protein, starch, fat, and salt balance of the food in cases of headache and mental disorder. An illustration of the utility of this measure has recently been provided by Warnock and Dudgeon.[3] They find that pellagra—itself associated in its origin with defective diet—is the chief cause of mental disorder in Egypt, and that in the management of such disorder, great benefit results from the addition of meat and milk to the diet.

The Spinal Cord.—In the majority of cases of polyneuritis columbarum the spinal cord differs little macroscopically from that of healthy birds. Occasionally it seems to be thinner than usual, and to have retracted from the walls of its bony canal. I have observed no accumulation of fluid in the spinal canal. A few cords have been examined microscopically after treatment by Marchi's method; in these degenerated fibres have been found here and there throughout the section and in the nerve-roots.

The Nerves in Pigeons.—Both sciatics were examined for diagnostic

[1] *Mental Hygiene*, Concord, N.H., 1919 (July), III, No. 3, p. 343.
[2] Weed and McKibben; *Am. Jour. Phys.*, 1919 (May), XLVIII. 531.
[3] Twenty-fifth Annual Report on Government Hospital for the Insane at Abbasayi, 1920.

purposes in a series of sixty-nine pigeons. The nerves were treated by Marchi's method, and examined in teased preparations. The results observed were as follows :

The Sciatics—(*a*) *Controls.*—(1) Typical Wallerian degeneration was present in seven control cases, equal in degree to that seen in many diseased birds. The degenerative change was equally well marked in both nerves in two cases, more marked in one than the other in one case, present in one nerve only in four cases. The number of diseased fibres varied greatly ; from two or three throughout the whole thickness of the nerve up to about one degenerated to every fifteen normal fibres. This higher percentage of diseased fibres was only found in one case.

(2) Lesser degrees of degeneration– " patchy degeneration," confined to limited areas of the tubules, sometimes presenting moderately large droplets of degenerated myelin, oftener represented by darkly-stained fine or coarse granules —were found in five other control cases.

(3) Degenerative changes were thus present in 33·3 per cent. of healthy pigeons, none of which exhibited any signs of nervous disease. These changes were due, in my opinion, to causes other than dietetic deficiency, since the birds received a very liberal dietary of mixed grains, including *mung dal* and sand. In view of this result, it is obvious that degenerative changes in the sciatic nerves of pigeons do not constitute a safe basis on which to estimate the effects of a peculiar dietary on the nervous tissues.

(*b*) *Diseased birds.*—(1) Degenerative changes were present in one or other or both sciatic nerves in thirty out of thirty-four diseased birds, or 88 per cent. These changes ranged from irregularity of outline and diffuse staining of the medullary sheath, to completely atrophic tubules empty of degenerated myelin or containing it only in isolated droplets (Fig. 80). These later stages of the degenerative process were most frequently observed in birds which survived the dietary for the longest period.

(2) I was unable to satisfy myself of the existence of any degenerative changes, detectable by Marchi's method, in four cases. These nerves were classed as normal.

(3) Degenerative changes were present in one nerve and not in the other in three cases.

(4) Degenerative changes were frequently much more marked in one nerve than in the other.

It is remarkable how slight may be the evidence of degenerative change, as demonstrable by Marchi's method, in the sciatics of diseased birds. In some cases, not more than three or four fibres throughout the whole thickness of the nerve could be definitely stated to be diseased. Very rarely about one fibre in five was found to be degenerated. Vedder's estimate of a maximum of 10 to 15 per cent. of diseased fibres has, generally speaking, been my experience. In two cases, however, this estimate was greatly exceeded.

It is evident, from the comparative frequency with which degenerative changes may be found in the sciatic nerves of pigeons in robust health, and from the fact

that certain cases of the experimentally-produced disease in pigeons are so readily and so rapidly curable by the administration of vitamin-containing solutions, that the extent of the nerve degenerations is rarely sufficient to cause permanent paralysis. The paralytic symptoms are mainly functional in character, due to impairment of function of nerve-cells. Death of nerve-cells is the exception, not the rule. No clinical experience is more remarkable than that which is afforded by the case of a bird, one day exhibiting in pronounced degree symptoms of the cerebellar type of the disease with frequent convulsive seizures in which it turns "cart-wheels" backwards, great inco-ordination and astasia, and the next, after treatment, say, with the alcoholic extract of the yolks of four

FIG. 80.—Degenerated nerve-fibres from the sciatic nerve of a case of polyneuritis columbarum.

eggs, capable of flying about the laboratory and of alighting with comparative ease on the edge of a table or other convenient perch. Residual paralysis in such a case is often hardly noticeable. Clearly no extensive amount of permanent damage to the cells of the central nervous system could have occurred when such rapid recovery is possible.

The Vagus.—I have found degenerative changes, usually of a patchy type, in the vagus of nineteen cases of polyneuritis columbarum out of thirty examined. Very occasionally these changes were observed in one nerve only, frequently they were of slight degree, and in three cases only were fibres seen exhibiting the typical Wallerian appearances.

Similar changes have been found in the vagus of control pigeons in six cases; in one of these a single fibre showing typical Wallerian degeneration was found.

The Nerves in Monkeys.—Portions of the femoral nerve or of its branches in the thigh were removed in all thirty-three animals for diagnostic purposes. These were treated by Marchi and Algeri's method for the demonstration of fatty degeneration in the myelin-sheath. The familiar appearances of Wallerian degeneration (Fig. 10) were taken as the criterion of degenerative change. In addition to these appearances, the staining of the myelin-sheath of some fibres was of a more diffuse and patchy character. As, however, such appearances are capable of being produced in nerves from apparently healthy animals, in consequence, it may be, of stretching at the time of removal, no nerve was classed as degenerated unless it contained some fibres exhibiting the characteristic Wallerian appearances. Minute precautions were taken at the time of autopsy to avoid injury to the portions of nerve removed for examination. While, therefore, my estimate of the degree of degenerative changes attributable to the various deficient dietaries may be too low, it is certainly not too high. The incidence of nerve-fibre degeneration in the peripheral nerves of the thirty-three animals was as follows: Controls, nil; autoclaved rice, two; autoclaved rice and butter, one; autoclaved food and onion, four; autoclaved food, butter, and onion, two. It would seem, from these results, that the incidence of nerve-fibre degeneration is largely a question of length of exposure to the dietetic deficiency. While the high percentage of cases exhibiting degenerative changes amongst animals fed on autoclaved food was, no doubt, due to deficiency of vitamin B, it is to be noted that animals receiving no butter in addition to autoclaved food showed a higher incidence of nerve-fibre degeneration than those which received butter. The number of degenerated fibres varied in each case within fairly wide limits. In monkey No. 29, fed on autoclaved rice and butter, two fibres only were encountered which presented typical Wallerian degeneration. In other cases the proportion was considerably higher, a rough estimate of the number of fibres involved being about 5 to 10 per cent. These results indicate that the weakness of the limbs, referred to in the chapter dealing with clinical observations, is to be attributed, in part at least, to degenerative changes in the nervous system. The Wallerian character of the degeneration (Fig. 10) points to degenerative change in certain cells of the central nervous system.

In view of the comprehensive and authoritative work of other observers—notably Richter, Vedder, and Clark—on the histology of the central nervous system both in experimental beri-beri and in the disease as it occurs in man, it has seemed to me unnecessary to repeat it. Enough cases have been examined to convince me of the accuracy of the view they have enunciated, that the paralytic symptoms observed in both avian and in human beri-beri are the result, not of a neuritis, but of a disturbance in function of the cells of the brain and cord. As a rule, degenerative changes in these nerves are not so advanced as to preclude recovery on the substitution of an efficient dietary or on the administration of vitaminic substances in suitable doses. In about 4 to 15 per cent. of nerve-cells, the degeneration is complete and death of their axones results; the extent of

recovery possible and the amount of residual paralysis are dependent on the extent of the permanent damage to nerve-cells. These changes in the central nervous system are in conformity with those which take place in other organs and tissues of the body ; they are no greater, nor are they more important. The fact that their symptomatic manifestations are so readily recognizable has caused undue prominence to be given to them, with the result that no less important pathological processes in other organs have been largely overlooked.

The Sympathetic System.—My examination of sympathetic nerve tissue has so far been confined to the ganglionic plexus of the intestines and to the ganglia

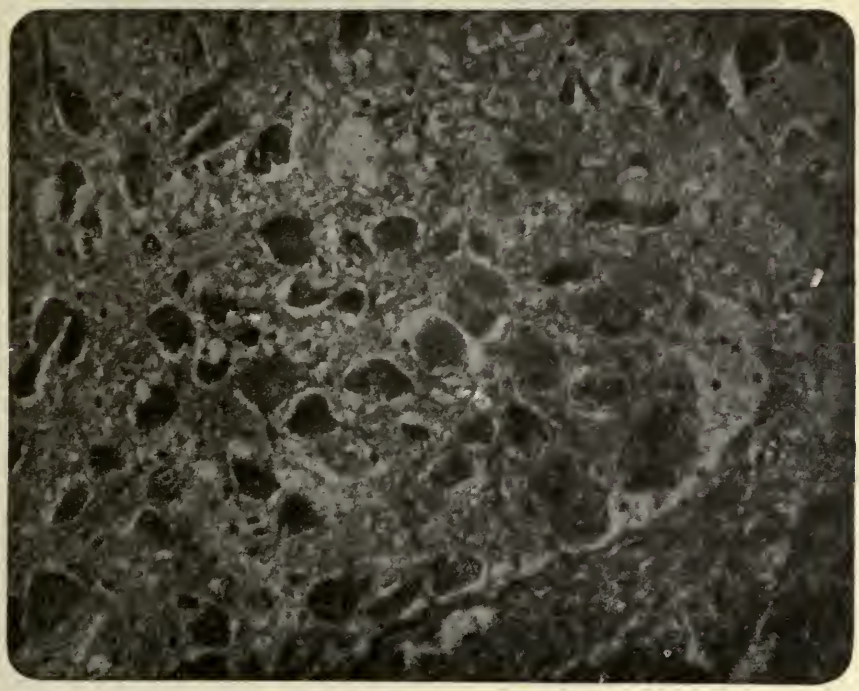

FIG. 81.—Ganglion attached to adrenal glands in pigeons ; from case of polyneuritis. × 250. Note degenerative changes in large cells.

attached to the adrenals in pigeons (Figs. 81 and 82). The staining methods employed were not such as are specially adapted to nerve-cell histology. Nevertheless, the contrast afforded in normal and in diseased birds leaves little room for doubt but that degenerative changes do occur in the nerve-cells of these ganglia.

The histology of the sympathetic system in human beri-beri has been fully studied by Ellis so long ago as 1898. He " examined a large number of nerves removed from patients dying of beri-beri, and met with many cases in which all the peripheral nerves were healthy, but in which some or all of the following nerves were markedly degenerated: viz., phrenic branches of the cardiac and pulmonary plexuses, the splanchnics, branches of the solar and renal plexuses,

branches to the mesentery and vasomotor branches to the aorta, renal, splenic, and tibial arteries." He writes: "in no case of death from beri-beri have I failed to find degeneration of either the phrenic, pneumogastric, or branches from the cardiac plexuses, showing, it seems to me, definitely that death invariably occurs in this disease from implication of some of these nerves." [1]

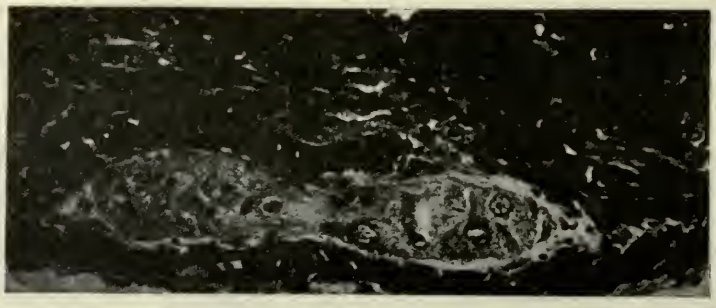

FIG. 82.—Section of upper intestine from a case of polyneuritis columbarum showing ganglion of Auerbach's plexus surrounded by hæmorrhages. The ganglion itself contains a few darkly-stained red blood-corpuscles. Intense hæmorrhagic infiltration of the muscular coats of the bowel surrounding the ganglion is present. The ganglion shows but one normal nucleus.

It is of great interest to find that Ellis thought degeneration of motor nerves was the main lesion in the paralytic form of human beri-beri, whereas in the wet form the sympathetic nerves were more frequently affected. My observations suggest that an intimate relation exists between disordered action of the adrenal glands, which form an integral part of the sympathetic system, and the wet form of this disease. The degenerative changes in the ganglia adherent to the adrenals are of great interest in this connexion.

[1] Vedder, *Beri-beri*, London, 1913.

CHAPTER XXIII

THE FUNCTION OF VITAMINS

HAVING surveyed, in the preceding chapters, the effects of lack of vitamins on the organs and tissues of the body, we are now in a position to form an estimate of the function which these indispensable substances subserve in the human economy. We have seen that—

(1) Vitamins are constant constituents of living tissues. Although they are present in very small amounts, the maintenance of health is dependent on their action.

(2) Vitamins do not themselves contribute to the energy-supply of the body, but they facilitate the utilization by it of the proteins, fats, carbohydrates, and salts of the food.

(3) Proteins, fats, carbohydrates, and salts cannot support life without vitamins nor vitamins without these proximate principles; they are complemental to each other. Without vitamins the body starves.

(4) A distinct relation exists between the amount of vitamins required and the balance of the food in proteins, carbohydrates, fats and salts; the efficacy of the vitamins is dependent on the composition of the food mixture.

(5) A distinct relation exists also between the amount of vitamins required and the rate of metabolic processes.

(6) Each vitamin plays a specific part in nutrition.

(7) It would appear that vitamin A is associated with the metabolism of lipoids and calcium, as well as with the chemical reactions requisite for growth and maintenance.

(8) Vitamin B appears to be associated with the metabolism of carbohydrates, with the chemical reactions and the functional perfection of all cells, and particularly of nerve-cells.

(9) Vitamin C appears to be associated with the metabolism of calcium, and with the chemical reactions of growing tissues.

(10) All vitamins are concerned in the maintenance of the orderly balance between destructive and constructive cellular processes.[1]

(11) One vitamin cannot replace another, although its function may be interfered with by the absence of another.

[1] *38th Rep. Med. Res. Com.*, 1919.

(12) The final result of their deficiency is the same whatever be the degree of deprivation; the greater the deprivation the more rapid is the onset of symptoms due to it, the lesser the deprivation the slower is the onset of symptoms due to it.

(13) Each vitamin exercises a specific influence on the adrenal glands; the effect of their deprivation on these organs is one of the most outstanding features of deficiency disease.

(14) Vitamins influence markedly the production of hormones, and of all external secretions.

(15) There is reason to believe that the capacity of any given cell for work is impaired in proportion to the degree of vitamin starvation.

(16) Vitamins aid the tissues in resisting infection.

(17) Vitamins, especially vitamin B, induce in the human and animal body the desire for food.

(18) Vitamins are one link in a chain of essential substances requisite for the harmonious regulation of the chemical processes of healthy cellular action. If this link be broken the harmony ceases or becomes discord, as it may cease or become discord if any other link be broken.

(19) The place of vitamins in the human economy must be considered in connexion with metabolism as a whole: in connexion with their relation to other essential food requisites, with their relation to the organs of digestion and assimilation, and with their relation to the endocrine regulators of metabolic processes.

Vitamins are as the spark which ignites the fuel mixture of a petrol-driven engine, liberating its energy; the spark is of no use without the fuel, nor the fuel without the spark—nay, more, the efficacy of the spark is dependent in great measure on the composition of the fuel mixture.

I set out to discover how the body goes sick in consequence of deficient foods, which are usually ill-balanced foods. I have found that what happens is this: in the absence of vitamins or in their inadequate supply, neither proteins nor fats nor carbohydrates nor salts are properly utilized; some are largely wasted, while others yield products harmful to the organism. In these circumstances life may be sustained for a longer or a shorter period, during which the body utilizes its reserve stores of vitamins and sacrifices its less important tissues to this end. But there is a limit beyond which such stores cannot be drawn upon, and once this is reached the cells of higher function—secretory, endocrine, and nerve cells—begin to lack vigour, and to depreciate in functional capacity, although the tissues may still hold considerable stores of vitamin. The disintegration process is delayed or hastened, lessened in severity in one direction or increased in severity in another, according as the food constituents are well or ill balanced, and according to the character of their lack of balance.

The most striking example of the altered metabolism of cells brought about by deficiency of vitamins is that afforded by the acute nervous symptoms of polyneuritis avium, and the rapidity with which normal metabolic processes can be re-established by the provision of vitamins; others will be found in the preceding pages. A further example may be given: namely, that provided by the

teeth of guinea-pigs fed on a scorbutic diet. Zilva and Wells [1] have found that pronounced cellular disorganization occurs, with disappearance of nuclei and of interstitial cement substances. This process of disintegration involves nerves, cells, blood-vessels, and odontoblasts, their place being taken by a new firm, fibrous structure devoid of cells, nuclei, or regular arrangement of constituted parts. This is a process with whose fundamental features the pathological changes in the various organs of the body have made us familiar. Lack of vitamins disturbs calcium metabolism ; it puts an end to regenerative processes ; it involves, with respect to the cells of higher function, the functional depression of the many, the death and failure of regeneration of the few. Its cardinal effect is depreciation of cellular function ; and depreciation of cellular function is the foundation upon which disease is built. Extreme deprivation means rapid dissolution and death ; partial deprivation means slow dissolution and disease.

It is this conception of the function of vitamins which holds out such wide promise in the cure of disease due to, or favoured by, their deficiency in the food, for though we cannot restore to life cells already dead, we can restore to normal the depressed functional capacity of the general mass of the body's cells. The conception that vitamins provide the cells of the body with the power—one might almost say the will—to work has this great merit, that it furnishes a working hypothesis on which to frame our treatment.

[1] Zilva and Wells, *Proc. Roy. Soc.*, 1919, XC, B, p. 505.

PART IV

PRACTICAL APPLICATION

CHAPTER XXIV

INTRODUCTION—ACUTE GASTRO-INTESTINAL DISORDERS

INTRODUCTION

In this part of the book I propose to deal only with the practical application of the results reached in the course of my own investigations. The detailed consideration of such common consequences of faulty food as **Defective Teeth, Scurvy,** and **Rickets** does not, therefore, come within its scope. Attention must, however, be directed to the important work of those who have made these subjects their special study. May Mellanby[1] has established a relation between defective teeth and rickets, and shown that the same causal agents are concerned in their production, and the same measures are applicable to their prevention. Zilva and Wells[2] have demonstrated a similar connexion between defective teeth and scurvy. Experimenting with guinea-pigs, they have reached the conclusion that the tooth is one of the first parts, if not the first part, of the system to be affected by deficiency of anti-scorbutic vitamin in the diet, and that even when scorbutic symptoms during life are so slight as to be almost unrecognizable, profound changes in the teeth may have occurred.

More recently Broderick[3] has shown that dental decay is largely dependent on endocrine insufficiency. My own work links up with that of these observers, by demonstrating that dietetic deficiency leads to endocrine insufficiency, and to depreciation of cellular function throughout the body.

The subject of scurvy has lately been exhaustively dealt with by Hess,[4] who has emphasized the important fact that " subacute infantile scurvy " and " latent scurvy " are much more common than has generally been supposed. It is certain that much ill-health in infancy and childhood is due to the want of fresh fruit and vegetable juices. It is well, I think, to credit each of the components of these juices, whether vitamins or salts, with a part in the production of the beneficial result which follows their administration, and not to attribute it solely to the specific effects of one component only.

In connexion with rickets, the work of E. Mellanby,[5] of N. Paton[6] and his collaborators, and of E. Pritchard[7] should be consulted.

[1] *Lancet*, London, 1918 (Dec. 7), p. 767.
[2] *Proc. Roy. Soc.*, 1919, XC, B, p. 505.
[3] *Brit. Dent. Jour.*, 1920, pp. 955–75.
[4] *Scurvy Past and Present*, Philadelphia and London, 1920, pp. 183 et seq.
[5] *Jour. Physiol.*, Proc. LII, xi, and Dec. 1918; *Lancet*, London, 1919.
[6] *Brit. Med. Jour.*, 1918, II. 625. [7] Ibid., 1919, II 627.

Throughout the course of this volume attention has been drawn to practical considerations as they have arisen in connexion with the various organs under study: **Pre-scorbutic States, Endocrine Disturbances, Pancreatic Insufficiency, Amenorrhœa, Malnutritional Œdema, Mental Disorders,** and **Enuresis Nocturna** have been referred to. There remain now to be considered certain other directions in which the results reached in the laboratory may be applied to the prevention and cure of disease. The practical application of these results is not, however, limited by my presentation of it, for it will be found, as the result of more extended clinical experience, that it has an even wider scope than I have indicated.

ACUTE GASTRO-INTESTINAL DISORDERS

Experiments with animals have led us to expect that acute intestinal disorders will be among the commonest of the consequences of deficient and ill-balanced food. We have seen that diarrhœa is frequent in deficiently-fed pigeons, and that diarrhœa and dysentery are frequent among deficiently-fed monkeys. We have seen also that both these symptoms can be alleviated or cured by the provision of a natural food; and that in pigeons the diarrhœa may be cut short, like the acute nervous symptoms, by the administration of vitamin-containing extracts. We have seen, also, that acute intestinal fluxes arise early in the period of subjection to the deficient diet. These observations have an important practical bearing in connexion with the genesis of such conditions as "infantile diarrhœa," "jail dysentery," and "famine dysentery."

Infantile Diarrhœa.—Among infants of from 0 to 2 years of age, the mortality from enteritis during the years prior to the war (1913 and 1914) averaged in Brussels 227, and in the surrounding district 410. During 1915 the corresponding figures were for Brussels 115 and for the surrounding district 194; during 1916, 73 and 104; during 1917, 65 and 95; and during 1918, 60 and 89. Demoor and Slosse,[1] in their report on this remarkable drop in the death-rate from infantile diarrhœa, are inclined to attribute the beneficent result to hereditary and race influences rather than to food. They record, however, that mothers were encouraged to suckle their children. To this end expectant and nursing mothers were specially provided for at maternal canteens, where from the fifth month of pregnancy up to the ninth month after the birth of the child they received, in addition to the ordinary war ration, a nutritive soup, one egg, 100 grams of meat or 150 grams of fish, potatoes and vegetables, a sweetened farinaceous dish, and one-quarter of a litre of milk. Special attention also was paid to the auxiliary feeding of infants that were not breast-fed; those from 1 to 3 months received half a litre of milk; those from 3 to 7 months one litre; those from 7 to 9 months half a litre of milk with half a litre of a "nutritive au cacao" made with milk; those from 9 to 14 months a litre of "nutritive au cacao"; and those from 14

[1] *Bull. d. l'Acad. Roy. de Méd. de Belgique,* 1920 (April 25).

months to 2 years one litre of cacao made with milk and water in equal parts. Coincident with these precautionary measures, the enormous drop in the mortality from infantile diarrhœa occurred. It seems hardly possible to escape the conclusion that this was cause and effect. It cannot, I think, be doubted that an important predisposing cause of infantile diarrhœa is the deficient feeding of infants which is so frequently a concomitant of artificial feeding. The health of the gastro-intestinal tract is dependent on the adequate provision of vitamins of every class, and in the maintenance of this health vitamin C plays a prominent part. The therapeutic value of fruit juices [1]—orange juice, grape juice, apple juice, peach juice, and tomato juice—in the treatment of infantile diarrhœa is beginning to be realized; and when it is remembered that orange juice contains volume for volume as much vitamin B as raw milk, and a very high content of vitamin C, while tomato juice is rich in all three vitamins, their value both as preventative and curative agents in infantile diarrhœa is the more fully appreciated. It is interesting to note that Mackenzie Wallis [2] has "obtained in epidemic diarrhœa of infants results identical" with those I have described in deficiently-fed animals—"particularly the characteristic changes in the pancreas."

Dysentery.—Unequivocal evidence has been brought forward that food deficiency favours the development of dysentery and that a well-balanced food rich in vitamins disfavours it. Workers in the Tropics have long known that cysts of *E. histolytica* may be present in the stools of perfectly healthy individuals, and absent from the stools in a proportion of cases possessing the clinical character of the type of dysentery called "amœbic" (Manson). I know of no work, however, designed to determine the percentage of *E. histolytica* carriers among natives of British India, although doubtless such exists; but Flu [3] has estimated that at least 10 per cent. of natives of the Dutch Indies are *E. histolytica* carriers, and has concluded that this estimate is probably much too low. Wenyon and O'Connor [4] have found 4·5 per cent. of *E. histolytica* carriers among healthy British troops in Egypt who gave no history of dysentery. They found also that 13·5 per cent. of healthy natives of Egypt were carriers of *E. histolytica*. It appears, therefore, that *E. histolytica* may be present in the healthy intestine without giving rise to dysentery until the conditions requisite for its growth upon and in the intestinal mucosa are provided by certain favouring circumstances. Among these malnutrition—including deficiency of vitamins—is one. It appears probable that bacillary dysentery is favoured in its origin by like circumstances. Amœbic dysentery is reported to have been produced in a limited number of apes by feeding them with *Entamœba histolytica* cysts; the malady is readily produced in monkeys that are amœbæ-carriers by feeding them on deficient food. Monkeys in confinement are not always sufficiently fed; in

[1] Zahorsky, J., *Missouri State Med. Assoc. Jour.*, 1920 (Aug.), XVII, No. 8, p. 317.

[2] Discussion on Vitamins, Brit. Med. Assoc., *Brit. Med. Jour.*, 1920 (July 31), p. 160.

[3] *Mededeelingen van den Burgerlijken Geneeskundigen Dienst in Nederlandisch-Indie, Deel*, 1918. VI. 113–16 and 164.

[4] *Jour. Roy. A. Med. Corps*, 1917, XXVIII, No 1, pp. 1–34, and No.. 2, pp. 151–87.

the production of amœbic dysentery in apes, by feeding the specific organism one would, in the light of the present observations, require to be assured of the sufficient nature of the animals' food before accepting the results as final. *Entamœba histolytica* is no doubt the specific infecting agent in amœbic dysentery, but that it can establish itself on a healthy intestinal mucosa is open to doubt. In the prevention of dysentery there are two precautions necessary: (1) The maintenance of the healthy and protective activity of the gastro-intestinal tract; and (2) the prevention of infection. The conditions necessary for infection of the intestinal mucosa differ little from those necessary for infection of the skin; these conditions are provided by ill-nourished, poisoned, and imperfectly functioning tissues. Improper food-supply is the most ready means of inducing such changes in the intestinal mucosa.

A further practical point relates to the treatment of dysentery. To enable the tissues to free themselves from the invading organism, vitamins must be provided. The invalid foods used in the treatment of dysentery are often dangerously deficient in these indispensable substances. "Famine dysentery," so well recognized in India during times of food scarcity, is to be explained by the facts here recorded; so also are the outbreaks of dysentery so frequent in stricken countries during the late war.

Jail Dysentery.—The demonstration of the influence of malnutrition in the causation of dysentery may have an important bearing on the prevalence of this malady in jails and asylums. The rice dietaries of Indian jails are, in those cases where I have ascertained their composition, often too close to the borderland of insufficiency with respect to their protein, fat, and vitamin content. Thus in one jail in the Madras Presidency, the "rice diet" consists of rice 20 ounces, salt ¾ ounce, tamarind ½ ounce, curry powder ¼ ounce, oil (vegetable) ½ ounce, dhal 5 ounces, vegetables 6 ounces. The rice is milled and lacks an adequate supply of vitamin B. This deficiency may, to some extent, be compensated for by the 5 ounces of dhal, provided that the dhal is not deprived of its germ and pericarp. But in Southern India, so far as I could ascertain, the dhal (*arhar*) chiefly eaten is without its pericarp. In Northern India "dhal urd" (Bengal gram) and "mung dal" are used—in these the pericarp is retained. Half an ounce of vegetable oil does not provide a sufficiency of fats or of vitamin A, while the amount of vitamin C contained in the vegetable components of this dietary is probably largely destroyed in the process of cooking. Such a ration is, therefore, too rich in carbohydrates and too poor in animal fats and proteins, while there is too small a margin of safety with respect to its vitamin-content. It seems probable that "jail dysentery" may to a great extent be prevented and cured by the more generous and judicious use of appropriate articles of food.

In this connexion it may be mentioned that so long ago as 1865 Dr. W. R. Cornish, of the Indian Medical Service, wrote as follows: "I never now hear of increase of bowel disorders and dropsies in a jail without at once suspecting tampering with the food or privation in the district furnishing the prisoners."

Reports of the greatly increased prevalence of enteritis, diarrhœa, and dysentery during the Great War are now plentiful. The observations here recorded appear to provide their pathological explanation. Both the acute effects of food deficiency on the intestines of human beings, as brought into prominence by the circumstances of the late war, and those observed as a result of animal experimentation, represent an extreme picture. They are the effects of food deficiencies more extreme than those that are widely encountered during peaceful phases of our civilization. But between this extreme on the one hand, and perfect nutrition on the other, there must often exist, even in times of plenty, intermediate degrees of imperfection which, when operative for long periods, must determine the departure of the gastro-intestinal tract from vigorous health. It is with the mean rather than the extreme that the physician is mainly concerned ; with the long-continued use of imperfectly balanced and moderately deficient foods rather than with complete avitaminosis ; with the beginnings of disease rather than with its end-results. The gastro-intestinal disorders occurring in deficiently-fed animals were more prone to arise in consequence of dietaries not only deficient in vitamins, but poor in protein and excessively rich in carbohydrates or fats, or both. With this combination the physician is familiar in practice, especially among artificially-fed infants and young children. It may be expected, then, that acute gastro-intestinal disorders of like kind, if not of like degree, will result in human beings from the long-continued use of food having these common faults.

CHAPTER XXV

CHRONIC GASTRO-INTESTINAL DISORDERS

In addition to the acute or more immediate effects of food deficiency on the digestive organs, others of more chronic course or more remote onset are connected in their origin with, or are due to, the same cause. Here again the experiences of the late war assist in determining the applicability of my observations in the laboratory to the human subject. Guarini [1] has reported forty cases of "large abdomen" occurring in soldiers who had been badly fed as prisoners of war. When in prison they had suffered severely from gastro-enteritis due to bad feeding. Months after their release the chief symptoms they presented were enlargement of the abdomen, especially in the upper part, inability to do hard work or to walk much, shortness of breath and constipation. In most of them the enlarged abdomen was tympanitic, while radiological examination showed gastric ptosis and marked meteorism, especially in the colon. These are examples of the remote effects of food deficiency in the human subject; it would hardly be possible to reproduce them more completely in animals than has been done in the case of monkeys fed on autoclaved food (Figs. 42, 42*a*), which survived dietaries deficient in growth vitamins for approximately three months. But Guarini's cases are paralleled by others of common occurrence outside prison camps. Any hospital extern will provide abundant examples of them amongst static, overworked and underfed young women. The conditions in prison camps have focussed attention on bad feeding as the cause of these forty cases among prisoners of war; the conditions of poverty, ignorance, habit, overwork, and improper choice of food are prison bars enough to account for these others. It has recently been stated that not less than 25 per cent. of all cases seeking relief at our clinics do so for gastro-intestinal disorders. Ill-health so common must have a very common cause. I submit that it is due largely to one great cause: the comparative absence of uncooked natural foodstuffs from our dietaries.

The derangements of bowel function to which food deficiency may ultimately give rise are:

(1) Impairment of the protective resources of the gastro-intestinal tract against pathogenic organisms.
(2) Impairment of secretory and digestive function.
(3) Impairment of assimilative power.
(4) Impairment of the neuro-muscular control of the stomach and bowel.

[1] *Rif. Med.*, 1920 (Jan. 20); *Abst., Brit. Med. Jour.*, 1920 (May 8), Epit., p. 73.

The three last are in large measure responsible for the first, since the protective resources of the tract include the normal production of the gastric, pancreatic, biliary, and intestinal secretions, the ordered processes of digestion and absorption, and the orderly transit of the gastro-intestinal contents along the digestive tube. If, then, in the light of these results, we consider the case of children fed, it may be from birth, on deficient and ill-balanced foods, and the frequency with which in later life such faulty foods continue to be used, we are in a position to realize the ultimate consequences of such foods and to anticipate the sequence of events leading up to grave derangement of bowel function. Since, also, food deficiency prepares the soil for bacterial growth, the resultant morbid states will vary with the nature of the organisms which may become implanted upon it. This knowledge, if it does not provide a complete explanation of such disorders as dyspepsia, dilatation of the stomach, gastric and duodenal ulcer, mucous disease, colitis, cœliac disease, chronic intestinal stasis, and intussusception will at least help to a better understanding of their genesis and of their treatment.

Chronic Gastro-intestinal Dyspepsia.—Digestive disturbances and dilatation of the stomach are so constantly present in deficiently-fed monkeys that they may be regarded as cardinal signs of deficiency disease. That they may arise from the same cause in human beings is illustrated by Guarini's cases referred to above. It is clear that no amount of gastric lavage can restore the stomach to normal function in the absence of an adequate supply of vitamins, while gastro-enterostomy must often yield disappointing results, as, indeed, it frequently does. When the derangement is definitely due to the absence of vitamins, the provision of these substances in the food will restore this organ to renewed activity in the human subject. The following is a case in point which came under my care about eighteen months ago:

A man, aged 60, had for twenty years been a confirmed invalid. He was a martyr to dyspepsia, and had a greatly dilated stomach, which he washed out three or four times a week—to his great exhaustion. He complained much of palpitation. He had not had a natural motion of the bowels for many years, but used a glycerin enema daily. He was very anæmic, and of a colour which one associates with cancer of the pylorus or pernicious anæmia. On examination I found a dilated stomach, a tender duodenum, "air-locks" in the small intestine, a tender cæcal region but no evidences of cancer, a dilated heart with irregular action and gallop rhythm on slight exertion, a low red blood-count with a colour index not proportionately reduced, no leucocytosis and a relative lymphocytosis. For many years he had been subsisting on a diet excessively rich in carbohydrates, deficient in suitable proteins and in vitamins. He never ate fresh fruit, and but rarely vegetables, and then overcooked. He complained of neuritic pains in the lower limbs, and felt that he was losing the use of them. As his diet was very similar to that of my monkeys, I resolved to treat him in the light of the results I had noted in those animals. He was put to bed, given a small quantity of raw milk by the mouth every two hours, and a solution of vitamins at night. Gradually the food was adjusted so as to contain an adequate supply of vitamins and of proximate principles in due proportion; it was made up mainly of milk, eggs, cheese, fish, fresh meat, fresh fruit, wholemeal bread, and green vegetables. He was deprived of his stomach tube and glycerin enema syringe and given paraffin only. The vitamin extract in solution was continued. He made rapid strides towards recovery; in two and a half

months he gained 10 pounds in weight, his anæmia and cardiac condition had greatly improved, he was freed of all symptoms of dyspepsia, and the bowels—aided by the paraffin—acted normally. Sixteen months later his doctor reported: "X is very fit; he still continues to have vitamins, and I find your vitamin-extract of great use in gastro-intestinal troubles."

I relate this case for two reasons: first, to emphasize the importance of a study of the "dietetic history" in every case of gastro-intestinal disorder; and secondly, to mention a lesson which it taught me. When the patient had been taking the vitamin-containing extract for ten days or so, he drew the attention of his medical attendant to the fact that his stools, which previously had been of a dirty white colour, offensive, and loaded with fatty acids, were now dark and well formed. So they remained until the supply of vitaminic extract with which he was provided from my laboratory ran out; then the stools again began to lose their dark colour, and to return to a white offensive state. On receiving a further supply of the extract, the stools assumed once more normal characters. This observation can have but one explanation, namely, that the vitaminic extract promoted the flow of bile and of pancreatic juice. Experimental confirmation of this clinical observation and of my own histo-pathological studies in monkeys is provided by the work of Voegtlin and Myer, who have shown that intravenous injection of a vitaminic extract of brewer's yeast has the same effect in increasing the flow of biliary and pancreatic secretions as has secretin. The case is of importance, also, because it illustrates the need for the provision of vitamins in a readily absorbable form. The flow of the biliary and pancreatic juices was not sufficiently excited by the vitamins in the food, because the processes of repair and regeneration of the digestive organs take place slowly. Pancreatic deficiency is, in my own experience, a comparatively common disorder. It may be recognized with sufficient accuracy by the bulky, offensive, light-coloured, fatty stools and their content of undigested muscle and fatty acid crystals.

The "vitamin extract" used in the treatment of this case was prepared as follows: To one quart of rectified spirit add a drop of glacial acetic acid; take the yolks of twenty-four fresh eggs, beat them up with an egg-beater, add the acidulated spirit; transfer the whole to a wide-mouthed bottle; allow to stand for several days, shaking vigorously from time to time; strain through muslin; filter the resultant yellow liquid through filter-paper; evaporate down to approximately one-third of its original bulk; the final product should contain enough spirit to prevent the growth of moulds. Dose one-twelfth part, or the equivalent of two eggs. A dose of this extract equivalent to four eggs, when evaporated to dryness and taken up in distilled water, will, on injection into the crop of a polyneuritic pigeon, cure it within twenty-four hours of all acute nervous symptoms, and will often relieve the diarrhœa from which it may be suffering. It will also cause copious defæcation in improperly fed and constipated fowls.

In the medical reports from war-stricken countries, we find constant references to the great increase in gastric dyspepsia and achylia which resulted in consequence of "the monotonous, voluminous, poorly digestible carbohydrate diet." [1]

[1] *Jour. Am. Med. Assoc.*, 1919 (April 26), LXXII. 1227.

Mucous Disease.—One of the earliest pathological evidences of deficient and ill-balanced foods, as observed in animals, is congestion of the gastro-intestinal mucosa (Fig. 19). Such a state of congestion may well give rise in children to the gastro-intestinal catarrh which characterizes " mucous disease." This disorder is very common among children who are fed largely on sterilized milk, artificial foods, white bread, polished rice, poor butter, overcooked vegetables, and excessive quantities of sugar. It is, in my experience, very amenable to dietetic treatment, yielding readily to limitation of carbohydrates and to a rationally balanced dietary of good vitaminic quality, aided by solvents of mucus and mild purgation.

Colitis.—It is hardly necessary to comment on the great frequency at the present day of colitis of ill-defined origin. The state of chronic anæmia, the unhealthy skin—often evidenced by acne or seborrhœa—the loss of weight, the lassitude, the backache, the colicky pains in the abdomen, the bouts of diarrhœa alternating with constipation, the mucous stools, and the neurotic condition of those afflicted by it—usually women—are familiar features of this intractable malady. One of the most constant results of food deficient in vitamins is colitis. It is so frequent that it may rank as a cardinal sign of vitaminic deficiency. It may arise as a result of the absence of vitamin B alone, although it was more frequently encountered in animals deprived of vitamins in general. Many of the other features of this malady, as seen in nervous constipated women, were reproduced in deficiently-fed monkeys—such as the anæmia and unhealthy skin and the loss of weight; even the congestion of the uterus and ovaries, which is so often present in women sufferers from colitis, was reproduced in monkeys. Unfortunately, most cases of this character in the human subject are of very long standing. I have myself no doubt that a proportion of them have resulted from the long-continued use of deficient foods from childhood onwards. I regard the experimental production of colitis as one of the most important results of these investigations. It indicates that, if the incidence of colitis is to be lessened in the future, attention must be directed to the dietetic habits of childhood, otherwise a chronic colitis is likely to be established and to prove most intractable. Too often in later life dietetic treatment causes improvement only to a certain point beyond which no further alleviation occurs. A frequent complication is the condition described as " controlling appendix " by Lane.

Cœliac Disease.—In an early report on the " Pathogenesis of Deficiency Disease " [1] I suggested that cœliac disease [2] might owe its origin to dietetic deficiencies. Its absence in breast-fed children, its onset between the ages of nine months and two years, the diarrhœa which so frequently precedes it, the cessation of growth, the ill-formed, pale, " oatmeal " stools, the frequent association of scorbutic symptoms, the abdominal distension, the afebrile nature of the malady, the diminished size of the liver, the blood-changes, the occurrence of

[1] *Brit. Med. Jour.*, 1919 (July 12), p. 36.

[2] Still, G. F., Lumleian Lectures, *Lancet*, 1918 (Aug. 10, 17, 24), pp. 163, 193, 227.

œdema, the muscular feebleness—all these are highly suggestive of the changes found to result in animals from food deficiencies. The malady is one with which I am not familiar in practice; I speak of it, therefore, with reserve. Mackenzie Wallis,[1] however, has stated that, in cases of cœliac disease which he had treated with a well-balanced diet rich in vitamins, " the results had been almost magical in that the stools rapidly assumed their normal colour and consistency, the weight of the patient increased and the girth of the abdomen decreased."

In connexion with my suggestion that cœliac disease might owe its origin to dietetic deficiencies, it is of interest to note that " in two experiments recently carried out at the Lister Institute, kittens given a diet deficient in fat-soluble A developed a condition showing a striking resemblance to that of children with cœliac disease: together with arrest of growth and distension of the abdomen there was muscular feebleness and apathy with a ' pathetic interest in food.' . . . These facts would suggest the conclusion that a deficient absorption of fat-soluble A accounts for the picture in cœliac disease " (Mackay).[2]

Chronic Intestinal Stasis.—It has been shown, in connexion with forty cases of " large abdomen " occurring among prisoners of war, that chronic intestinal stasis can arise in the human subject as a remote result of deficient food. Professor Arthur Keith has drawn attention to two anatomical factors which he regards as of primary importance in its causation: (1) Defective action on the part of the abdominal musculature; and (2) a lesion of the neuro-muscular system of the intestine. The histo-pathological changes occurring in deficiently-fed pigeons and monkeys indicate one means by which both the abdominal musculature and the neuro-muscular system of the gastro-intestinal tract can be simultaneously impaired in functional capacity. Deficiency of certain food factors leads to atrophy of all muscular tissue, as well as to disordered function or actual degeneration of nervous tissue throughout the body. The abdominal musculature and the nerve elements controlling it must of necessity suffer along with other muscular and nervous tissues. It may be concluded, then, that defective action on the part of the abdominal musculature will ultimately result as a consequence of deficiency of vitamins.

In addition to this functional defect on the part of the abdominal wall, we find, in pigeons, guinea-pigs, and monkeys starved of vitamins, unquestionable evidence in the wall of the intestine itself of neuro-muscular lesions of great significance. We are, I think, justified in applying these results to the genesis of stasis in the human subject, more especially as this condition has actually been found to result from bad feeding in prisoners of war. As a factor in the production of chronic intestinal stasis we must regard with suspicion human food which does not conform to standard in respect to its balance and vitamin-content. There can be no doubt that the food of children among the poorer, and often among the richer, classes is frequently dangerously faulty in these regards. Subsistence on such food from infancy onwards is calculated to lead to defect

[1] Discussion on Vitamins, Brit. Med. Assoc., 1920, *Brit. Med. Jour.*, 1920 (July 31), p. 160.

[2] Mackay, Helen M. M., *Brit. Med. Jour.*, 1920 (Dec. 18), p. 929.

of the abdominal musculature, to neuro-muscular lesions of the intestine, and to degenerative changes in the glandular elements of its mucous membrane. Indeed, the pathological changes in the large bowel in stasis, as described by Professor Keith, are strikingly similar to those I have enumerated as occurring in animals fed on ill-balanced food deficient in vitamins. He describes the morbid changes as affecting two systems—the glandular and the neuro-muscular: "The chief change in the muscular coats of the diseased great bowels removed from cases of enterostasis is a fibrosis which affects mainly the tissue between the outer and inner coats of the bowel, the intermediate stratum which ensheathes the myenteric plexus. Degeneration in areas of the musculature, particularly of the outer longitudinal coat, also occurs. In every case there are inflammatory changes varying in degree. There are many marked changes in the lining glandular epithelium, and in the submucous coat. One notes also that there is engorgement of the subperitoneal vessels, and that the subperitoneal tissue is much thicker and denser than is normal."[1] Having regard to the fact that the pathological processes I have described are of an acute nature, and induced by intensive vitaminic deprivation, whereas those recorded by Professor Keith are chronic, the similarity between them leads me to believe that deficient and ill-balanced food, when consumed from an early age, has a fundamental influence in causing the lesions found in stasis. However this may be, we must regard with suspicion an influence which is capable of providing at once the anatomical conditions necessary for the development of stasis, and the facilities for systemic infections which are known to result from it.

Gastric and Duodenal Ulcer.—Attention has been drawn to the occurrence of gastric ulcer in three out of ten monkeys fed on autoclaved food. Ulcers of the stomach and duodenum were also encountered in guinea-pigs fed on crushed oats and autoclaved milk. Deficient and ill-balanced foods may thus be added to the list of chemical, mechanical, toxic, nervous, and bacterial agencies capable of producing superficial hæmorrhagic erosions and acute ulcers of the stomach and duodenum. The changes resulting in the stomach and duodenum in consequence of food deficiencies are comparable to those which occur as a result of thyroid and adrenal insufficiency, and may, indeed, be due in some part to the functional derangement of these endocrine organs consequent on the food defects. The question arises whether partial long-continued avitaminosis may not be responsible in some measure for the production of chronic ulceration of these viscera. The food fault leads both to a state of lowered resistance to infection and to ill-health of the stomach and duodenal mucosa, so that organisms, such as streptococci, swallowed by the mouth or arriving by way of the blood-stream might in this state become the more easily implanted on an area of eroded mucous membrane. The changes produced in the stomach are such as may be expected to lead to achylia, so that infection by way of the mouth would be rendered easier. Ivy[2] has shown that two factors are necessary to the establishment of chronic

[1] Lane, *Chronic Intestinal Stasis*, 4th edition, 1918, p. 202.
[2] *Arch. Intern. Med.*, 1920 (Jan. 15), XXV, No. 1, pp. 6–31.

ulceration of the stomach in dogs: (1) A general lowered resistance, and (2) a temporary hypo-acidity or achylia. When these conditions are present, chronic ulceration can be produced in these animals by feeding them with streptococci. "Therefore, given an abrasion of a pathologic gastric mucosa, a lowered resistance by disease or disturbed nutrition, accompanied by hypo-acidity, we have factors that make it possible for bacteria swallowed or in the blood-stream to become implanted in the abrasion, and to produce local inflammation, induration, congestion and œdema, and a chronic ulcer" (Ivy). I am not in a position to offer positive proof of hypo-acidity or achylia in my experimental animals, except in so far as histological evidence may be accepted as such. But it is difficult to believe that, in the presence of the degenerative changes I have described in the gastric mucosa, the digestive juices can be produced in normal quantity and quality. If this be admitted, then all other factors necessary for the production of gastric ulcer are provided as a result of the deficient food.

The origin of such ulceration would thus fall into line with the development of amœbic dysentery in deficiently-fed monkeys which carry in their intestines *Entamœba histolytica*; and with the development of keratomalacia in rats deprived of vitamin A, which, as reported by Bulley,[1] can be prevented by minute attention to general hygiene and to the cleanliness of the eyes. These maladies would thus appear to develop in consequence of two factors: the lowered resistance of the tissues induced by the food deficiency, and the presence of a pathogenic micro-organism.

Intussusception.—The very frequent occurrence of intussusception in monkeys fed on deficient food is of great interest. The majority of these intussusceptions were produced in the death agony, but a proportion presented appearances suggestive of an earlier onset (Fig. 42). I have hesitated to attach much importance to their occurrence, since intussusceptions are often met with in laboratory animals at necropsy; but the greatly increased incidence of intussusception amongst children in Germany during the very lean years of the late war has been commented on in the writings of German physicians.[2] Without going too far, we may safely say that children who are properly fed will be less liable to suffer from intussusception. No doubt there is nothing new in such a statement, but I do not think we have realized hitherto that the neuromuscular control of the bowel is dependent in great measure on the adequate provision of vitamins in the food.

It may be asked, and with reason, how a condition of food deficiency can be considered to give rise to such a wide range of gastro-intestinal disease as that which includes infantile diarrhœa, chronic gastro-intestinal stasis, cœliac disease, gastric ulcer, and intussusception. To this I reply that the varying susceptibilities of different individuals, and of the same part of the gastro-intestinal tract in different individuals, are largely responsible for the diversity of results where the

[1] *Biochemical Jour.*, 1919, XIII. 103.

[2] Rubner, M., "Effects of Substandard Diet on German Population," *Jour. Am. Med. Assoc.*, 1919, LXXIII, No. 3, p. 168.

same food fault is in operation. A second factor is the wide variation which may occur in the faulty food, each combination of faults being in some degree responsible for peculiar effects. A third factor is the variations in the gastro-intestinal flora of different individuals; for just as *Entamœba histolytica*, when present, may impart to the gastro-intestinal disorder resulting from the food deficiency its own specific features, so also may it be expected that other pathogenic agents will impart theirs.

CHAPTER XXVI

PELLAGRA

GOLDBERGER and his colleagues have established the fact that a close relationship exists between food deficiency and pellagra. They consider that the deficiency may be one of suitable protein, of vitamins, of mineral salts, or more probably of a combination of two or more of these.[1] The work of the Committee of Inquiry, regarding the prevalence of pellagra among Turkish prisoners of war in Egypt, has also emphasized the connexion between pellagra and defective protein-supply to the body tissues. This Committee considered that the defective protein-supply may be due either to inadequate intake of protein of good biological value or to the malassimilation of such protein. It remains now to consider how far my experiments have a bearing on the etiological problems connected with this malady. It will have been noted that the symptoms and morbid anatomical changes occurring in monkeys fed on autoclaved food, exhibit a close parallelism to those found in pellagra. This is evidenced by the loss of appetite, the headache, the wasting, the unhealthy skin, the malnutrition of the nervous system, and especially by the gastro-intestinal derangements. The last are in both instances among the earliest manifestations of morbidity. Diarrhœa, often with mucus and blood, is a conspicuous symptom in pellagra, as it is in the case of monkeys fed on autoclaved food. Gastric derangement is common to both. Failure of pancreatic and intestinal digestion, with the rapid passage of the gastro-intestinal contents along the digestive tube, are features present in both states; so also are intense colitis and proctitis. Moreover, in pellagra " the walls of the intestine are extremely thin—as thin as paper even—so that they are semi-transparent " (Roaf)[2]—a state which is conspicuous also in deficiently-fed monkeys. In other respects, too, the conditions found post mortem are very similar. The parallelism extends to profound suprarenal inadequacy, the presence of which is suggested by the clinical features of pellagra[3]; fatty degeneration of the cortex of the suprarenals has been reported by Manson-Bahr.[4] Now, in the monkeys the main food fault was deficiency of vitamins. This deficiency gave rise to grave endocrine disturbance and especi-

[1] *Jour. Am. Med. Assoc.*, 1918, LXXI, No. 12, p. 944; Bull. 121, Hyg. Lab. U.S.P.H.S., 1920 (Feb.).

[2] *Proc. Roy. Soc. Med.*, Sect. Therap. and Pharmacol., 1920 (Jan.), XIII, No. 3, p. 24.

[3] *Report on Pellagra among Turkish Prisoners of War*, Alexandria, 1918 (Dec. 31).

[4] Quoted by Bigland, *Lancet*, 1920 (May 1), p. 947.

ally to suprarenal disturbance. It caused the gastro-intestinal lesions, and was primarily responsible for the imperfect assimilation of protein which occurred in these animals. It seems probable, therefore, that deficiency of vitamins and the consequent disturbance of digestive and endocrine functions play an important part in the production of pellagra. In the experimental diet employed by Goldberger for the production of pellagra in convicts, the food deficiency was of three orders at least: (1) Deficiency of suitable protein; (2) deficiency of growth vitamins; and (3) deficiency of salts. This diet has been shown by Sullivan to produce polyneuritis in fowls. It may be concluded, therefore, that deficiency of vitamin B was an important factor in the production of the endocrine and digestive disturbances in convicts. Goldberger himself draws attention to the smaller average supply of recognized vitamins in the dietaries of pellagrous than of non-pellagrous households.[1] It is, too, a conspicuous feature of all dietaries used for purposes of treatment in pellagra—the effects of which are so beneficial—that while they enrich the food in protein of good biological value, they enrich it also in vitamins, on which the health of the endocrine and digestive organs is dependent. From the evidence brought forward in this volume, it appears that sufficiency of protein will not render a food safe in the absence of a sufficiency of vitamins, and that a sufficiency of vitamins will not render a food safe in the absence of a sufficiency of protein. The experiments of Sullivan indicate that, when vitamins are provided, the protein available in a pellagrous diet for the repair of body waste is utilized.[2] My investigations show that this utilization is rendered possible by the restoration of endocrine and digestive function. Consequently I am led to believe that pellagra may result either from deficient protein supply or from deficient protein assimilation consequent on vitamin insufficiency or from a combination of both these causes. In this connexion the observation of Voegtlin [3] and his colleagues that vitamin extracts of liver and thymus, when added to the diet of sufferers from pellagra, induce definite improvement, while vitamin extracts made from yeast and rice polishings do not, is of much interest. There is some evidence that a third factor—infection—may contribute to the onset of this malady,[4] but this appears to be operative chiefly in the presence of defective food-supply.

But the subject of "pellagra" has an interest other than the etiological one, in that included under this term are cases of gastro-intestinal disorder which are not accompanied by the rash characteristic of this malady—cases of so-called "pellagra sine pellagra." Whether or not such cases of gastro-intestinal disorder are rightly so included, their inclusion serves a useful purpose if, from the point of view of their true causation and their appropriate dietetic treatment, it leads the physician to recognize the one and to apply the other. Such a case of "pellagra sine pellagra" is described by Roberts[5] as follows: "A mother of several children, doing a great deal of hard work, with no vacation and no servants,

[1] *Jour. Am. Med. Assoc.*, 1920 (May 29), LXXIV. 1520.
[2] *U.S. Pub. Health Service Hyg. Lab. Bull.*, 120, 1920 (Feb.), pp. 127–56.
[3] *Hyg. Lab. Bull.*, Washington, 1920 (Jan.), No. 116, pp. 7–34.
[4] *Rep. on Pellagra among Turkish Prisoners of War*, Alexandria, 1913 (Dec. 31).
[5] *Jour. Am. Med. Assoc.*, 1920 (July 3), LXXV, No. 1, p. 21.

suffering from perineal laceration, constipation, visceroptosis, loss of appetite, and none too varied or appetizing, diet—here is a pellagrous candidate. Too often flurries of diarrhœa, loss of subcutaneous fat, pinkish face and hands, roughened elbows and knees, raw tongue-tip, weakness, low (blood) pressure and rising pulse, but no definite typical eruption—this is 'pellagra sine pellagra.'" Such pictures of chronic intestinal derangement are familiar enough. I have dealt with their relationship to food deficiency under different, and perhaps more appropriate, headings—chronic gastro-intestinal dyspepsia, chronic gastro-intestinal stasis, and colitis. These so-called cases of "pellagra sine pellagra" serve to emphasize one of my main themes—namely, that a common cause of chronic gastro-intestinal disorder is deficient and ill-balanced food. It matters little what we call it if we but recognize its cause.

CHAPTER XXVII

BERI-BERI

FEW at the present day are disposed to doubt the importance of the part played by lack of vitamins in causing the syndrome known as beri-beri. But there are some who call in question the teaching of those who attribute beri-beri solely to this deficiency. For my own part, I am convinced that this divergence of opinion is due to two causes: first, that under the generic term "beri-beri" we include more than one malady; and, second, that due importance is not always attached to infectious agencies in precipitating or determining the onset of this syndrome in persons subsisting in a state of partial avitaminosis.

During the course of my studies of deficiency diseases I circularized all administrative medical officers in India with a view to obtaining, through civil surgeons under their jurisdiction, precise information as to the endemicity of beri-beri throughout India. As a result of this inquiry, it was found that the food factor alone did not suffice to account in all localities for the peculiarities of its geographical distribution. With comparatively few exceptions, the endemic foci of this disease in India are to be found on the east coast littoral and along the course of rivers flowing eastwards. Sporadic cases, or even small outbreaks, may occur elsewhere, but for the most part its home is on the east coast. From the numerous detailed reports which I received, there was no indication of any material differences in the dietetic habits of people in localities where beri-beri prevailed and of those where it did not prevail. As a rule the dietaries represented approximately the same degree of avitaminosis. So that, admitting the importance of the food deficiency in its causation, one was compelled to seek for some additional factor to account for the endemic occurrence of beri-beri in some localities and not in others. This factor I thought might be found in the quality of the rice eaten in endemic centres. I therefore experimented with eight different rices in common use in India. It was not found that the rice used by sufferers from beri-beri was exceptionally potent in causing polyneuritis columbarum. Indeed, all eight rices took twice as long to produce the malady in pigeons as did highly polished rice. So that in actual practice human beri-beri arises as a result of less complete degrees of avitaminosis than are usual in experimentally-produced polyneuritis in birds. I had thought that the rice eaten by sufferers from beri-beri might have been more highly polished, more mouldy, more deteriorated by storage, or that the character of the soil in which

it had been grown might have been responsible for a supposedly exceptional power to produce beri-beri; but the experimental test lent support to none of these assumptions. It was noticeable, however, that endemic foci of the disease were frequently to be found among communities exceptionally highly infected with diseases such as malaria, ankylostomiasis, and gastro-intestinal diseases generally. This association was not, however, constant; for while in some areas the beri-beri was associated in a conspicuous way with a high incidence of ankylostomiasis, in others no such association could be traced. It was suspected, therefore, that, while infectious diseases in general might play a part in precipitating the onset of beri-beri, no infectious disease could be credited with a special action in this regard. This suspicion was strengthened by the results of a former experimental experience. On that occasion I had to deal with the presence of *Bacillus suipestifer* among pigeons used for experimental purposes. As this experience presents many illuminating features, which have, I think, a bearing on the genesis of beri-beri, I recount it here in brief.[1]

(1) Thirty-six semi-wild pigeons were confined in three compartments of a large cage made by netting off a concrete-floored animal room; twelve birds occupied each compartment, a single sheet of netted wire of wide mesh alone separating them. The birds in one compartment acted as controls; those in the second were fed on raw Rangoon rice; those in the third on boiled Rangoon rice. The experiment lasted 30 days. During this time the controls remained healthy; of those fed on raw rice, seven developed polyneuritis within 10–20 days, one died from other causes, and four escaped the disease; of those fed on boiled rice, nine developed polyneuritis within 20 days, and three escaped the disease. In all cases dying of polyneuritis degenerative changes were present in the sciatic nerves. It will be noted that the time of onset of polyneuritic symptoms was very rapid, since in uncomplicated cases raw Rangoon rice produces polyneuritis columbarum in an average period of 55 days. The blood and internal organs of six cases were examined bacteriologically; *Bacillus suipestifer* was obtained in all, often in pure culture. Similar bacteriological examinations were made in eight birds, fed on rice, which had escaped the disease; a few colonies of *B. suipestifer* were obtained from the liver, spleen, and kidney in four cases. The blood and organs of four controls were similarly examined; in three cases they were sterile; in a fourth and apparently healthy bird, a few colonies were obtained from the liver, spleen, and kidney. In this experiment no case showed hydropericardium or œdema in any form. The polyneuritis was of the type usually spoken of in the literature as "fulminating"; no case showed the typical cerebellar symptoms characteristic of polyneuritis columbarum, although the polyneuritis was extreme.

(2) This experiment was repeated. The compartments of the cage were used in a reverse order; that previously occupied by controls was now occupied by birds fed on raw Rangoon rice, and vice versa. The experiment was continued for 100 days. *B. suipestifer* was again encountered in twenty cases of

[1] McCarrison, *Ind. Jour. Med. Res.*, 1914–15, II. 369, and 1919, VI, No. 3, p. 337.

polyneuritis during the course of this experiment. Its virulence appears, however, to have been considerably lessened, as the great majority of the cases did not occur until after the twentieth day. Among the birds that survived longest, cerebellar symptoms were frequent. One had well-marked hydropericardium; two others had a few drops of fluid in the pericardial sac. In this experiment the type of the disease was mixed and the birds did not die so rapidly.

(3) The experiment was repeated once more, but each bird was isolated in a separate cage. Two died of starvation in nine and twelve days respectively; they had refused to eat the rice. A third died of polyneuritis on the fifteenth day; in this case *B. suipestifer* was present, and the disease was fulminating. The remaining nine cases showed typical polyneuritis columbarum with cerebellar symptoms; their heart's blood and organs were sterile. One case out of the nine had marked subcutaneous œdema of the abdomen and inner side of the thighs and thorax, which was recognizable clinically; another had hydropericardium. In this experiment the segregation had the effect of preventing the spread of *B. suipestifer*, and true uncomplicated alimentary polyneuritis columbarum formed the bulk of the cases.

(4) Inoculation experiments were next carried out to determine the virulence of the organism, and the nature of the symptoms produced by it in healthy well-fed animals. It was found that it caused paralysis of the limbs and death in healthy pigeons, fowls, and rabbits (Figs. 3 and 4). Attenuated cultures were used to immunize pigeons and fowls against the organism, and such immunized birds, when fed on Rangoon rice, although not segregated, developed typical cerebellar polyneuritis avium.

The results of this experiment may be summarized as follows: (1) The organism encountered was itself capable of causing polyneuritis in healthy well-fed animals on subcutaneous inoculation. (2) Symptoms of polyneuritis resulted more rapidly in birds deprived of vitamins when this organism was present than when it was not. The types of polyneuritis met with were more mixed, birds dying early in the experiment rarely exhibiting cerebellar symptoms, although paralyses were marked, while those dying later did as a rule present cerebellar symptoms. (3) Birds could be protected from the infective type of polyneuritis by proper feeding and by immunization. (4) Immunized birds fed on Rangoon rice developed only the alimentary type of polyneuritis avium. Thus the cases of polyneuritis occurring in these experiments group themselves into three categories:

(1) Cases due solely to avitaminosis: true polyneuritis columbarum.
(2) Cases due to avitaminosis *plus* infection.
(3) Cases due solely to the infecting agent: infective polyneuritis columbarum.

The character of the symptoms in all three categories was essentially asthenic and polyneuritic. But they varied according as the organism or the avitaminosis was dominant in their production. In the former case they were the result of a

true neuritis, and were acute and fulminating in type ; in the latter they were the result of degenerative and functional changes in neurons, they were of slower onset and not fulminating in type. In the former the temperature was rarely below 104° F. (the average normal being 107° F.) and cerebellar symptoms were not present ; in the latter it was often 100° F. or lower at the height of the disease, and cerebellar symptoms were usually present. The post-mortem appearances also differed : in polyneuritis with accompanying infection the liver, spleen, and kidneys were enlarged and congested, while hydropericardium was rare (8·3 per cent.) ; in polyneuritis without accompanying infection the liver, spleen, and kidneys were atrophic, and œdema was more marked and more common (22 per cent.).

It remains now to apply these observations to human beri-beri ; they present a number of features which may, I think, help to explain the etiological problems connected with it. It will be noted from Table XVI, in which polyneuritis columbarum *without* accompanying infection, polyneuritis *with* accompanying infection, and human beri-beri are contrasted, that the two last more closely resemble each other than the first and third. Polyneuritis *without* accompanying infection differs from human beri-beri in that the liver, the spleen, and the kidneys are diminished in size in the former and increased in size in the latter. This difference disappears when human beri-beri and polyneuritis columbarum *with* accompanying infection are contrasted. Further, the infective form of polyneuritis avium resembles human beri-beri more closely clinically than does the non-infective form : in the last the temperature is markedly subnormal and cerebellar symptoms are present, in the first these features are absent.

These results led me to express the belief that, while vitamin deficiency is an essential etiological factor in the genesis of beri-beri, such deficiency is rarely so complete as to be the sole agency responsible for it.[1] I consider that in the presence of avitaminosis, be it complete or partial, infections, capable either of causing polyneuritis themselves or of precipitating the nerve degeneration to which the subjects are predisposed, are liable to occur and to modify the etiological, symptomatic, and morbid anatomical features of this malady. Pathogenic agents, of whatever kind, that are capable of further depressing the impaired metabolic resources of the body, and especially that of the endocrine regulators of metabolism, may be excitants of beri-beri, and convert a state of potential morbidity into one of actual disease. The organisms need not always be such as will produce polyneuritis on inoculation, although in some instances they may possess this power—as judged by the experience with *Bacillus suipestifer*. Many of those who have practised in the Tropics will be familiar with cases of beri-beri occurring as a sequel of dysentery ; and while it is possible, even probable in some cases, that the dietaries employed in the treatment of dysentery may be such as to precipitate the onset of beri-beri in persons predisposed to it by previous food conditions, yet the further possibility is not to be overlooked that organisms having themselves a specific action on nerve tissue may sometimes be the

[1] *Ind. Jour. Med. Res.*, 1919 (Jan.), VI, No. 3, p. 351.

responsible agents concerned. In this connexion I would draw attention to the action of certain late lactose fermenters of the dysentery group, such as the *Bacillus dispar* of Andrewes, in causing paralysis of the hind limbs when injected into rabbits. Infection by such an organism, especially in the presence of some degree of avitaminosis and of a lowered resistance of neurons, may be expected to give rise to symptoms indistinguishable clinically from beri-beri. Certain rapidly growing *staphylococci*, also, may cause, when introduced into the gastro-intestinal tract, symptoms of polyneuritis with or without those of enteritis. An instructive instance of an outbreak due to this cause has recently been furnished by Farnell and Harrington.[1]

TABLE XVI

CONTRASTING THE POST-MORTEM APPEARANCES IN POLYNEURITIS COLUMBARUM AND HUMAN BERI-BERI

Organs.	Polyneuritis Columbarum.	Human Beri-beri.	Polyneuritis Columbarum with Coexistent Infections.
Heart . .	Atrophy; frequent dilatation right heart: sometimes œdema of heart.	Hypertrophy: frequent dilatation right heart. Weight of heart 13·37 ounces as compared with 9 ounces in controls (Ellis).	Atrophy, dilated right heart: two cases showed hæmorrhages on its surface and into its substance.
Spleen . .	Atrophy pronounced.	Hypertrophy: weight 9·27 ounces as compared with 6·28 ounces in controls (Ellis).	Often enlarged.
Pituitary .	Tendency to enlarge in males only.	No records.	Usually hyperæmic (examined in six cases only).
Adrenals . .	Marked enlargement with increase of epinephrine-content.	Enlarged (Sprawson): epinephrine content increased in acute cases (Ohno).	Enlarged: usually without corresponding increase of epinephrine-content (six cases only examined).
Thymus . .	Great atrophy.	No record: enlargement of thymus referred to by Nagayo.	Undergoes great atrophy in septicæmic states.
Testicles . .	Great atrophy.	No records.	May undergo great atrophy.
Ovary . .	Atrophy marked.	No records: amenorrhœa reported (Vedder).	May undergo great atrophy.
Pancreas . .	Atrophy marked: sometimes ecchymoses.	No records: pancreatic insufficiency mentioned by Briandat and Lalung-Bonnaire.	Atrophic: usually hyperæmic (six cases only examined).
Liver . .	Slight atrophy: frequently hyperæmic.	Enlarged: usually hyperæmic (Scheube, Bentley); rarely congested (Ellis).	Enlarged and very congested.
Stomach . .	Atrophy: may contain pathogenic bacteria.	Congested 54·4 per cent. of cases (Ellis); hyperæmia, ecchymoses, erosions (Miura).	Frequent congestion.
Duodenum .	Hyperæmia and ecchymoses: atrophy.	Hyperæmia and ecchymoses (Scheube); duodenitis (Wright).	Hyperæmia and ecchymoses.

[1] *Amer. Jour. Med. Sci.*, 1920 (July).

TABLE XVI (*continued*)

Organs.	Polyneuritis Columbarum.	Human Beri-beri.	Polyneuritis Columbarum with Coexistent Infections.
Intestines	Atrophy: hyperæmia: ecchymoses.	Hyperæmia and ecchymoses 100 per cent. (Scheube); catarrh (Miura); congestion ecchymoses (Wenrich, Anderson, Simonds, and others).	Ditto in three cases; very pronounced; whole bowel filled with blood in one.
Lungs	Œdema rare; weight slightly increased.	Œdema common: hyperæmia and œdema 100 per cent. (Scheube); 36 per cent. (Pekelherring and Winkler) 62 per cent. (Ellis); 80 per cent. (Yamagiwa).	Œdema rare.
Kidneys	Slight atrophy: frequently hyperæmic.	Enlarged and congested the rule (Yamagiwa, Ellis, Bentley, Scheube, and others).	Enlarged and congested.
Thyroid	Slight atrophy: congestion very rare.	No records.	Congestion and enlargement the rule.
Brain	Very slight atrophy: may be hyperæmic or anæmic or normal appearance. No œdema.	Hyperæmia and œdema (Scheube); œdema (Bentley); anæmia (Yamagiwa).	Hyperæmic.
Meninges	Occasionally hyperæmic; rarely anæmic.	Hyperæmia (Yamagiwa).	Hyperæmic.
Cord	Rarely slight atrophy: no change in its membranes.	Anæmic (Yamagiwa); congested and œdematous (Bentley); œdema (Scheube).	No records.
Skin	No appreciable change, probably thinner.	Œdema: purple or green-grey spots; ecchymoses have been reported.	Dark-coloured.
Subcutaneous tissues	Complete disappearance of fat; œdema rare.	Œdema common 55 per cent. cases (Scheube).	Œdema rare.
Ascites	Rare—1 case in 35.	Common 50 per cent. cases (Scheube); 40 per cent. (Yamagiwa).	Rare.
Hydrothorax	Rare—1 case in 35.	Common 25 per cent. (Scheube); 90 per cent. (Yamagiwa).	Rare.
Hydropericardium	29 per cent. of cases in one series; 13·1 per cent. in another; 75 per cent. in a series of young birds.	Very common; 75 per cent. (Scheube); 98 per cent. (Pekelherring and Winkler); 64 per cent. (Ellis); 53 per cent. (Yamagiwa).	8·3 per cent.
Muscles	Great atrophy: rarely œdematous.	Pale, atrophic (Bentley); atrophy (Baels, Scheube); œdematous (Anderson, Wenrich).	Dark-coloured.
Vessels	Abdominal vessels often congested.	Usually congested.	Usually congested.
Bones	Very brittle, the bone marrow reduced.	No records.	No records.

Turning now to the literature for corroboration of these observations, one finds it in Sprawson's account of beri-beri in Mesopotamia.[1] His clinical

[1] *Quart. Jour. Med.*, 1920, XIII, No. 52, p. 338.

and epidemiological studies have led him to divide cases of beri-beri into three classes:

(1) Class A: occurring in persons not previously subjected to avitaminosis and of infective origin.
(2) Class B: occurring in persons previously subjected to long-continued partial avitaminosis, and precipitated in their onset by some illness, fatigue, or other depressing cause.
(3) Class C: occurring in persons subjected for several months to a more or less complete avitaminosis; in these the vitaminic deficiency is the sole cause of the malady.

Sprawson's clinical studies have thus led him to conclusions practically identical with those I had reached as a result of animal experimentation. The similarity in results of the clinical observations and experimental results bears close analysis. Thus in Class A (Sprawson), corresponding to infective polyneuritis avium, the nervous symptoms were more in evidence than the cardiac symptoms, while œdema was absent or comparatively slight. In Class C, corresponding to true polyneuritis columbarum, the cardiac symptoms were more prominent and œdema was the rule. Class B was intermediate between these two, and usually presented cardiac symptoms as well as œdema.

Articles are published from time to time insisting on an infectious element in beri-beri, and while in some the infectious argument is often pressed at the expense of the alimentary one, it would seem that in others the arguments are well founded. Thus Razetti [1] reports that beri-beri did not exist in Venezuela until it appeared in Guiana. It had been imported from Brazil, and is, according to this observer, now spreading northwards, although the manner of life and the food of the population in Venezuela are said not to differ from those of a century ago.

From these epidemiological, clinical, and experimental considerations I am led to believe that under the generic term "beri-beri" are included two disease entities: the first due to deficiency of vitamins in association with an ill-balanced diet; the second due to infection. The malady may also arise in consequence of a combination of these two factors: deficient and ill-balanced food and infection.

[1] Risquez: *Gaceta Médica de Caracas*, 1919 (April 15), XXVI, No. 7, p. 82.

CHAPTER XXVIII

THE SELECTION OF FOOD

HAVING arrived at an estimate of the extent and variety of morbid changes to which food deficiency gives rise, there remains to be considered the practical application of the observed results to the prevention and cure of disease in the human subject. Of foremost importance in this connexion is the study of the dietetic habits of the sick, and the adjustment of their dietaries by a judicious selection of natural foods. It is not an easy matter to secure a complete "dietetic history"; patients are often vague about what they eat and how much they eat; but when they find that one is not satisfied with vague statements, they respond as a rule by providing information on which reliance can be placed. Having secured a "dietetic history" as complete as possible, the food *eaten* should then be considered from five points of view, that is to say as to (1) deficiency of vitamins, (2) deficiency of protein of good biological value, (3) deficiency of inorganic salts, (4) excess of carbohydrates, and (5) excess of fats. In practice it will usually be found that, if the dietary does not contain a fair proportion of protective foods, it will be faulty in one or more of the above respects. It is of the first importance to realize that it may be faulty although the range and variety of foods used may be wide. The following is a case in point:

Some time ago I was consulted with regard to a boy, aged nine, whose parents were in good social position. He was surrounded with every comfort, and so far as housing, hygiene, and happy home surroundings were concerned the conditions under which he lived were perfect; yet he did not thrive. He was pale, thin, weedy, "with a miserable appetite" and irregular teeth: he suffered from boils, and from "night terrors" so severe as to cause his parents grave alarm. He was said to have "a thickened colon," but his bowels were regular and "his internal arrangements excellent." His history was as follows: Born in the East, he was nursed by the mother for the first month, after which breast-feeding was discontinued because of the mother's health. He lost weight and had diarrhœa. He was brought to England at the age of five months, and remained there in apparent health until fourteen months old. On returning to the East he developed croup and bronchitis, and "never did well there after that." He was, however, "never ill, although never vigorous." He was "always white and quiet and with little appetite." Just after he reached the age of three years,

his parents " took fright at his steady loss of weight " and brought him to England. He was seen by a consultant, who said " he was terribly anæmic, had a tendency to adenoids, but nothing organically wrong." He was " put on a strict diet, given raw meat, iron, cocoa, and no fruit except juice, while his milk was cut." He grew stronger in the course of a year or so, and " was never actually ill after that but for bad colds." Sometimes he had " mysterious bouts of abdominal pain " thought to be " indigestion." He also complained of pain in the knee if he walked much. This was thought to be due to " muscular strain from a weak ankle." So he reached the age of six years, at which period his " appetite was miserable, and he had no interest in any kind of food." He was therefore taken to a consultant again, who thought " his adenoids appeared worse, but did not advise operation." Six months later he had tonsillitis with " a mysterious rash, which was pronounced to be neither scarlatina nor measles." Shortly after this he was found to have " slight curvature of the spine," and was ordered " massage and exercises." His " appetite never improved, and he got very easily tired after any exertion." His " second teeth came slowly and overcrowded." His dentist said " his jaw was too small, and must be stretched," and that this was due to " tonsils and adenoids." He suggested a throat specialist, and the tonsils and adenoids were removed. He " appeared to improve." Later he got " violent pain in the stomach," which was considered to be due to " thickening of the colon." Slight mucus was then noticed in the stools, but as his bowels were regular, no further attention was paid to this symptom. Raw fruit was prescribed, and another specialist consulted, who considered the boy's state of health was due to " imperfect breathing," and that in consequence he was " much developed below the waist and too hollow-chested." He advised " two hours lying down on a hard surface, with the chest supported on a sandbag, so as to force the boy to breathe with the top of his chest." For some time he had been having a cold bath every morning, and doing ten minutes' exercise of the most strenuous kind after it. Thus he reached the age of nine years. A short trip to Cornwall, where he had a different kind of food, improved him, and he gained a little weight, which was partially lost on his return to his own home—a home situated in one of the healthiest and most bracing parts of England. At this point I saw the boy. He was pale, hollow-chested, especially over the right chest, thin and ill-developed, his ribs showing, his abdomen slightly protuberant. His motions were large and dry, and covered with a coating of slime. His stomach was slightly dilated, and the whole colon tender, especially from the splenic flexure downwards. His teeth were irregular and his jaws narrow. He had the scars of recent large boils on the buttocks, and a large angry-red boil on the hip. I could find no other evidence of organic disease. His mother was greatly distressed at the severity of his " night terrors." I asked her to prepare for me a statement of everything he ate and drank throughout the day. This she did with a perfection of detail most admirable. This was the boy's dietary :—Breakfast, 8 a.m. : soup-plate of porridge (not wholemeal) with a spoonful of Jamaica treacle ; rasher of bacon with potatoes or fried bread ; or, " buttered eggs," made

with Cook's dried eggs and margarine, on toast; or, "fish cakes," made with cod or hake, potato, and a Cook's dried egg; or, "fish pie" made the same way; or, a slice of cold ham; or, "soused mackerel," or mackerel rolled in oatmeal and fried; one "tiny piece of toast" and margarine, or a small piece of white bread and marmalade or jam; two teacupfuls of milk (boiled), coloured with tea. 1.15 p.m., Lunch: roast beef or mutton, generally New Zealand or Canterbury lamb; potatoes, some baked with the meat, some boiled; French beans, or marrow, or mashed turnip, or spinach or cauliflower; sometimes stewed beef with onions, carrots, etc., or haricot mutton done in hotpot with vegetables; or cottage pie; or minced meat or stewed meat shape, the last about once a week; stewed damsons or blackberries or pears with junket, cornflower, or rice shape, or custard made with milk and custard powder, or milk pudding once a week. When he had recooked or "made-up meat" (cottage pie, etc.), he had in addition some kind of suet pudding, either steamed ginger pudding or raisin or lemon pudding, with a hot treacle sauce, or white sauce, or lemon and arrowroot sauce, or a fruit pudding made of stewed fruit with suet crust. On Sundays he had fruit tart or pudding made of stewed fruit poured on white bread and allowed to soak, and afterwards turned out cold with custard poured over it. Sometimes cheese and bread after his pudding, not often. Never a second helping of anything. One glass of water and a piece of butter-scotch completed the luncheon meal. Tea, 4.30 p.m.: three pieces of bread and butter (margarine), sometimes white bread, often brown or "Veda" malt bread; rarely took jam or honey; sometimes had a slice of cake; two teacups of milk (boiled) coloured with tea. Supper, 7.30 p.m. (taken in bed): a teacupful of "Ovaltine" made with milk; two gingernut biscuits or two shortbread biscuits or two slices of bread and margarine. Surely this was a dietary varied enough and liberal enough; especially so as it had been supplemented during the last three months with a raw banana, apple, or pear the first thing in the morning. Yet the boy did not thrive, and had "a miserable appetite."

Now, on examining this elaborate dietary, it is noticeable that, despite its variety, it was for this boy, with his low food intake, deficient in vitamin A and in vitamin B. It was also not rich enough in vitamin C. In short, it did not contain an adequate allowance of the natural foods—wholemeal, milk, butter, fresh eggs, raw fruit, and raw leafy vegetables. I classed the case, therefore, as being similar to that of monkeys fed on autoclaved food, whose symptoms are loss of appetite, loss of weight, anæmia, unhealthy skin, and colitis. The boy's symptoms were loss of appetite, loss of weight (or more properly failure to put on weight), anæmia, unhealthy skin, and colitis. Accordingly he was weighed, and put on the following diet:

7.30 a.m.: Glass of hot water with the juice of an orange in it.
8.30 a.m.: Three-quarters of a pint of warm fresh milk with the yolk of one fresh egg beaten up in it; oatcake and fresh butter as much as he cared to eat; one English apple.
12 noon: A drink of water.

1.15 p.m., Lunch: Freshly-cooked English beef or mutton, or liver twice a week; potatoes cooked in milk, served and eaten with the milk in which they were cooked; a large raw tomato; one young lettuce of ten small leaves; stewed fruit with enough sugar to neutralize acid taste; small piece of cheese; oatcake, butter.
4 p.m.: A drink of water or weak tea; nothing to eat.
Supper (two hours before bedtime): As for breakfast, but without the apple.

As an alternative to oatcake, wholemeal bread or standard bread was allowed. The boy rested for one hour after the midday meal. His cold baths and exercises were stopped, with the exception of breathing exercises at an open window. His mother was instructed to let him run wild, and to give him a dose of Gregory's powder once or twice a week. The result of this treatment was remarkable. He increased in weight, his "night terrors" ceased after the first five days of treatment, his appetite returned, and he often remarked of his food, "This is delicious!" He began to "eat well," and at the end of one month he had gained 3 pounds 3 ounces in weight, in spite of a heavy cold. His mother reported: "He is certainly better in every way, more vigorous, a better colour, and eating splendidly; he has had no night terrors and no abdominal pain." By the end of five months the boy's general health had greatly benefited: his weight steadily increased and the colitis gradually improved, indicating that his previous ill-health was due largely to faulty food. The identity in kind of his symptoms to those of my monkeys fed on autoclaved food is remarkable. It is not maintained that another boy might not have flourished on the very varied dietary he had been receiving: the point is that this boy did not flourish on it, and therefore that it was inadequate for him. Reading through his history, one notes the slow, sure onset of colitis due to the deficient food and especially to the lack of sufficient vitamins. One wonders, too, whether the removal of the adenoids and tonsils, the "stretching of the jaws" by an elaborate odontological device, the two hours spent in a recumbent position on a hard surface, would have been necessary had the boy's food from his earliest infancy contained an adequate supply of the unsophisticated foods that nature intended him to have.

An instructive case of another order may be referred to here: that of a lady, aged thirty-three years, who suffered from headache, loss of power of concentration, and exhaustion. The following narrative, in her own words, written several years before she consulted me, minutely describes her condition:

"A feeling as of a heavy weight inside the head; a dull ache rather than an actual pain; makes the brain feel dulled and irresponsive; a starved feeling in the brain; a stupefied feeling requiring continual effort of will to get brain to act; loss of power of concentration, difficulty in organizing thoughts and in putting thoughts into words; effort at concentration intensifies the discomfort. A contracted feeling in the face and around the eyes; a contracted expression of face; numbness in top of the head; dislike of facing the light; nervousness in meeting people and having to talk. A feeling of exhaustion and lack of nervous energy. Drowsiness or torpor in morning, and difficulty in keeping awake. Short relief afforded by taking food, especially tea or coffee; relief lasts about ten minutes after a meal. As a rule especially hungry when

head is bad, and do not feel satisfied (by food). Wish for strong concentrated foods—cheese, chocolate, etc., to counteract the " used-up " feeling. It began in 1910 (at age of twenty-three). At first at long intervals and faintly; did not recognize it as anything definite for years; gradually increased year by year till by the autumn of 1914 it was perpetually present, only occasionally—perhaps once a fortnight or so—would it lift altogether for a day or two. In the spring of 1916 had a rest cure—eight weeks in bed—which improved it a good deal, but did not cure, although have been leading since then an extremely quiet, healthy, and happy life, without worries, fatigues, or anxieties. Frequently, and for weeks at a time, wake up with it, not having had it overnight; is not improved by using glasses for reading, nor by aspirin, phenacetin, etc."

The patient, having undergone a number of diverse treatments, continued her narrative as follows:

" More and more convinced, looking back, that cause is to be found in the way health was being steadily run down over period of years. After leaving school at age of nearly nineteen, was very well, in spite of perpetual indigestion; and was fat, weighing over 9 stone. Soon began life of continual rush, continuing, with strenuous holidays, for four years; indigestion on the increase, when gradually this (condition of the brain) made itself felt. Was starved for want of being able to eat anything like a normal amount, got thinner, and as head grew worse life became more of a strain, until about the age of twenty-seven weighed 7½ stone, head perpetually bad, power of concentration weakened, state of nervous exhaustion, and failure altogether."

At this point in the patient's history she had the rest cure, which afforded some measure of relief; but after resumption of her normal manner of life the benefit derived from it did not last. So matters went on until, about one year ago, her doctor prescribed thyroid extract, from which she derived greater benefit than from any treatment adopted hitherto. She had been taking thyroid extract, in ¼-grain doses, thrice daily, for nearly a year when she consulted me, and had come to rely upon it as her only means of securing comparative comfort. She felt that a return to her former state was inevitable should she discontinue its use. Here, then, was a case giving a history of " perpetual indigestion "—relieved to a considerable extent by the use of an abdominal belt—of headache, of lack of mental concentration, and of nervous and physical exhaustion, these last being considerably ameliorated by the use of thyroid extract. She was thin, sallow, anæmic, and always cold; her expression was strained, her fingers so swollen with chilblains that she could not remove her rings; the tongue was dirty, the stomach dilated, the cæcal region tender, the pulse feeble, the systolic blood-pressure 100, the thyroid gland not palpable. At my request she prepared a detailed statement of a sample week's dietary. On examining it I found it to be markedly deficient in the " protective foods "—milk, eggs, wholemeal bread, glandular organs, butter, fresh fruit and leafy vegetables. It was composed for the most part of tea, coffee, white bread, cake, jam, margarine, bacon, dried eggs, frozen meat, sugar, rice, tinned fish, and pastries. She was excessively fond of fats, which she consumed in large amounts in the form of margarine and bacon fat. Her appetite was small and the intake of food subnormal. Clearly her dietary was deficient both as to quantity and

vitamin-content. I surmised, therefore, that her state was comparable to that of my monkeys which had been fed on autoclaved food and butter. In these there had resulted (1) anæmia, (2) loss of weight, (3) gastro-intestinal disorder, (4) increase in weight of the brain, (5) atrophy of the thyroid, (6) adrenal insufficiency. The patient presented all these signs of deficiency disease. The gastro-intestinal disorder was manifested in the dirty tongue, the gastric dilatation, and the tender cæcal region ; the thyroid insufficiency in the small size of the gland, and in the benefit afforded by thyroid medication ; the adrenal derangement in the feeling of cold, the low blood-pressure, the feeble pulse, and the chilblains ; the anæmia and loss of weight were obvious. I resolved, therefore, to discontinue the use of the thyroid extract—much to my patient's alarm—and to try the effect of a well-balanced dietary, rich in vitamins of every class, similar to that used in the previous case. The result was remarkable. For the first six days of treatment the headache and feeling of exhaustion returned with their old intensity, so that all the patient's will power was required to prevent her resorting to the thyroid extract. From the seventh day forward, with but two slight relapses lasting a few hours, improvement was rapid and continuous. Within a fortnight her chilblains completely disappeared, although the weather was extremely cold, and she was free of headache and the feeling of exhaustion. At the end of three months the patient reported herself as " extraordinarily well," without having had resource to thyroid extract, and much better than she had ever been even with its aid. She is of good colour, looks many years younger, her headache of ten years' standing is gone, her cardio-vascular, digestive, and endocrine functions are apparently normal, and to all appearances she is permanently relieved of her distressing disabilities—and this without resort to medicinal treatment of any kind.

These examples suffice to emphasize that it is not among the poor and needy alone that we are to seek for the evidences of disease or malfunction of organs due to faulty food. Such evidences will be found in abundance among the well-to-do, of whatever age, whose food is deficient in natural and protective ingredients, and especially among those who suffer from anæmia, loss of appetite, dyspepsia, pain in the stomach, flatulence, debility, neuralgia, neurasthenia, headache, disordered action of the heart, colitis, stasis, and visceroptosis. Sufficient experimental, pathological, and clinical evidence has been advanced to show that in deficient and ill-balanced food we have at least one cause for these manifestations of morbidity. Certain it is that in patients presenting them, and whose food is faulty, improvement will result in proportion to the stage of the malady at which correction of the dietetic errors is begun.

These examples emphasize also that it is not on the variety of the food presented to the individual, but on the quantity actually eaten, on its balance, on its content of vegetable residue and salts, and especially on its vitamins, that the nutritive value of a food and the health of the individual depend.

It is agreed by all workers on the problems of nutrition that vitamin A is frequently deficient in the food ; but because of the " anti-neuritic " cloak under

which the true function of vitamin B has so long been hidden, it is less readily agreed that this also is frequently insufficient. I admit that it is difficult to deprive a dietary of this factor; but since it is not known how much of it is needed for perfect nutrition in human beings, it is best to err on the safe side, and to see that in all cases the food contains plenty of it. Nature gives us a fair hint as to its necessity; for we find it in abundance in the natural foodstuffs which man ought to eat and frequently does not. It requires little laboratory experimentation, therefore, to show that some people, especially the young, habitually take too little of it, either for growth or maintenance.

As for vitamin C, we are accustomed to recognize its insufficient supply only when the gums begin to bleed or the tissues begin to show signs of hæmorrhagic effusions. But the evidence brought forward in preceding chapters indicates that, long before these grosser evidences of insufficiency manifest themselves, the health of the gastro-intestinal tract and of the adrenal glands has begun to suffer. It is not enough, then, that the supply of vitamin C should be sufficient to prevent scurvy; it should be sufficient to play adequately its part in maintaining the digestive and endocrine organs in health; this sufficiency can only be secured by the inclusion in the dietary of an abundance of raw fruit and vegetables. There are no more important ingredients of a properly constituted food than these, since they contain vitamins of every class, recognized or unrecognized.

In the selection of foods, or in estimating the value of a patient's diet, it is sufficient in practice to see that he receives an adequate supply of natural protective food ingredients. It is hardly necessary to emphasize that these natural foods must be used in a form which does not depreciate their vitamin-value, and in a form suitable to the age and state of digestion of the individual. Thus in infants and young children, fruit and vegetable juices will be used instead of the whole product; while such articles as wholemeal bread and nuts will be presented only to gastro-intestinal tracts capable of dealing with them. Similarly, in cases of gastro-intestinal disorder, vitamin-containing extracts or fruit and vegetable juices may alone be tolerated until the tract has had time to recover in some measure its normal tone and digestive powers. Nor is it necessary to abandon foods in common use; all that is required is to reinforce these with natural foodstuffs in quantities sufficient to provide an adequate supply of vitamins, suitable protein, and salts for the varying needs of individuals.

Unfortunately, milk, butter, fresh eggs, raw fruit, and leafy vegetables are at the time of writing both costly and difficult to procure. But I venture to think that these drawbacks to their more extended use will be met when the necessity for their provision is fully realized. The extension of the allotment scheme, communal vegetable gardens, the establishment by municipal authorities of dairy and poultry farms, and the importation of less frozen meat and more oranges suggest themselves as means by which natural foods may be made available in abundance and at a low cost.

I have written of three vitamins, because three are known, not because it has been proved that there are only three. But whether there be only three

or legion, they will be found to exist—and this is the important point—in the foods made in nature's laboratory, in quantities and in combinations adequate for the due digestion and assimilation of the natural foodstuffs with which they are associated in nature. The subdivision of vitamins into many classes is not without the risks attendant on decentralization. Vitamins, like other essential constituents of the food, are not to be regarded as independent of the assistance derivable from their associates in the maintenance of nutritional harmony. Each vitamin is but a member of a team, and the team itself but a part of a co-ordinated whole.

APPENDIX

INCLUDING TABLES REFERRED TO IN CHAPTERS DEALING WITH THE ADRENAL GLANDS AND MALNUTRITIONAL ŒDEMAS

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INCLUDING TABLES REFERRED TO IN CHAPTERS DEALING WITH THE ADRENAL GLANDS AND MALNUTRITIONAL ŒDEMAS

TABLE I

INCIDENCE OF ŒDEMA WITH SPECIAL REFERENCE TO THE WEIGHT OF THE ADRENAL GLANDS IN THIRTY-ONE CASES OF POLYNEURITIS COLUMBARUM OCCURRING IN ADULT BIRDS FED ON MILLED AND AUTOCLAVED RICE

Number of Pigeon.	Sex.	Weight before Experiment in grms.	Weight after Experiment in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Body-weight in mgrms.	Evidences of Œdema.
14	Male	270	145	35	130	No œdema.
16	,,	340	190	50	147	1·5c.c. of fluid in the pericardium.
17	,,	270	175	43	159	No œdema.
52	,,	340	240	31	91	Do.
55	,,	290	160	27	93	Do.
22	,,	300	230	41	136	Do.
37	,,	250	190	29	116	Do.
45	,,	275	175	33	120	Do.
46	,,	340	270	37	108	Do.
48	,,	275	220	53	192	2 c.c. of fluid in pericardium.
43	,,	260	185	56	215	No œdema.
40	,,	300	175	33	110	Do.
24	,,	300	180	30	100	Do.
53	,,	260	185	40	153	Do.
58	,,	340	200	54	158	Œdema abdomen and groin; ascites; hydropericardium.
47	,,	330	195	70	212	Marked œdema of tissues.
23	,,	280	160	43	153	2 drops of fluid in pericardium.
50	,,	290	165	36	124	No œdema.
19	Female	220	170	32	145	Do.
18	,,	270	170	37	137	Do.
21	,,	280	230	18	64	Do.
39	,,	350	200	22	63	Do.
42	,,	280	160	47	168	2·5 c.c. of fluid in pericardium.
13	,,	260	160	25	96	No œdema.
54	,,	300	190	65	216	Do.
51	,,	250	170	35	140	Do.
60	,,	240	135	62	258	2·5 c.c. of fluid in pericardium.
15	,,	280	145	38	135	No œdema.
41	,,	310	180	50	161	2·5 c.c. of fluid in pericardium.
57	,,	290	190	91	314	13·5 c.c. of fluid in pericardium.
56	,,	300	150	42	140	No œdema.

NOTE.—In this and similar tables, the weights of the adrenals per kilogram have been calculated against the original body-weight of the birds.

Analysis of Table I:

(1) The incidence of œdema in these cases was 29 per cent., there being 22 cases without evidence of œdema, and 9 cases with evidence of œdema.

(2) The average weight of the adrenals per kilogram of body-weight in 35 healthy pigeons which were controls to this experiment was 95 milligrams.

TABLE II

INCIDENCE OF ŒDEMA WITH SPECIAL REFERENCE TO THE WEIGHT OF THE ADRENAL GLANDS IN TWENTY-NINE CASES OF POLYNEURITIS COLUMBARUM OCCURRING IN YOUNG AND GROWING BIRDS FED EXCLUSIVELY ON AUTOCLAVED RICE.

Number of Pigeon.	Sex.	Weight before Experiment in grms.	Weight after Experiment in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram in mgrms.	Evidences of Œdema.
83	Female	255	180	29	113	No œdema.
85	,,	210	155	43	204	Hydropericardium: 3·5 c.c.; slight œdema at auriculo-ventricular junction of heart.
86	,,	250	190	45	180	Hydropericardium: 0·25 c.c.
87	,,	215	165	49	228	Hydropericardium: 0·5 c.c.; marked œdema at auriculo-ventricular junction of heart.
88	,,	235	190	45	191	Hydropericardium: 0·25 c.c.
107	Male	225	190	65	254	Hydropericardium: 3·5 c.c.; slight ascites: œdema of lungs.
111	,,	245	140	53	216	Hydropericardium: one drop only; well-marked œdema at auriculo-ventricular junction.
112	Female	240	170	39	162	No œdema.
116	Male	230	145	72	313	Hydropericardium: 1 c.c.; marked œdema at auriculo-ventricular junction of heart.
121	Female	245	140	40	163	No œdema.
119	,,	200	130	70	350	Hydropericardium: 2 c.c.; œdema of lungs; well-marked œdema at auriculo-ventricular junction of heart.
146	Male	240	175	35	145	No œdema.
143	,,	210	120	47	228	Œdema of lungs.
155	,,	270	150	37	140	No œdema.
108	Female	215	145	58	270	Hydropericardium: 7 c.c.; œdema of lungs: muscles very moist.
109	,,	220	130	60	272	Hydropericardium: 0·5 c.c.; blood-stained with clot; œdema of lungs.
110	Male	240	150	68	283	Hydropericardium: 1·5 c.c.; well-marked œdema at auriculo-ventricular junction of heart.
148	,,	240	180	54	225	Hydropericardium: 0·5 c.c.
140	,,	230	190	52	226	Hydropericardium: 0·25 c.c.; intense œdema at auriculo-ventricular junction of heart.
150	,,	290	180	68	234	Hydropericardium: 0·5 c.c.; slight œdema at auriculo-ventricular junction of heart.
117	Female	255	150	81	317	Hydropericardium: 2 c.c.; œdema at auriculo-ventricular junction of heart; œdema of lungs.
118	,,	220	125	55	250	Hydropericardium: 0·8 c.c.; slight œdema at auriculo-ventricular junction of heart.
144	,,	215	130	38	176	No œdema.
145	Male	280	150	74	264	Do.
149	,,	250	145	31	124	Do.
151	Female	280	150	45	160	Do.
153	Male	300	170	55	183	Do.
154	Female	230	130	35	152	Do.
156	Male	280	150	30	107	Do.

(3) The average weight of the adrenals per kilogram of original body-weight in 22 cases of polyneuritis columbarum without evidence of œdema was 127 milligrams.

(4) The average weight of the adrenals per kilogram of original body-weight in 9 cases of polyneuritis columbarum presenting evidence of œdema was 196 milligrams.

(5) Minimum weight of the adrenals per kilogram of original body-weight in any case of the series presenting evidence of œdema was 147 milligrams.

(6) The number of cases of polyneuritis columbarum having adrenals weighing 147 milligrams per kilogram of original body-weight or over was 13: (*a*) Those with evidence of œdema—9; (*b*) those without evidence of œdema—4.

Analysis of Table II:

(1) The incidence of œdema in these cases was 58·6 per cent.: there being 12 cases without evidence of œdema, and 17 cases with evidence of œdema.

(2) The average weight of the adrenals per kilogram of original body-weight in controls was 95 milligrams.

(3) The average weight of the adrenals per kilogram of original body-weight in 12 cases of polyneuritis columbarum without evidence of œdema was 157·4 milligrams.

(4) The average weight of the adrenals per kilogram of original body-weight in 17 cases of polyneuritis columbarum with evidence of œdema was 249·4 milligrams.

(5) The minimum weight of the adrenals in any case of the series presenting evidence of œdema was 180 milligrams.

(6) The number of cases of polyneuritis columbarum having adrenals weighing 180 milligrams or over was 19: (*a*) Those with evidence of œdema—17; (*b*) those without evidence of œdema—2.

TABLE III

SHOWING THE EPINEPHRINE-CONTENT IN THE ADRENAL GLANDS AND THE TOTAL EPINEPHRINE PER KILOGRAM OF BODY-WEIGHT IN TEN HEALTHY CONTROL PIGEONS[1]

Number of Pigeon.	Final Weight of Pigeon in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Body-weight in mgrms.	Total Epinephrine in Glands in mgrms.	Total Epinephrine per Kilogram of Body-weight in mgrms.
242	350	30	85·7	0·090	0·257
255	230	22	95·6	0·051	0·221
256	210	24	114·2	0·054	0·257
257	220	22	100·0	0·052	0·238
258	240	18	75·0	0·045	0·187
259	280	22	78·5	0·052	0·187
260	240	22	91·6	0·051	0·212
261	270	24	88·8	0·054	0·200
262	270	23	85·0	0·060	0·222
263	240	25	104·0	0·045	0·187
Average	255	23·2	91·8	0·0554	0·216

Analysis of Table III:

(1) In healthy pigeons in this series, the weight of the adrenals per kilogram of body-weight ranged between 75 and 114 milligrams.

(2) The total amount of epinephrine in the healthy glands ranged between 0·045 and 0·090 milligram.

[1] McCarrison, *Proc. Roy. Soc.*, B, 1919, XCI. 104.

(3) The average epinephrine-content *per gram of gland* in 10 healthy pigeons was 0·0023 gram.

(4) The total amount of epinephrine per kilogram of body-weight ranged between 0·187 and 0·257 milligram.

TABLE IV

SHOWING THE EPINEPHRINE-CONTENT IN THE ADRENAL GLANDS AND THE TOTAL EPINEPHRINE PER KILOGRAM OF BODY-WEIGHT IN TWELVE CASES OF *DRY* POLYNEURITIS COLUMBARUM RESULTING FROM AN EXCLUSIVE DIET OF AUTOCLAVED RICE [1]

Number of Pigeon.	Original Weight of Pigeon in grms.	Final Weight of Pigeon in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Original Body-weight in mgrms.	Weight of Adrenals per Kilogram of Final Body-weight in mgrms.	Total Epinephrine in Glands in mgrms.	Total Epinephrine per Kilogram of Original Body-weight in mgrms.	Total Epinephrine per Kilogram of Final Body-weight in mgrms.
238	240	170	25	104	147	0·045	0·187	0·264
223	230	140	29	126	207	0·045	0·195	0·321
222	270	210	40	148	190	0·084	0·311	0·400
228	245	170	21	85	123	0·048	0·195	0·282
243	250	210	62	248	295	0·138	0·552	0·657
241	230	160	33	143	206	0·057	0·247	0·356
237	260	150	41	157	273	0·090	0·346	0·600
250	190	155	27	142	174	0·075	0·394	0·483
226	250	190	31	124	163	0·090	0·360	0·473
246	200	130	55	275	423	0·105	0·525	0·807
230	250	180	37	148	205	0·090	0·360	0·562
224	260	160	30	115	187	0·045	0·173	0·250
Average	239	168	36	151	216	0·076	0·320	0·454

Analysis of Table IV:

(1) In 12 cases of *dry* polyneuritis in this series the weight of the adrenals per kilogram of original body-weight ranged between 85 and 275 milligrams; the weights of the adrenals were within the limits of health in 2 cases only.

When calculated against the final body-weight of the birds, the weight of the adrenals per kilogram ranged between 123 and 423 milligrams; in no case was the weight of the adrenals within the limits of health.

(2) The total amount of epinephrine in the adrenal glands from these cases ranged between 0·045 and 0·138 milligram. In 10 cases out of 12 the total amount of epinephrine was within the limits of health, but on a higher average than that of health.

(3) The average epinephrine-content *per gram of gland* in 12 cases of *dry* polyneuritis was 0·0021 gram, or practically the same as in health.

(4) The total amount of epinephrine per kilogram of original body-weight ranged between 0·173 and 0·552 milligram; it was within the limits of health in 5 cases out of 12.

When calculated against the final body-weight of the birds, the total epinephrine ranged between 0·250 and 0·807 milligram; in all cases, with one exception (No. 224), the total epinephrine per kilogram of body-weight exceeded the limits of health.

Analysis of Table V:

(1) In 10 cases of *wet* polyneuritis in this series the weight of the adrenals per kilogram of original body-weight ranged between 145 and 478 milligrams; in no case was this weight within the limits of health.

When calculated against the final body-weight of the birds, the weight of the adrenals

[1] McCarrison: *Proc. Roy. Soc.*, B, 1919, XCI. 105.

TABLE V

SHOWING THE EPINEPHRINE-CONTENT IN THE ADRENAL GLANDS AND THE TOTAL EPINEPHRINE PER KILOGRAM OF BODY-WEIGHT IN TEN CASES OF *WET* POLYNEURITIS COLUMBARUM RESULTING FROM AN EXCLUSIVE DIET OF AUTOCLAVED RICE [1]

Number of Pigeon.	Original Weight of Pigeon in grms.	Final Weight of Pigeon in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Original Body-weight in mgrms.	Weight of Adrenals per Kilogram of Final Body-weight in mgrms.	Total Epinephrine in Glands in mgrms.	Total Epinephrine per Kilogram of Original Body-weight in mgrms.	Total Epinephrine per Kilogram of Final Body-weight in mgrms.
227	250	170	60	240	352	0·102	0·408	0·600
244	210	160	47	223	293	0·090	0·428	0·562
232	260	180	58	223	322	0·150	0·576	0·833
254	230	140	76	330	542	0·129	0·560	0·902
253	180	130	57	316	438	0·120	0·666	0·923
229[2]	230	190	110	478	578	0·105	0·456	0·552
247	230	135	72	313	533	0·105	0·456	0·777
233	270	170	90	333	529	0·120	0·444	0·705
236	240	170	35	145	205	0·120	0·500	0·705
245	220	140	71	322	507	0·165	0·750	1·178
Average	232	158	67·6	292	429·9	0·1206	0·5244	0·7737

per kilogram ranged between 205 and 578 milligrams ; in no case was this weight within the limits of health.

(2) The total amount of epinephrine in the enlarged adrenals from these cases ranged between 0·090 and 0·165 milligram. In no case was the epinephrine-content within the limits of health, although in one case (No. 244) it was as low as the maximum limit found amongst 10 healthy birds.

(3) The average epinephrine-content *per gram of gland* in 10 cases of *wet* polyneuritis was 0·0018, or slightly below that of health.

(4) The total amount of epinephrine per kilogram of original body-weight ranged between 0·408 and 0·750 milligram ; in all cases, including No. 244 referred to in para. (2) above, it greatly exceeded the limits of health.

When calculated against the final body-weight of the birds, the total epinephrine in the body ranged between 0·552 and 1·178 milligram, the excess over that found in health being very pronounced.

TABLE VI

SHOWING THE AVERAGE EPINEPHRINE-CONTENT OF THE ADRENAL GLANDS AND THE AVERAGE QUANTITY OF EPINEPHRINE PER KILOGRAM OF BODY-WEIGHT IN HEALTHY PIGEONS AND IN PIGEONS SUFFERING FROM *DRY* AND *WET* POLYNEURITIS [3]

Original Weight of Pigeons in grms.	Final Weight of Pigeons in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Original Body-weight in mgrms.	Weight of Adrenals per Kilogram of Final Body-weight in mgrms.	Total Epinephrine in Glands in mgrms.	Total Epinephrine per Gram of Gland in grms.	Total Epinephrine per Kilogram of Original Body-weight in mgrms.	Total Epinephrine per Kilogram of Final Body-weight in mgrms.	Class of Pigeons.
245	255	23·2	94	91·8	0·0554	0·0023	0·226	0·216	Healthy.
239	169	36·0	151	216	0·0762	0·0021	0·321	0·456	Dry polyneuritis.
232	158	67·6	292	429	0·1206	0·0018	0·524	0·773	Wet polyneuritis.

[1] McCarrison : *Proc. Roy. Soc.*, B, 1919, XCI. 106.
[2] Streptococcic infection.
[3] McCarrison, *Proc. Roy. Soc.*, B, 1919, XCI. 108.

The results in Tables III, IV, and V are expressed as averages in Table VI, and are represented graphically in Fig. 74.

TABLE VII

INCIDENCE OF ŒDEMA WITH SPECIAL REFERENCE TO THE WEIGHT OF THE ADRENAL GLANDS IN TWENTY CASES OF POLYNEURITIS COLUMBARUM OCCURRING IN YOUNG BIRDS FED ON AUTOCLAVED RICE, FRESH BUTTER, AND FRESH ONIONS

Number of Pigeon.	Sex.	Weight before Experiment in grms.	Weight after Experiment in grms.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Body-weight in mgrms.	Evidences of Œdema.
210	Female	310	175	58	187	No œdema.
211	Male	260	150	41	157	Do.
212	Female	260	150	38	146	Do.
213	,,	275	200	62	225	2·5 c.c. hydropericardium; slight œdema at auriculo-ventricular junction of heart.
214	Male	275	175	37	134	No œdema.
216	Female	310	150	56	180	Do.
218	,,	250	130	32	128	Do.
219	,,	240	160	33	137	Do.
220	,,	300	160	60	200	Do.
221	Male	240	175	41	170	Do.
198	Female	300	150	46	153	Do.
199	,,	240	130	44	183	Do.
200	,,	250	165	28	112	Do.
201	Male	330	200	31	94	Do.
202	,,	290	200	59	203	0·5 c.c. hydropericardium; œdema at auriculo-ventricular junction of heart.
203	,,	260	145	70	269	No œdema.
204	Female	250	160	41	164	Do.
206	,,	300	220	28	93	Do.
207	,,	270	150	35	130	Do.
208	,,	325	190	51	157	Do.

Analysis of Table VII:

(1) The incidence of œdema in these cases was 10 per cent.: there being 18 cases without evidence of œdema, and 2 cases with evidence of œdema.

(2) The average weight of the adrenals per kilogram of body-weight in 20 control pigeons receiving butter and onions in addition to their natural food was 68·3 milligrams.

(3) The average weight of the adrenals per kilogram of original body-weight in 18 cases of *dry* polyneuritis was 155 milligrams.

(4) The average weight of the adrenals per kilogram of original body-weight in 2 cases of *wet* polyneuritis was 214 milligrams.

(5) The minimum weight of the adrenals per kilogram of original body-weight in any case in the series presenting evidence of œdema was 203 milligrams.

(6) The number of cases of polyneuritis having adrenals weighing 203 milligrams per kilogram of original body-weight or over was 3 : 2 with evidences of œdema and 1 without.

From Table VIII it is seen:

(1) That pigeons fed on autoclaved rice died, or were killed at the height of the disease, in periods ranging from 24 to 95 days: the average for 39 cases being 50·7 days.

(2) That cases of polyneuritis columbarum exhibiting evidence of œdema at autopsy

TABLE VIII

GIVING DETAILS REGARDING TIME OF DEATH, AND EPINEPHRINE-CONTENT OF THE ADRENAL GLANDS IN THIRTY-NINE CASES OF POLYNEURITIS COLUMBARUM RESULTING FROM AN EXCLUSIVE DIET OF AUTOCLAVED RICE

Number of Pigeon.	Days under Experiment.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Original Body-weight in mgrms.	Evidences of Œdema.
244	24	47	224	Hydropericardium: 0·25 c.c.; œdema at auriculo-ventricular junction of heart.
243	28	62	248	Nil.
155	28	37	140	Nil.
146	30	35	145	Nil.
143	30	47	228	Œdema of lungs.
148	32	54	225	Hydropericardium: 0·5 c.c.; œdema at auriculo-ventricular junction of heart.
140	32	52	226	Hydropericardium: 0·25 c.c.; intense œdema at auriculo-ventricular junction of heart.
150	32	68	234	Hydropericardium: 0·5 c.c.; slight œdema at auriculo-ventricular junction of heart.
107	34	65	254	Hydropericardium: 3·5 c.c.; ascites; œdema of lungs.
116	35	72	313	Hydropericardium: 1·0 c.c.; marked œdema at auriculo-ventricular junction of heart.
149	36	31	124	Nil.
156	36	30	107	Nil.
254	36	76	330	Hydropericardium: 0·25 c.c.; ascites; œdema at auriculo-ventricular junction of heart.
253	38	57	316	Œdema at auriculo-ventricular junction of heart only.
250	38	27	142	Nil.
112	39	39	162	Nil.
246	44	55	275	Nil.
247	48	72	313	Hydropericardium: 4·5 c.c.; ascites: 2 c.c.; œdema of lungs.
245	50	71	322	Subcutaneous œdema; œdema at auriculo-ventricular junction of heart.
111	51	53	216	Hydropericardium one drop only; marked œdema at auriculo-ventricular junction of heart.
248	52	35	175	Nil.
253	53	45	225	Nil.
154	53	35	152	Nil.
144	59	38	176	Nil.
151	60	45	160	Nil.
121	60	40	163	Nil.
119	61	70	350	Hydropericardium: 2 c.c.; œdema of lungs; œdema at auriculo-ventricular junction of heart.
145	64	74	264	Nil.
153	74	55	183	Nil.
88	76	45	191	Hydropericardium: 0·25 c.c.
109	76	60	272	Hæmopericardium: 0·5 c.c.; œdema of lungs.
118	76	55	250	Hydropericardium: 0·8 c.c.; œdema at auriculo-ventricular junction of heart.
108	77	58	270	Hydropericardium: 7 c.c.; œdema of lungs; œdema of muscles.
110	79	68	283	Hydropericardium: 1·5 c.c.; marked œdema at auriculo-ventricular junction of heart.
86	80	45	180	Hydropericardium: 0·25 c.c.
87	80	49	228	Hydropericardium: 0·5 c.c.; marked œdema at auriculo-ventricular junction of heart.
83	90	29	113	Nil.
85	91	43	204	Hydropericardium: 3·5 c.c.; œdema at auriculo-ventricular junction of heart.
117	95	81	317	Hydropericardium: 2 c.c.; œdema at auriculo-ventricular junction of heart; œdema of lungs.

were encountered at irregular intervals between the minimum period of 24 days, when the first case of *wet* polyneuritis was met with, and the maximum period of 95 days when the last case of *wet* polyneuritis was met with.

(3) That 22 cases out of 39, or 56·4 per cent., presented serous effusion or other evidence of œdema.

TABLE IX

SHOWING DETAILS REGARDING TIME OF DEATH, AND EPINEPHRINE-CONTENT OF THE ADRENAL GLANDS IN TWENTY-NINE CASES OF POLYNEURITIS COLUMBARUM RESULTING FROM A DIET OF AUTOCLAVED RICE AND BUTTER

Number of Pigeon.	Days under Experiment.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Original Body-weight in mgrms.	Total Epinephrine in mgrms.	Total Epinephrine per Kilogram of Original Body-weight in mgrms.	Evidences of Œdema.
332	20	40	175	0·072	0·300	Nil.
331	21	32	152	0·074	0·352	Nil.
325	22	48	208	0·040	0·173	Nil.
319	24	35	134	—	—	Nil.
314	25	45	166	—	—	Nil.
320	25	30	120	—	—	Nil.
321	26	48	200	—	—	Nil.
305	28	32	110	—	—	Nil.
328	29	35	134	0·060	0·230	Nil.
307	29	42	161	—	—	Nil.
326	30	38	158	0·057	0·237	Nil.
323	31	32	139	0·051	0·221	Nil.
318	33	34	113	—	—	Nil.
329	33	34	150	0·048	0·218	Nil.
310	35	37	148	—	—	Nil.
312	35	28	103	—	—	Nil.
306	36	41	157	0·055	0·211	Nil.
308	36	35	116	0·034	0·113	Nil.
322	36	35	134	0·058	0·223	Nil.
330	37	40	190	0·066	0·314	Œdema at auriculo-ventricular junction of the heart only.
313	42	35	134	0·051	0·196	Do.
333	42	41	141	0·105	0·362	Hydropericardium: 0·5 c.c.; œdema at auriculo-ventricular junction.
315	43	34	113	0·069	0·230	Œdema at auriculo-ventricular junction of heart only.
311	43	57	190	0·204	0·680	Hydropericardium: 0·15 c.c.; œdema at auriculo-ventricular junction.
304	44	103	343	0·195	0·650	Hydropericardium: 10 c.c.; œdema of lungs and at auriculo-ventricular junction of the heart.
316	44	30	111	0·060	0·222	Nil.
317	44	26	130	0·056	0·280	Nil.
324	45	42	190	0·135	0·613	Hydropericardium: 0·5 c.c.; œdema at auriculo-ventricular junction.
327	45	18	85	0·076	0·361	Nil.

Analysis of Table IX:

(1) Pigeons fed on autoclaved rice *plus butter* died, or were killed at the height of the disease, in periods ranging from 20 to 45 days, the average for 39 cases being 33·9 days.

(2) Cases of polyneuritis columbarum exhibiting evidence of œdema at autopsy were

met with only during the last 9 days of the experiment: from the thirty-seventh to the forty-fifth day.

(3) Seven cases presented evidence of œdema, or 24·1 per cent.: of these, 3 exhibited only serous degeneration of the band of fat at the auriculo-ventricular junction of the heart without other evidence of œdema, while 4 exhibited serous effusions in addition to serous degeneration of the auriculo-ventricular band of fat.

TABLE X

SHOWING THE EPINEPHRINE-CONTENT IN THE ADRENAL GLANDS AND THE TOTAL EPINEPHRINE PER KILOGRAM OF BODY-WEIGHT IN TWENTY HEALTHY CONTROL PIGEONS

Number of Pigeon.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Body-weight in mgrms.	Total Epinephrine in mgrms.	Total Epinephrine per Kilogram of Body-weight in mgrms.
264	22	84	0·051	0·196
265	28	112	0·060	0·240
266	18	81	0·060	0·272
267	20	86	0·060	0·260
268	20	95	0·050	0·238
269	21	91	0·099	0·430
270	18	81	0·040	0·181
271	18	81	0·060	0·272
272	25	89	0·070	0·250
273	27	117	0·080	0·347
274	25	108	0·051	0·221
275	22	104	0·050	0·238
276	18	72	0·051	0·204
277	20	86	0·040	0·173
278	20	86	0·044	0·191
279	20	86	0·032	0·139
280	27	135	0·060	0·300
281	21	91	0·060	0·260
282	18	81	0·060	0·272
283	24	126	0·080	0·421

TABLE XI

SHOWING THE RESULTS OF EIGHT EPINEPHRINE ESTIMATIONS IN PIGEONS FED EXCLUSIVELY ON AUTOCLAVED RICE

Number of Pigeon.	Days under Experiment.	Weight of Adrenals in mgrms.	Weight of Adrenals per Kilogram of Original Body-weight in mgrms.	Total Epinephrine in mgrms.	Total Epinephrine per Kilogram of Original Body-weight in mgrms.	Evidences of Œdema.
335	24	47	223	0·106	0·504	Hydropericardium: 0·25 c.c.; œdema at auriculo-ventricular junction.
334	28	62	248	0·153	0·612	Nil.
345	36	76	330	0·143	0·621	Hydropericardium: 0·25 c.c.; ascites; œdema at auriculo-ventricular junction.
341	38	27	142	0·083	0·436	Nil.
344	38	57	316	0·133	0·738	Œdema at auriculo-ventricular junction only.
337	44	55	275	0·116	0·580	Nil.
338	48	72	313	0·116	0·504	Hydropericardium: 4·5 c.c.; ascites: 2 c.c.; œdema of lungs.
336	50	71	322	0·183	1·307	Subcutaneous œdema; œdema at auriculo-ventricular junction.

The data afforded by Tables, IX, X, and XI are contrasted in Table XII.

TABLE XII

Cases.	Weight of the Adrenals per Kilogram of *Original* Body-weight in mgrms.		Total Epinephrine in Glands in mgrms.		Epinephrine-content per Gram of Gland in grms.	Total Epinephrine per Kilogram of Original Body-weight in mgrms.		Food.
	Range.	Average.	Range.	Average.	Average.	Range.	Average.	
Healthy pigeons	72–135	94	·040–·099	·079	·00268	·139– ·430	·255	Mixed grains; greens
Dry polyneuritis	85–208	141	·034–·076	·057	·00166	·113– ·361	·241	Autoclaved rice *with butter*
Dry polyneuritis	142–275	221	·083–·153	·117	·00243	·436– ·612	·541	Autoclaved rice *without butter*
Wet polyneuritis	141–343	216	·105–·204	·159	·00264	·362– ·680	·576	Autoclaved rice *with butter*
Wet polyneuritis	223–330	299	·106–·183	·137	·00207	·504–1·307	·734	Autoclaved rice *without butter*
Cases having serous degeneration at the auriculo-ventricular junction only:								
3 (Table IX) .	113–190	145	·051–·069	·062	·00170	·196–·314	·246	Autoclaved rice *with butter*
1 (Table XI) .	316	316	·133	·133	·00233	·738	·738	Autoclaved rice *without butter*

From the data afforded by Table XII the following facts emerge:

(1) Whereas cases of *dry* polyneuritis resulting from an exclusive diet of autoclaved rice had a total epinephrine-content of the adrenal glands markedly in excess of health, cases of *dry* polyneuritis resulting from a dietary of autoclaved rice *plus butter* had a total epinephrine-content rather less than that of health.

(2) Cases of *wet* polyneuritis, whether resulting from an exclusive diet of autoclaved rice or from a diet of autoclaved rice *plus butter*, had an epinephrine-content of the adrenal glands greatly in excess of that of health.

(3) In cases of polyneuritis in which the only evidence of œdema was serous degeneration of the band of fat at the auriculo-ventricular junction of the heart, the epinephrine-content of the adrenal glands was high in non-butter-fed pigeons and low in butter-fed pigeons.

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