THE PATHOGENESIS OF DEFICIENCY DISEASE.*

[WITH SPECIAL PLATE.]

BY

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(Abstract.)

In perusing the literature of disease due to deficiency of certain accessory food factors one cannot fail to be struck by the fact that however complete our observations have been in some directions there are others in which inquiry has been almost wholly neglected. The want of substances essential for the normal metabolism of the human or animal body suggests the need for examining the effects of their deficiency on the organs responsible for digestion and assimilation and for the regulation of metabolic processes. Yet our knowledge of these effects is very scanty. The influence of "vitaminic" deficiency on the adrenal glands, on the pancreas, on the liver and the spleen, is, so far as I can ascertain from available literature, unknown; while that on the thyroid apparatus has been but incompletely studied. Nor are we better informed with respect to other important structures of the body, as, for example, the pituitary gland and the reproductive organs. It has seemed to me desirable, therefore, to attempt to fill some of these gaps in our knowledge.

The morbid anatomical findings which I have to record will, I hope, aid in a clearer comprehension of the genesis of diseases resulting from deficiency of certain accessory food factors—not only as regards their grosser evidences, as exemplified by beri-beri, but also as regards their minor manifestations. It is rare that the practising physician, outside the tropics, meets with morbid states resulting from complete deprivation of accessory food factors. My own clinical experience leads me to believe that many are the minor maladies associated with the incomplete provision of these substances in the food of children especially, or with their incomplete assimilation. Be this as it may, the laboratory experience gained in the prosecution of this research has afforded me no small measure of assistance in dealing with cases of "bilious vomiting," acidosis, mucous disease, and other metabolic disorders of childhood which have of late been referred to me. I desire, therefore, to draw the attention of physicians, especially those connected with the great children's hospitals, to the effects of "vitaminic" deficiency not only on the central nervous system, but also on the liver, the pancreas, the spleen, the pituitary, the thymus, the thyroid, the reproductive organs, and the adrenal sympathetic system; the functional perfection of all being of such vital importance to the growing child.

In considering these problems in the laboratory it is necessary to observe the results of "vitaminic" deficiency

in healthy animals and also to consider them in connexion with other pathogenic factors which may operate in nature. For example, both inanition and a diet too rich in starch and too poor in "vitamines" lead to depression of biliary, pancreatic, and gastro-intestinal function. If these organs are exposed in addition to the influence of toxic or bacterial agencies, their depression will be manifestly greater. The purity of laboratory experimentation is rarely repeated in nature. The manifold toxic influences to which human beings are subjected under conditions of food deficiency must play an important part in further depressing the functional activity of these organs and tissues on which normal metabolism is dependent. The toxic products of intestinal bacteria or intestinal parasites may thus assume a rôle of high importance in the genesis of morbid states which are, no doubt, initiated by the dietetic defect.

During the year 1914, and during 1918, I fed a large number of pigeons on a diet consisting solely of polished rice—that is to say, on a diet composed mainly of starch, with less than 10 per cent. of protein, and with complete absence of accessory food factors; 168 of these birds developed polyn neuritis avium within the period of the experiments. The heart's blood and the internal organs of 142 birds so fed were examined bacteriologically at autopsy; of these, 94 were

found to have had concurrent septicaemic infections of various kinds, while the heart's blood and organs of 48 were sterile. Four out of 142 had tuberculous disease of the lungs or abdominal viscera, or both.

Seventy-two pigeons were employed as controls; the blood and internal organs of 63 were examined bacteriologically at the time of

death. Six were found to have septicaemic infections of various kinds; two had tuberculous peritonitis. The incidence of tuberculous disease in the pigeons employed was thus 2.7 per cent. The organs of a large number of these birds were weighed immediately after death.

CONCLUSIONS.

The following conclusions have been reached as a result of clinical, morbid anatomical, histological, and bacteriological observations. For details of the research the full paper, which will be published in the *Indian Journal of Medical Research*, should be consulted.

1. The absence of certain accessory food factors from the dietary—improperly termed "anti-neuritic"—leads not only to functional and degenerative changes in the central nervous system, but to similar changes in every organ and tissue of the body. The morbid state to which their absence gives rise is not a neuritis.

2. The symptom-complex resulting from the absence of these substances is due (a) to chronic inanition; (b) to

* The commonly accepted terminology applied to those accessory food factors the lack of which is the essential cause of beri-beri has been retained in this paper, but there are objections to the term "anti-neuritic vitamins." This matter of terminology is dealt with in the full paper.

Chart showing weights of organs, per kilo of body weight, from control pigeons (35 in number) and from pigeons suffering from avian beri-beri (34 in number). Organs sterile. Note the great hypertrophy of the adrenal glands and the great atrophy of the thymus, the reproductive glands, the spleen, and the pancreas in diseased birds. Weights of organs calculated against body weight of birds at the time the vitamin-free diet was commenced. Black columns = control pigeons; shaded columns = diseased pigeons; T = testicle; O = ovary.

* The original paper of which this is an abstract contains full experimental, clinical, and morbid anatomical details. It will appear in an early number of the *Indian Journal of Medical Research*.

derangement of function of the organs of digestion and assimilation; (c) to disordered endocrine function; (d) to malnutrition of the nervous system, and (e) to hyperadrenalinaemia.

3. Certain organs undergo hypertrophy; others atrophy (Figs. 1 and 2). Those which hypertrophy are the adrenals. Those which atrophy, and in the order of severity named, are the thymus, the testicles, the spleen, the ovary, the pancreas, the heart, the liver, the kidneys, the stomach, the thyroid, and the brain (see chart). The pituitary gland showed in adult birds a slight tendency to enlargement in males only.

4. The enlargement of the adrenals is a true hypertrophy in so far as it is associated with a proportionate increase of the glands' adrenalin content. The quantity and quality of adrenalin in the hypertrophied organ is, area for area, approximately the same as that found in the adrenals in health. The hypertrophy is equally well marked in both sexes.

5. Oedema has invariably (100 per cent.) been associated with great hypertrophy of the adrenal glands, while 85 per cent. of all cases having great hypertrophy of these organs had oedema in some form. The amount of adrenalin, as determined by physiological methods, in such cases has been considerably in excess of that found in cases not presenting this symptom, and greatly in excess of that found in normal adrenals.

6. Inanition gives rise to a similar state of adrenal hypertrophy, and to a similar state of atrophy of other organs, the brain excepted.

7. The oedema of inanition and of beri-beri is believed to be initiated by the increased intracapillary pressure which results from the increased production of adrenalin, acting in association with malnutrition of the tissues. Failure of the circulation and venous stasis may subsequently contribute to it. Age is an important factor determining its occurrence. This finding is held to account in great measure for the occurrence of "war oedema" amongst prisoners of war in Germany.

8. Wet beri-beri and dry beri-beri are essentially the same disease; the former differs from the latter in the greater derangement of the adrenal glands.

9. Gastric, intestinal, biliary and pancreatic insufficiency are important consequences of a dietary too rich in starch and too poor in "vitamines" and other essential constituents of the food. It is suggested that some of the obscure metabolic disorders of childhood might be examined from this viewpoint as well as from that of endocrine gland starvation.

10. A state of acidosis results from the absence of so-called "anti-neuritic vitamins"; this state is due to the imperfect metabolism of carbohydrates and to acid fermentation of starches in the intestinal tract. Clinically, it is evidenced by progressive slowing and deepening of the respirations.

11. Great atrophy of muscular tissue results from deficiency of accessory food factors; it is due in part to the disturbance of carbohydrate metabolism in consequence of disordered endocrine function, in part to the action of the adrenals in supplying blood to the vegetative organs of the body at the expense of the muscles.

12. Profound atrophy of the reproductive organs is an important consequence of "vitaminic" deficiency. It leads to the cessation of the function of spermatogenesis

(Figs. 3 and 4). In the human subject such degrees of atrophy would result in sterility in males and in amenorrhoea and sterility in females. This finding is held to account in great measure for the occurrence of "war amenorrhoea."

13. The central nervous system atrophies little; paralytic symptoms, when they occur, are due mainly to impaired functional activity of nerve cells; much more rarely to their degeneration.

14. It is thought that, because of their atrophy out of all proportion to other tissues, the thymus, the testicles, the ovary, and the spleen provide a reserve of accessory food factors for use on occasions of metabolic stress. This reserve, however, is rapidly exhausted.

15. The bones are thinned, and there is a loss of bone marrow.

16. The red cells of the blood are diminished by about 20 per cent.

17. The whole morbid process is believed to be the result of nuclear starvation of all tissue cells. Even the adrenals, which alone of all organs of the body undergo enlargement, show on section changes in some of their cells indicative of nuclear starvation. Accessory food factors are nuclear nourishers.

18. Finally, although deficiency of certain accessory food factors is the essential etiological agent in the genesis of beri-beri, it is held that infectious and parasitic agencies are often important causes determining the onset of symptoms.

"Vitaminic" deficiency renders the body very liable to be overrun by the rank growth of bacteria.

Kymographic tracings of arterial blood pressure in sheep weighing 35 lb. I. Injection into jugular of an emulsion of both adrenals, weighing 16 mg., from a healthy pigeon. II. Injection into jugular of 1/10 mg. of adrenalin (commercial solution 1 in 1,000). III. Injection into jugular of an emulsion of both adrenals, weighing 28 mg., from a pigeon which died of inanition. IV. Injection into jugular of an emulsion of both adrenals, weighing 72 mg., from a pigeon which died of beri-beri with pronounced oedema.

COLONEL A. W. SHEEN, A.M.S.(T.F.), of Cardiff, at present consulting surgeon, War Hospital, Southern Command, India, recently contributed to the *Indian Medical Gazette* a paper on the principles of military orthopaedics and on the constitution of an orthopaedic hospital. He advised that such a hospital should be placed in a bracing locality, easily accessible by railway, and that, in addition to the ordinary hospital departments, it should have electro-therapeutic, hypnotic, massage, and mechanotherapeutic departments, measuring room, bath and x-ray rooms, an operation room, a splint and appliance department, and workshops where the men can do real work and at the same time overcome disabilities. Cases should be grouped in wards according to their nature. In conclusion, he laid it down that early diagnosis and early continuous treatment in large specially staffed and completely equipped hospitals are essential. The motto of such a hospital should be "patience and perseverance."

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FIG. 1.—Adrenals and testicles from a healthy adult pigeon. Upper poles of testicles slightly everted to show the underlying adrenals. Average weight of adrenals per kilo of body weight in adult male pigeons 100.5 mg.; average weight of testicles in ditto per kilo 4.943 grams.

FIG. 2.—Showing effect of a vitamin-free diet on the adrenals and testicles. From a case of avian beri-beri in pigeon. Note the great hypertrophy of the adrenals and the enormous atrophy of the testicles. Average weight of adrenals per kilo of body weight in male pigeons which have died of beri-beri 139.5 mg.; average weight of testicles in ditto 0.4015 gram.

FIG. 3.—Section of normal testicle of pigeon. $\times 95$.

FIG. 4.—Section of pigeon's testicle ($\times 95$), showing effect of a diet deficient in "antineuritic vitamins." Note great contraction of tubules, thickening of intertubular tissue, and almost complete absence of sperm elements.