A British Medical Association Lecture

ON

SOME CONSIDERATIONS ON DISORDERS OF GROWTH.*

BY

HUGH THURSFIELD, M.D., F.R.C.P.,

PHYSICIAN, HOSPITAL FOR CHILDREN, AND ASSISTANT PHYSICIAN, ST. BARTHOLOMEW'S HOSPITAL, LONDON.

THERE is an old philosophical doctrine of the meaning of the universe expressed in the words Πάντα ῥεῖ—everything is in a state of flux; nothing is stable. That is true of life in general and of human life in particular. Growth and development, degeneration and decay, are inevitable laws of Nature as we say—that is, these processes represent in our experience the recurring phenomena of life without a known exception. In our own department of the study of the phenomena of human life, in medicine, when we deal with the adult our principal business is the appreciation of the processes which lead to degeneration and decay, and we endeavour to influence conditions in such a fashion as to retard the operation of the inevitable law. But in the study of the infant and the child our attention is to a large degree concentrated on the opposite principle, the law which governs growth and development.

Till the middle of the nineteenth century our knowledge remained much as it had been in all the previous centuries of man's existence, but with the promulgation of the doctrine of evolution and natural selection an immense stimulus was given to the study of the development of the human being. New fields of investigation were opened and the modern science of physiology began to provide the ancient art of healing with new ideas. The results of the study of the thyroid gland introduced us to the functions of the glands of internal secretion, and speculations on the nature of inherited qualities and their transmission stimulated research into the origins of growth and development.

When we ask why the infant grows and develops, the answer which our present knowledge must give is that there are two principal factors: one the inherent stimulus which is common to all young life, which we recognize as a law of Nature; this we can analyse to a certain degree, and perhaps we may succeed in time in modifying it consciously in human life as we have succeeded in the vegetable and animal kingdoms. Eugenics is the branch of science which seeks this end. The other factor, over which we gain more control as time passes and knowledge increases, may be called the external factor, the law that growth cannot occur without a supply of the material which is to be built into the growing tissues, and even so can occur normally only if the material supplied is properly distributed and regulated by the various structures which we have learnt to regard as governing growth. These governing structures are the glands of internal secretion, and our knowledge of them, though it increases, is still pitifully small.

We can therefore recognize two spheres in which we can attempt to control growth—the ante-natal period and the period of growth after birth; and two factors which between them determine the nature and the course of growth—the glands of internal secretion, and the material supplied to them. It is obviously in the period after birth and in the nature of the material supplied that our best opportunity lies of influencing the development of the infant; but the ante-natal period is of increasing importance, and in one direction at least we have gained a measure of control over the ductless glands. The field thus sketched out is clearly far too wide for a comprehensive review, and I propose to select a few points in it for consideration.

THE ANTE-NATAL PERIOD.

Congenital defects have always attracted much attention, but our knowledge of their causation is singularly small. Many of these defects are local and apparently the result of some aberrant impulse in the inherent principle of growth. A good example is the congenital abnormality of the heart, or the congenital absence of some bone such as the radius. Some such events we classify under "atavism" or "reversion to type"—phrases which may help us to grasp the exceeding complexity of the human body as it exists at the present time, but throw no light on the stimulus which provokes the reversion. Such events we neither understand nor can attempt to control. On the other hand, we know that tuberculosis or alcoholism in the parents leads to a high percentage of mental deficiency in the offspring; and that a disease such as syphilis can be transmitted to the unborn child. Yet when we have counted all the recognized factors which influence the development of the foetus we are left with the great bulk of congenital abnormality wholly unexplained. We do not in the least understand why one of a pair of twins should be a Mongolian idiot, and the other a normal child; or why one child in a long family should be born with achondroplasia. You will be able to recall dozens of other examples in which as yet our knowledge is absolutely nothing. But we know enough of the facts of inheritance to be able to predict the probability of haemophilia in a given family; and we have mastered therapeutics sufficiently to secure that the child of a mother who was herself born a cretin should be a normal individual. Again, recent experimental work, to which I shall recur, seems to point to the fact that the absence or deficiency of certain elements of food in the diet of the pregnant or nursing mother has a marked influence on the growth and development of the offspring, and especially upon its skeleton.

But in the ante-natal period there remains a vast mass of unknown, unguessed-at factors which can only very slowly be revealed by the advance of eugenic study and the knowledge derived from researches on inheritance in animals and plants. Meanwhile, we in this generation must be content to do the recording and the classification so that the date of the revelation of the underlying principles may be hastened.

THE PERIOD AFTER BIRTH.

Physiology deals with the function of the living organism, and its most obvious field of research is that which includes the supply of material to the increasing tissues; and though we know that growth may be stimulated by other factors of environment, such as air, light, and exercise, yet the quantity and quality of the food clearly holds the first place. Physiology early established the normal curves of infant growth and engaged in the task of analysing the quantities and qualities of the known chemical elements which go to the building up of the tissues.

Vitamins.

Towards the end of the nineteenth century it had become clear that besides the proteins, fats, carbohydrates, and mineral salts which compose the essential chemical elements of food there must be other, hitherto unrecognized, substances essential to life. This was, of course, not a new idea—it had long been familiar to clinicians brought into contact with cases of scurvy; but the hypothesis was not accepted by all clinicians and was far from proof. Physiology sought the proof by the method of exclusion from the diet of everything except the recognized chemical elements. There was an interval before they were able to reach the desired standard of purity, but in the first decade of this century Hopkins at Cambridge was able to demonstrate conclusively that a diet of standard purity, though complete in quantity and quality as recognized by chemical analysis, was insufficient to maintain growth, and if continued led to death, usually from intercurrent infection. I need not detain you with the subsequent history. I will merely remind you that it is now established that over and beyond the recognized chemical elements of food there are three accessory food factors, or vitamins—fat-soluble A, water-soluble B, and the antiscorbutic factor C. Whether there are others than these is undecided. McCollum and his fellow workers at one time considered that fat-soluble A really contained two separate elements—one necessary to growth, the other necessary for the normal production of bone. More recently they have claimed the existence of a fourth vitamin, D, which is antirachitic, but at present the

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claim is not substantiated. It is possible that other vitamins exist, but with our present knowledge it is not very probable.

The discovery of these accessory food factors is of the first importance in our study of the disorders of growth. It is clear that no normal growth can occur in their absence, but we do not yet know clearly what are the effects of a mere deficiency in quantity. Nor shall we know this with accuracy until the efforts of the physiologists have succeeded in isolating the vitamins and determining their actual composition.

Vitamin C.—However, with vitamin C, the antiscorbutic factor, some progress in this direction has been made, and it is possible to estimate the quantity per kilo of body weight of orange juice or cabbage juice necessary to protect a guinea-pig against scurvy. In the infant it has long been known to clinicians that the effects of a scurvy-producing diet require some time to show themselves and that there are degrees of severity in their manifestations. With our knowledge of vitamin C some of this variability is explained. The milder cases and those which develop only after a long course of the scurvy-producing diet are presumably those in which antiscorbutic is not wholly absent but is present in insufficient quantity. And in those cases which are severe or develop after an extremely short interval of the scurvy diet the factor is presumably absent altogether. But clinical observation, stimulated by such considerations, has gone further, and Hess and others have shown that there is what we may call a latent or subacute scurvy which has not hitherto been recognized. There is a group of infants of from 3 to 6 months of age in which growth is defective, irritability pronounced, and there is obvious pain on handling. If such an infant is supplied with orange juice in good quantity these symptoms almost at once disappear and normal growth is resumed. Such infants have usually been fed either on food which is notoriously defective in antiscorbutic quality or breast-fed by mothers whose own diet has been similarly defective. I have in the past year seen two such cases, and the result of the addition of antiscorbutic to their food is striking. I think that besides the obvious haemorrhagic disorder of the older infants we must recognize the existence of a milder and less obvious scurvy which may attack the infant in the early months of life. We must further recognize that the nursing mother, though in normal circumstances amply supplied with vitamin C and able to transmit it to her infant, may be so situated that her own supply fails, and that with the failure the infant is exposed to scurvy. The remedy is to secure for every nursing mother an ample supply of the vitamin-containing foods, such as fresh fruit and fresh vegetables. On the whole the dangers of an insufficient supply of vitamin C are well understood; the chief addition to our knowledge is the appreciation of these minor and earlier manifestations in infants, whether fed artificially or by the breast.

Vitamin B.—On the whole, again, vitamin B, the water-soluble factor, seems to be very seldom, so far as our present knowledge goes, a factor in delay of growth. It is present so abundantly in so great a variety of foods, and it is so little affected by cooking processes, that a deficiency in this respect is hardly to be expected. I had hoped that a deficiency in this respect might be the explanation of our failure to deal successfully with some of the cases of infantile atrophy, but all clinicians are united in agreeing that the supply of this factor has no influence on the disorder. Nor have the results of administering yeast to older children suffering from chronic wasting disease been any more satisfactory. The claims of the manufacturers of patent foods may in this respect be entirely disregarded.

Vitamin A.—It is round the fat-soluble vitamin A that the greatest controversy rages and the most doubt exists. It is clear from the experimental work that without vitamin A growth fails; and it is also clear that if vitamin A is absent or deficient normal calcification of bone cannot take place. But it is also becoming clear that a failure or a deficiency in vitamin A is not the sole cause of rickets. In the controversy which has taken place the contention on the one side has been that rickets is essentially a deficiency disorder, and on the other that it is in the main caused by external conditions, especially by the absence of sufficient light and exercise. There are two facts which appear to me to stand out from the mass of experimental work on this subject: one that it is difficult to produce rickets in an animal who is provided with a proper amount of vitamin A, of calcium, and phosphorus; the other that rickets is apt to be seen in animals whose diet is ample in these respects if the other conditions of their life are unfavourable. From some other experiments it would seem possible that these two apparently irreconcilable facts are in reality corollaries of each other. It would appear, for instance, that if the experimental animal is exposed to light—either sunlight or the light of the mercury vapour lamp—a much smaller amount of vitamin A is sufficient to inhibit the rickety changes in bone than is required by the animal who is brought up in the comparative darkness of the laboratory. Whatever the ultimate outcome of the investigations into the relationship between vitamin A and rickets, it is clear that the clinician must, as he has been doing for many years past, recognize that for his rickety patient an ample supply of animal fats is necessary. Fortunately all the researchers are agreed that cod-liver oil is a substance especially rich in fat-soluble A, so that by the simple addition of this drug to the food of an artificially fed infant the worst manifestations can be avoided.

I emphasized just now the importance to the pregnant or nursing mother of a supply of antiscorbutic factors. It would appear from some recent experimental work that the pregnant mother has also especial need of an ample supply of fat-soluble A. In Korenchevsky's experiments the young rats of two separate litters were weighed on the thirty-sixth day of their lives—both litters had been fed by their mothers and both mother rats had received during lactation exactly the same food. The one mother had, however, during her pregnancy received cod-liver oil in addition to the basal diet which both had; the young of this mother weighed on the average three times more than those of the other litter. Other similar experiments go to prove that a rat mother who is fed during her pregnancy on a diet defective in vitamin A will produce young with defective bone formation, due to a deficiency of calcium in the periosteum, and will herself tend to show a marked thinning of the bones.

Osteogenesis Imperfecta.

It is impossible with these experiments in our minds not to think of that obscure disorder of human growth which is best termed osteogenesis imperfecta. You will remember that there are infants born with so great a tendency to fracture of the bones that life is impossible; that others manage to retain a hold on life but with an extraordinary tendency to fractures and to marked curvature of the long bones; that others, again, with comparatively few fractures yet have bones so thin and slender that violence which would do no damage to a normal individual causes fractures. These various conditions have unfortunately been christened with a great variety of names, so that it is often difficult in reading of them to determine how far they are distinct disorders. My own impression is that there is but one disorder—osteogenesis imperfecta—and that fragilitas ossium, osteopsathyrosis, and infantile osteomalacia are merely varieties of severity. If this is correct I think it possible that Korenchevsky's experiments may indicate the cause of this disorder of growth: a lack of vitamin A during the pregnancy, and possibly a defective supply of calcium and phosphorus. From some other experiments it seems to be possible that the lack of vitamin A is the actual cause of the lack of calcium absorption. At any rate it is obviously the duty of the physician to ensure a good supply of vitamin A to the pregnant mother—an easy task, even when for any reason animal fats are difficult to procure or to digest, for cod-liver oil in quite small quantities contains vitamin A in abundance.

Glands of Internal Secretion.

I have but touched the fringes of the subject in talking of vitamins, but I hope that I have been able to emphasize the great importance of the discovery, and the new field of hypothesis which it has opened. I must pass on to another portion of the subject—the relationship of the glands of internal secretion to growth and development. We are leaving to a large extent the sphere of experimental medicine and entering that of clinical observation, and too often

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straying into that of mere surmise. So much has been written and is still being written on the ductless glands that it comes as something of a shock to realize how little we really know, and how much of what we sometimes consider knowledge is in reality nothing more than ingenious speculation. We know something of the influence of the thyroid on growth; less of the pituitary; and still less of the adrenal glands. We know that the interstitial tissue of the sexual glands, the testes and the ovaries, is of great importance for normal development. We believe that the parathyroid and the thymus have an intimate relationship with certain disorders. And we are just now apparently on the edge of conquest of a new sphere of control, in the isolation of the active principle of the internal secretion of the pancreas. I do not wish to enlarge on these topics. I want to turn your attention in a slightly different direction.

We have seen, in considering the subject of vitamins, that if you supply sufficient quantity and quality of food the young animal will grow in a normal fashion. But he will only do so if the glands which control growth are working naturally and in harmony with each other. If there is, for instance, a defect of the thyroid secretion growth will be abnormal; the creature will not cease to grow, but the increasing tissues will be distributed in the body in an abnormal way—the skeleton will develop abnormally; the fatty tissue will be excessive and curiously localized; and the mental powers will be defective. It is as if you had presented an architect with the richest material in proper proportion and asked him to build a shrine, and though he has used the material he has built a deformed and unsightly hovel. So it is also with a defect of the pituitary secretion, and with the victims of a defect of the interstitial tissue of the sexual glands. In the one case the failure of the pituitary architect may produce a "Fat Boy of *Pickwick*"; in the other the failure of the interstitial architect may produce the deformity of the body which we call the "eunuchoid" type. In the case of the cretin we have to a certain extent mastered the secret and can by addition of thyroid extract procure a more or less normal growth; in the hypo-pituitary abnormality we are only tentatively feeling our way; in the "eunuchoid" type there is, so far as I know, as yet no real success.

I want to digress for a moment to speak of the hypo-pituitary type. There is a group of children who exhibit a tendency to become very fat and at the same time to develop the fat especially in the hips, thighs, and abdomen; in addition their genital organs retain the infantile type, and towards puberty they exhibit none of the secondary sexual characteristics. Fröhlich was, I believe, the first to point out that this abnormality was sometimes associated with a tumour of the anterior portion of the pituitary gland, and it is often known as "Fröhlich's syndrome." What is perhaps not so well appreciated is that such a syndrome is often only a temporary phenomenon, and that after a time normal growth is resumed. The presumption is that there is a functional disorder which for a time diminishes the available amount of the necessary internal secretion. I have had some success in treating such children with extracts of the whole pituitary gland. One boy in particular was brought because he could not keep awake either in school or even at his meals. In this, as in his general appearance, he recalled Dickens's description of the Fat Boy. He had no sign of a pituitary tumour, but when placed on extract of the whole gland he became almost normal. He was discharged, but after an interval his father appeared asking for more of the tablets as the only means of keeping him awake. More often, however, therapeutic efforts fail: we do not know enough of the conditions.

In such forms of abnormal growth there is an inherent defect in the functions of the glands of internal secretion, but there are other conditions in which we have reason to suppose that the alteration of the secretion is brought about by factors over which we may learn to gain a degree of control. For example, it is a notorious fact that after some infectious diseases growth may take place with unusual rapidity. After an attack of typhoid fever, for instance, the adolescent may suddenly increase several inches in height; while the adult may become alarmingly stout. On the other hand, there are two diseases of childhood which in my own experience exert the opposite effect. Both diphtheria and tuberculous peritonitis may for a time completely stop growth in height and weight, and I think it is usually a matter of a couple of years before growth is resumed, so that either of these diseases may leave a permanent mark. In these instances I think we are obliged to look for an explanation to some functional disorder of the glands of internal secretion, and I am at present trying the effect of increasing doses of thyroid on one such case, with the result that he has put on a pound a month since he began the drug, whereas for the previous year the total increase had been less than two pounds.

Somewhat in the same category I should feel inclined to place the celebrated case recorded by Byrom Bramwell, in which the addition of pancreatic extract transformed in a year or two a real dwarf into a small but fairly normal individual.

Lastly there is a group which is much less hopeful but which is, from our present standpoint, of great interest—the group of "renal" dwarfs. They were recognized and described by Morley Fletcher in adolescents some years ago and have been written about a good deal since. But quite lately my colleague Donald Paterson has shown that there is a similar group with characteristic lesions in the skeleton recognizable by *x*-ray examination, occurring in the infant; and I have recently had in my charge a child of 7 years who seems to me to represent another type of the same abnormality. Whether their dwarfism is due to an internal secretion of the kidney, or can more justly be referred to a poisoning of the sources of growth, is a matter which must be left for later research.

There is, of course, much more that could be said on such a subject, but I hope that I have succeeded in sketching the intimate relationships which appear to exist between the materials and the architects: that the architects cannot work without the proper materials, and that improper material may impair the powers of the architect for a short time or even permanently; and that with architects of inferior powers or out of harmony with each other good material may be built into monstrosities.

The Middlemore Lecture, 1922, ON REFRACTION.

DELIVERED AT THE BIRMINGHAM EYE HOSPITAL
BY
T. HARRISON BUTLER, M.D., B.CH.OXON.,
SURGEON, BIRMINGHAM EYE HOSPITAL.

(*Abridged.*)

DR. RICHARD MIDDLEMORE founded this lecture in order that it might year by year afford the medical men of the Midlands an opportunity to hear the latest views upon an ophthalmic subject of general interest. I therefore do not apologize for selecting refraction as my subject.

The field for refraction is unlimited, and it is quite impossible for ophthalmic surgeons to handle the whole. At the present time the majority of the cases are dealt with either in hospitals or by men who do not possess a medical training. There is no reason why much of this work should not be undertaken by the general practitioner to the advantage of himself and his patient. If he decide to take up refraction he must adopt modern methods and learn retinoscopy.

Refraction cannot be learnt from books, and retinoscopy demands considerable practice. Probably the average man will require three months' constant work in an eye clinic before he attains the necessary accuracy. This period will not be wasted, for both from the standpoint of diagnosis and treatment a working knowledge of ophthalmology, not excluding refraction, is indispensable to the up-to-date physician.

THE OBJECTS OF REFRACTION.

The object of refraction is to make the patient comfortable, not the solution of a problem in optics. Glasses are prescribed to enable an individual to see clearly, and to relieve symptoms caused by errors of refraction and of muscle balance. It does not follow that spectacles which

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