THE RATIONALE OF PARATHYROID THERAPY.

BY

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CHRONICITY of disease implies a stage in a pathological process at which neither the defence of the body nor the attack of the invading organism is making headway, but where the condition is that of an almost evenly balanced conflict. It is a balance between the effect of the parasite on the host and that of the host on the parasite, for in the first case the host has for some reason failed to respond sufficiently to the attack, and in the second the parasite is kept sufficiently in check to prevent an overwhelming onslaught. The main defence of the host lies in its cellular response, indicated by the mobilization of leucocytes and by the production of certain substances collectively called the antibodies. It is obvious that in chronic infections this response is insufficient to defeat the invading organism, and though it is easy to say that the resistance of the body has become weakened, such a statement explains nothing and affords no clue to the means of helping the body to victory.

It is impossible to assume that the reactions of the body to an infecting organism are limited merely to the mechanical mobilization of pre-existing cells and chemical substances. Both cells and antibodies are the end-products of other processes, for they must originate from some definite source, since neither is capable of reproduction in the blood stream. It is therefore behind these end-points of immune reaction that we must search for a clue to the failure of somatic response in chronic infections. Where the infection is of long standing, it is necessary materially to increase the rate of production of the leucocytes, and it cannot be assumed that the leucocyte-producing tissues alone of the body cells commence a proliferation due directly and entirely to the incidence of infection. Some means must therefore be found of stimulating certain tissue functions, and so the problem at once assumes a nutritional aspect. It may be recalled that the usual means of combating disease is by "keeping up the patient's strength"—that is to say, by decreasing tissue breakdown as far as possible by keeping the patient at rest, and by giving a nourishing diet; for many years therefore the basis of treatment of infections has been essentially the conservation of tissue energy.

THE SYMPATHETIC RESPONSE TO DISEASE.

The non-volitional activities of the body—and among them immune reactions must be reckoned—are for the most part under the control of the autonomic system, and closely associated with the latter is the group of endocrine glands. Through the agency of this double system the metabolic tone of the body is kept at a standard level, which is recognized as the physiological normal, and since metabolism and resistance are so closely related it is not unreasonable to turn to this system in search of the cause of failure of the body to react to infective processes. The autonomic system and its associate glands are generally divided into two groups—the thoraco-lumbar or sympathetic system, with which are associated the thyroid, suprarenal, and pituitary glands; and the cranio-sacral or parasympathetic system, to which are conjoined the pancreas, the parathyroids, and perhaps the thymus. If now we consider the symptoms of an acute infection it is not difficult to see which of these two systems becomes first affected. Acute infection is accompanied by fever, tachycardia, shivering, sweating, increased metabolism, and hyperglycaemia; all these are signs of overaction of the sympathetic nervous system, and they may also be produced in some degree by overaction of the thyroid gland. If these symptoms are perpetuated the picture of a chronic wasting febrile disease is presented, and may be exemplified by the later stages of phthisis. The tendency of this syndrome is towards death, since the rate of katabolism is greater than that of anabolism, and therefore we find that the general

treatment of such conditions has been by rest and adequate nutrition, the indirect method of increasing resistance by limiting tissue breakdown.

There is another biochemical sign in acute infections which is of importance—it is the loss of calcium from the body; it has been recorded by a considerable number of observers and in a wide variety of diseases. There is evidence that this also is a sign of sympathetic overaction, for it may be produced by hyperthyroidism, while the parathyroid glands, which belong to the opposing system, are the regulators of calcium metabolism. I have observed disturbances of calcium metabolism in ulcerative conditions, and it has been shown that if the calcium deficiency which occurs is rectified by means of parathyroid administration the ulcer will also heal, the two processes running concurrently. Bruning and others consider that "trophic ulceration" is due to sympathetic overaction, and that while hypersympathicotonia leads to tissue degeneration and necrosis, vagotonia leads to tissue regeneration and repair. On these lines they treated a series of cases of varicose ulcer by periarterial sympathectomy and obtained satisfactory results. To sum up: the signs of sympathetic overaction include fever, tachycardia, sweating, hyperglycaemia, calcium loss, and a tendency to ulceration. All these are clinical signs of acute infection with the exception of the last, which, however, often appears in chronic infective states.

The acute infection has so far been considered, but it is easy to imagine a condition of less severity in which the symptoms are less marked and in which the infection is less acute. There may only be a low degree of fever, barely perceptible tachycardia, and yet the diagnosis of infection can often be proved bacteriologically. In such conditions some degree of hyperglycaemia and a decreased content of active calcium in the serum may be found, so that signs of sympathetic overaction are still present. We have now arrived at the picture of a chronic infection in which a low-grade sympathetic overaction is present, but yet in which the sympathetic function is greater than in the normal subject. For instance, in chronic nephritis there may be no clinical signs of sympathetic overaction, and yet calcium loss and hyperglycaemia have been frequently recorded.

Bacterial infection tends therefore to the disturbance of the balance between the sympathetic and the parasympathetic systems, the effect of the latter being outweighed by that of the former. If this be translated into terms of the endocrine glands, we may say that the thyroid overacts and submerges the action of the parathyroid glands. Examples of this antagonism are not uncommon, and it is frequently found that where a case is making progress on parathyroid therapy, the exhibition of thyroid substance will lead to retrogression.

THYROID FUNCTION AND RESISTANCE.

It is quite clear that in infection the sympathetic system is first affected and that its main activity is an acceleration of metabolism together with increased efforts of elimination. This action cannot, however, be regarded as a purpositive one, but it is more in the nature of an irritative effect by the bacterial toxins upon the sympathetic system. The question may even be raised whether the febrile response is of real assistance, and here the phenomena of immunizing animals may be of value. Sestini observed that the thyroid gland of guinea-pigs showed signs of hyperplasia and intense cellular activity during immunization against *B. typhosus*. Kepinow and Metalnikow experimented upon the tuberculin reaction in guinea-pigs and found that the febrile response was closely connected with the thyroid gland since thyroidectomy prevented its occurrence; removal of the thyroid did not, however, prevent the guinea-pigs from dying.

There is apparently no relation between the degree of febrile response which follows a vaccine injection and the degree of immunity thereby established, and it becomes questionable whether the febrile reaction is an advantage or the reverse. The results of the injection of a full dose of vaccine are parallel to a mild acute infection in regard to the clinical and biochemical signs, and in both instances

a negative phase of resistance is produced. The time of occurrence of the negative phase is coincident with that of the sympathetic response; in an acute infection vaccine therapy in the acute stage may have serious consequences, and an acute infection supervening in the negative phase after vaccine injection may be equally dangerous. There is no proof that thyroid overaction produces either maintained leucocytosis or favours the production of antibodies; such evidence as there is points to an opposite effect. It appears that the febrile response to infection has but little real value, except that it may aid in the elimination of a certain amount of toxic material by increasing the blood supply to the eliminative organs. It is also of interest to note that fever is usually regarded as a sign of danger and not of protection, that efforts are made to reduce it, and that the favourable course of disease is judged largely by the diminution of the intensity of the fever. Much has been written concerning the action of the thyroid as a "detoxicating organ," and though the statements are usually of a vague and indefinite character, there seems to be a gradually growing idea that the destruction of toxic substances occurs actually within the gland. No satisfactory proof of this theory has ever been forthcoming, and there is no evidence that thyroxin or thyroid gland can destroy toxic substances *in vitro*. The theory seems to be based largely on the hypertrophy of the thyroid in infections and in pregnancy, but the possibility does not seem to have been considered that such hypertrophy may be a reaction to chronic irritation, just as any other tissue may hypertrophy under similar conditions.

PARASYMPATHETIC FUNCTION.

Chronicity of infection may therefore be due in part to a continued overaction of the sympathetic system, and a simultaneous depression of parasympathetic activity which may be relative or absolute. It must also be remembered that the endocrine glands may suffer direct damage in disease and that their function may therefore be interfered with; in addition the function of the parasympathetic glands may be further affected by the thyroid hypersecretion. That such damage may be done to the parathyroid glands is shown by the not infrequent occurrence of tetany in acute and chronic toxic conditions. The function of the parasympathetic system is essentially towards the conservation of tissue energy, whereas that of the sympathetic is to accelerate metabolism even to the ultimate destruction of life. Normally these two systems are in equilibrium, and it seems reasonable to suppose that when this balance has been upset by infection one method of inducing adequate resistance to the disease will be to restore the endocrine balance to its normal state. It has already been pointed out that the sympathetic response to a vaccine injection does not produce a high degree of immunity, and that it is not until the sympathetic response is over that immunity becomes established. The injection of dead organisms limits the extent of the sympathetic response in point of time, but where an infection is present it is probable that the continuous irritation of the sympathetic system prevents, or at least delays, the re-establishment of the normal sympathetic-parasympathetic balance.

PARATHYROID FUNCTION AND RESISTANCE.

If this view of chronic infection is correct, the reasonable method of dealing with the condition is by increasing the parasympathetic function. If we regard the balance between the sympathetic and the parasympathetic as being represented by the balance between thyroid and parathyroid, then the means of counteracting thyroid overaction would be by parathyroid administration. The susceptibility of animals to infection after parathyroidectomy is well known; in common with other observers I have found that parathyroid therapy is of value in a wide variety of chronic infective states. In such different conditions as varicose ulcer, rheumatoid arthritis, and sprue, among others, it has been shown that an increase of the parasympathetic element by parathyroid therapy leads to a marked improvement. In such differing states there can be no question of any specific action of the preparation used upon the infecting organism, and it is evident that the phenomena of resistance to disease lie deeper than the leucocyte and the antibody. Moreover,

I have found that where a chronic infection is present and where the leucocyte count is low, the administration of parathyroid substance has led to a considerable increase in the leucocyte count, indicating an effect upon the leucocyte-producing tissues. Similar effects, but of a less decided character, may be obtained by the injection of soluble calcium salts, and this supports the statement that calcium loss is one of the signs of sympathetic overaction. It is of interest to note in this connexion the powerful action of ultra-violet light upon disorders of calcium metabolism such as rickets, and also the curative effect of sunlight on such chronic infective states as tuberculosis. One might conjecture that ultra-violet light has a depressant action upon the sympathetic system or that it stimulates the parasympathetic.

ENDOCRINE BALANCE.

It seems, therefore, that the problem of chronic infection resolves itself into the problem of equilibrium between the sympathetic and the parasympathetic systems, represented by the thyroid and the parathyroid glands respectively. It is not difficult on these lines to understand the incidence of chronic sequelae after acute infections, although the acute attack has apparently been overcome successfully and though the sequelae may be remote in point of time. The endocrine balance which was disturbed in the acute attack has never in reality returned to normal; a new equilibrium has been established on a different level which will still permit of an apparently normal existence. This new balance contains a sympathetic element greater than the normal, and signs of hyperthyroidism after severe illness are not uncommon. The patient is therefore left with a degree of parasympathetic deficiency and its accompanying susceptibility to infection. This is the condition which has been called "latent tetany," though a better term would be "chronic parathyroid insufficiency."

To recapitulate: the immediate response to infection, just as to physical attack, is an overaction of the sympathetic system. If the severity of the infection is of such a degree that it can be immediately overcome by the existing defences, there are no further ill results. If, however, the invading organism is not rapidly destroyed, the sympathetic irritation is continued and recovery does not take place or is long delayed; the condition becomes chronic, for under the existing condition of sympathetic overaction the resistant powers present at the onset of infection are not adequately reinforced. But if the activity of the parasympathetic can be stimulated, the re-establishment of the normal balance between the two systems permits recovery. As the body is kept in health by the normal balance between sympathetic and parasympathetic, so must this balance be re-established at the normal level for recovery to occur from an illness by which it has been disturbed.

Such a conclusion must lead to the consideration of all infective states on a similar basis, since the major phenomena of resistance to disease are not specific to the infecting organism in any sense of the word. The body reacts to all infections of equal severity in the same way—namely, by those phenomena which are collectively termed inflammation—and the only substances which are specific to the infecting organism are the antibodies. There is no evidence that these substances are produced to any great extent by the immediate sympathetic response, and experimental evidence suggests that thyroid activity does not facilitate their formation. They are a later development; in immunizing animals they appear after the negative phase at a time when the balance between sympathetic and parasympathetic is being restored. The leucocytes and the antibodies are not themselves necessarily affected by the disturbance of endocrine balance; the effect is upon the tissues as a whole, and therefore includes the sites of leucocyte production. In disease the body must be regarded as an organism with limited means of reaction, and it is those factors which control the physiologically normal state which will afford a clue to the control of abnormal or pathological conditions.

CONCLUSION.

The rationale of parathyroid therapy is therefore simple; it is a means of re-establishing the normal endocrine balance of the body, which infection has disturbed. Emphasis is

laid on the point that the balance between sympathetic and parasympathetic must be brought back to normal level; adequate resistance to disease is not a function either of the sympathetic system or of the parasympathetic system, but of the equilibrium between them. Disease may occur equally when either system is overacting at the expense of the other, and it is probable that the great success of prophylactic vaccination as compared with the more meagre results of curative vaccination may depend on the fact that in the former case the subject is healthy and is in a state of endocrine equilibrium, whereas in the latter case other conditions prevail. Any tissue performs its functions best when under physiologically normal conditions, and it cannot be supposed that the tissues which are concerned in the mechanisms of defence are exceptions to this rule.

EPIDEMIC HICCUP AND ENCEPHALITIS LETHARGICA.

REPORT OF A CASE OF EPIDEMIC ENCEPHALITIS SHOWING LETHARGY, CRANIAL NERVE PALSIES, MYOCLONUS, AND HICCUP,

BY

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The purpose of this communication is to report a case of epidemic encephalitis exhibiting in one individual many of the varied manifestations of this protean disease.

M. M., aged 16, a healthy-looking well developed girl, was admitted to the London Hospital on July 18th, 1923. The mother says she had St. Vitus's dance as a child. In November, 1918, she had an acute illness. She was in bed a week with severe headache, sleepy all day but restless at night, and delirious for a day or two. She did not complain of visual impairment or diplopia at that time. Drooping of the right eyelid was noted by the doctor who attended her, but the mother said it has been present since infancy, and this is corroborated by photographs. She made a good recovery. This was possibly a previous attack of encephalitis.

Three months before admission she began to have attacks of hiccup two or three times a week; the attack would last a few minutes and then stop spontaneously.

Two months before admission she became acutely ill with severe headache. She slept all day, was hard to rouse, and became "a little light-headed at night." She vomited several times and the temperature is said to have been 104° F. She was in bed two days, and on getting up found that objects looked blurred, and she saw double, and has done so ever since—has felt languid and has had occasional attacks of hiccup as before.

Eight days before admission an attack of hiccup began which continued until admission; and she did not sleep at all on the previous night. The mother states that the patient has been always rather excitable, but more so since her illness two months ago.

Condition on Admission.

Mental State.—On admission she was restless, excitable, and talkative; smiling and laughing during examination. In spite of having hiccupped persistently for eight days she was apparently in no way depressed or fatigued by her condition, but, on the other hand, was rather amused at it; she was able to give an intelligent account of her illness; and her memory was unimpaired. Her mental state was thus similar to that of the myoclonic cases described by Ellis, though the excitement was less extreme and there was no delirium.

Hiccup.—When admitted she was hiccupping about 120 times a minute. Synchronous with each contraction of the diaphragm was a relaxation of the musculature of the abdominal wall and a sharp dilatation of the alae nasi. The frequency of the hiccup was diminished during speech, but it was not completely inhibited and often cut short a word; laughter caused a similar partial inhibition. She complained of a sensation of stiffness around the lower ribs. The hiccup ceased as soon as she was given a hot bath, within two hours of admission, and before she had had any sedative drug.

Myoclonic movements occurred in the upper limbs and the abdominal walls, but have never been very marked. In the upper limbs there were slight jerking movements of flexion of the elbow, wrist, and fingers, and pronation of the forearm occurring every few seconds. In the abdomen even before the hiccup ceased slight twitches of the abdominal muscles were seen, which did not occur so frequently and did not synchronize with it. When the hiccup ceased it was possible to examine these movements alone. They occurred seven or eight times a minute almost entirely in the upper abdomen and chiefly in the upper right quadrant, the umbilicus being drawn sometimes straight upwards, but usually obliquely upwards and to the right. The movements were associated with a weakness of the upper abdominal wall for voluntary movement, the umbilicus moving downwards when the head was

raised from the pillow against resistance. The abdominal reflexes are of interest; the response in the right upper segment was very brisk as compared with the reactions in the other segments, and consisted of a sharp primary twitch, followed by a series of smaller twitches occurring at irregular intervals for several seconds. The reflexes on the left side and in the lower segments on the right side were normal. The myoclonic movements were thus associated with an increased reflex excitability of the same segment of the abdominal wall.

Cranial Nerves.—The fundi were normal, vision was unimpaired, and the visual fields normal. Photophobia was present, with a reflex spasm of the orbicularis oculi on illuminating the homolateral eye. The pupils were somewhat dilated, equal and regular. There was an extremely sluggish and unsustained reaction to light and on accommodation, but a slightly brisker response on convergence, which was poorly carried out. There was a slight weakness of the external rectus on each side with a corresponding convergent strabismus and diplopia on extreme lateral fixation to either side. Slight ptosis of right eyelid. No nystagmus. The uvula was drawn to the right on phonation. The other cranial nerves and the remainder of the nervous system showed no abnormality.

Condition One Month after Admission.

She had had no recurrence of the hiccup (August 15th), but was still abnormally sleepy at times, and occasionally complained of pain behind the eyes. The mental excitability was less pronounced, but the myoclonic movements were slightly more marked. Involuntary elevation of the eyebrows and blinking of the eyes were noted, while, in addition to the movements described before, occasional contractions were observed in the sternomastoids, the pectorales, the small muscles of the hands, and both quadriceps extensors; flexion and extension of the toes also occurred. The abdominal movements were unchanged; there was some flattening of the right upper segment on raising the head against resistance; the abdominal reflexes were brisker on the right than on the left, especially in the right upper segment, where the response still consisted of a series of three or four successive twitches. The cranial nerve palsies were less marked. The response of the pupils to light was brisker, as was also the reaction on convergence. The reaction on accommodation was still sluggish and ill sustained. Photophobia was still present. The weakness of the external recti was extremely slight, there being now no obvious strabismus, and only slight blurring of the image on extreme lateral fixation to either side. The slight ptosis of the right eyelid was unchanged.

When in 1917 von Economo first described the condition the well known lethargic type of the disease, with somnolence, lethargy, and ocular palsies leading to ptosis, strabismus, and pupillary disturbances, greatly predominated. Later it began to be realized that the manifestations were much more varied and widespread. The occurrence of cases closely resembling paralysis agitans began to attract attention, and still later the excited and myoclonic and choreiform types of the disease and the occurrence of epidemic hiccup became recognized.

In the excited and myoclonic patients and in epidemic hiccup the lethargy so typical of the more ordinary forms of the disease is replaced by mental excitement, delirium, and insomnia. Cases in which myoclonic movements were present occurred sporadically in 1918, but it was not until the end of 1919 that they became prevalent. They were described as a form of acute epidemic encephalitis in January, 1920, by Sicard and Kudelski, and Ellis¹ reported three cases in this country in that year. The characteristic of this variety is the occurrence of twitching of the muscles of the limbs, and rhythmic shock-like movements of the abdominal muscles, which may be so severe as to shake the bed with each contraction. Cranial nerve palsies may or may not occur.

Although cases of hiccup were noted by von Economo in 1917, hiccup did not occur in epidemic form until the end of 1919, when an outbreak coincided with the epidemic of the myoclonic form. Hall² quotes Boyd as describing an outbreak of epidemic hiccup which occurred in Winnipeg in the autumn of 1919, and preceded an outbreak of the lethargic form of the disease. The same authority quotes Dargein and Plazy, who describe a case in which lethargy and ocular palsies developed a fortnight after recovery from an attack of epidemic hiccup. But Hall concludes that "at the present time no dogmatic statement of the relationship of the two conditions seems warranted."

CONCLUSION.

The above case, therefore, is of interest. The patient after suffering for a month from intermittent brief attacks of hiccup, developed a typical though mild attack of the lethargic form of encephalitis with ocular