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Department for the Army

CLINICAL INHIBITIVE FUNCTION SECRETION

(PSEUDO-HYPERTENSION)

Delivered at the
By CHARLES MACA
Resident Physician in the
for Inhibition; and

Every medical man has
a certain number of cases
which, in spite of all the
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multiple malady.

The Liverpool Hospital



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CLINICAL LECTURE
ON THE
INHIBITIVE FUNCTIONS OF GLANDULAR
SECRETIONS ON SOME CHRONIC
DISEASES.

(PSEUDO-HYPERTROPHIC PARALYSIS; LYMPH-
ADENOMA).

Delivered at the Liverpool Royal Southern Hospital.

By CHARLES MACALISTER, M.B. EDIN., M.R.C.P. LOND.,

Honorary Physician to the Stanley Hospital; Physician to the Home
for Incurables; and Clinical Tutor to the Royal Southern
Hospital, Liverpool.

EVERY medical man has more or less constantly under his care a certain number of cases suffering from chronic ailments, which, in spite of all that can be done to mitigate their symptoms or to arrest their progress, advance and ultimately end fatally; and in a home for incurables these unfortunate patients accumulate, and by their sufferings and hopelessness stimulate one to wonder whether in many of the cases nothing can be done to cure or to arrest absolutely their diseases.

About eighteen months ago I was much struck by what appeared to be the direct consequence of the removal of the uterine appendages in the cases of two young married ladies whom I had known to be previously active and healthy; for, almost immediately after recovering from their operations, each of them developed osteo-arthritis, which has since progressed, and is slowly but surely crippling them. It occurred to me as a possibility that in these women some element had been taken away which was essential to the articular structures, and without which their cartilages were unable to exist; and this consideration led me at once to inquire carefully into the histories of all the numerous cases of osteo-arthritis in the Home for Incurables, when I found that, almost without exception, there had been some disorder of uterine or ovarian function before the articular disease had commenced.¹ The investigations which I have been conducting relative to the association which I suspect to exist between the ovarian function, or that of some other connected organ, and osteo-arthritis are not by any means completed; but these cases have opened a field for clinical observation, and have placed before us a problem the solution of which may perchance lead directly or indirectly to the discovery of remedies for some hitherto incurable maladies.

¹ The Liverpool Home for Incurables is for females only.

Osteo-arthritis is a type of a number of other diseases of which the outstanding and essential feature consists in the atrophy or non-production of an individual tissue element in the body; but, on the other hand, we have to bear in mind that there is another class of cases in which precisely the opposite condition obtains, and in which there is an over-production of some one tissue, the remaining structures being unaffected, or being only secondarily injured. These clinical facts have brought vividly before me a consideration not only of the wonderful way by which in health the proportion which any one set of tissue elements bears towards its neighbours is preserved, but also of the circumstance that, under pathological conditions, that balance may be upset; and that individual structures may be picked out and influenced in such a way that they either grow too abundantly or are not produced perfectly, or their production ceases altogether; and I have for long been persuaded that there are influences, probably of glandular origin, in the economy which have for their function the control of the growth or development, or of the maintenance in their fully formed conditions, of some of the various textures of the body, and which by their presence preserve the normal proportions between the bodily constituents, or which, being suppressed or perverted, allow of their over- or under-production as the case may be.

In considering this matter we have to recollect in the first place that in many of these diseased conditions (as examples of which we might mention lymphadenoma, where there is an overgrowth of some of the glandular elements; osteomalacia, a condition in which the bones soften from within outwards; and pseudo-hypertrophic paralysis, in which we find an overgrowth of the fibrous structures in the muscles) we are able to say pretty definitely that they are not the result of nervous influences—they are not trophoneuroses—and, acting upon this presumption, we can safely premise that the affected tissues must depend for their nutrition, or for their maintenance in the fully formed condition, or for the control of their growth (or prevention of their overgrowth), upon something which is brought to them by the blood.

The materials which are necessary for the growth and nutrition of the body as a whole are derived from the foods ingested, and a local increase of nourishment by increased blood supply will cause a local hypertrophy, but in this case there is an overgrowth of all the natural constituents of the part, with retention of its form and structure; and, on the other hand, if there be a local cutting off of nourishment by diminishing the blood supply to a part, there is a corresponding amount of atrophy of all the constituent elements of that part; but there are no foods that I know of which, either by being taken in too large or in too small an amount, will lead to overgrowth or to atrophy of individual structures; and I am inclined to the belief that there are some substances elaborated by glandular structures within the body which exert a controlling influence over the growth of individual tissues, and that in those diseased conditions in which such hyperplasia or hypoplasia of a single tissue element takes place there is an absence or perversion of the secretion which physiologically controls the growth of that particular constituent. In the blood we have a tissue in which we know that there is not only a constant production of new corpuscles going on, but also a destruction of corpuscles; both processes appear to take place in glandular organs, and I do not think

it outrageous to reason that in the solid and stationary tissues, which cannot be taken to a gland, there may be an analogous process of production and destruction, with the difference that the glandular secretions are brought to the tissues; and just as disease of the spleen and lymph glands is associated with anæmia or leucocythæmia, may not disease of those glands whose secretions control the growth of the solid tissues lead also to the over- or under-production of those tissues? It will, I have no doubt, be agreed that if there be any soundness in this theory, its clinical significance will be of the greatest importance, for if we can discover the particular secretions which, by their absence or perversion, are instrumental in bringing about diseases of the kinds I have named, may we not, by supplying them from glands of the lower animals, do something towards arresting or even curing them?

With this idea before me, there has come the determination to put the matter to the test, but the difficulty has always been to choose the gland with which to experiment in any given case, and consequently proceedings have been somewhat empirical. I have, however, had the opportunity of applying the principle in several diseases, and in two of them at least the results have been sufficiently encouraging to warrant my mentioning them.

PSEUDO-HYPERTROPHIC PARALYSIS.

Pseudo-hypertrophic paralysis is a disease which is peculiarly appropriate to my argument, because, notwithstanding the descriptions which have been given of changes in the cord by various authors, it is now pretty generally admitted that there is no central nervous lesion to account for it, and that there is simply an overgrowth of the fibrous structures between the muscular elements, that is, there is a cirrhosis of the muscles, and the microscope shows in some cases the young and newly-forming fibrous tissue elements. I need not go particularly into the various clinical appearances observed in the disease, beyond reminding you of the great muscular weakness induced by the atrophy of the proper muscular substance; of the way in which in an advanced case the child walks on its toes with its heels drawn up; of the lordosis and of the inability to rise without assistance from the supine position—all these, and the characteristic way in which it climbs up its legs, are well enough known; but there are some clinical facts which seem to me to have a most important bearing when we regard the malady in connection with our present subject. In the first place, the patient is invariably a child, and it is extremely rare to find the disease beginning after the fourteenth year, and in the second place (and I think this very suggestive), the younger the patient is at the period of onset, the more rapid is the course of the disease, so that if it begins after the sixth or eighth year its progress is much slower than when the initial symptoms are observed during infancy; indeed, in the case of a youth aged 18 who has been under my care for the past fifteen months, who did not begin to suffer from any weakness in his legs until four years ago, there has been extremely little progress, so that he has been able to continue his work pretty constantly, and I cannot see that his condition is materially different now from what it was when he first presented himself, whereas in two sisters in whom the earliest

symptoms were noticed in the eighth and ninth years respectively, the course of the disease has been comparatively rapid.

This absence of the disease after adolescence made me think that the condition might be due to the premature cessation of some secretion which during early life possibly exercises an inhibitory function over the production of the fibrous parts of the muscles, and I thought naturally of the thymus gland, since its activity seems to be essential to the first few years of life, its rate of growth up to the end of the second year being out of all proportion to that of the child, and its functional activity appearing to continue up to the end of the seventh, eighth, or even the fourteenth year. The age limits of the commencement of pseudo-hypertrophic paralysis and of the functional activity of the thymus are therefore about the same, and it is a suggestive circumstance that, if the disease begins at a period when the thymus is normally becoming inactive, its rate of progress is correspondingly slow; whereas, if it commences during the time when we suppose that the gland is or ought to be active, there is a rapid course and a relatively early termination to the life of the individual.

I have at present under my care three cases of pseudo-hypertrophic paralysis, one of them a girl, aged 14, who has been exhibited as a typical example of the disease on more than one occasion. Her difficulty in walking began five years ago, and, on her admission to the Stanley Hospital in the middle of last February, she presented all the usual phenomena. She was quite unable to get up if placed on her back, she had extreme lordosis, and a plumb line dropped from the seventh cervical vertebra fell 2 inches away from the sacrum. She habitually stood and walked upon her toes, and any attempt to bring her heels down to the ground resulted in her falling. Each calf measured $11\frac{1}{2}$ inches. This child has been taking a thymus gland every day for about a month (with the exception of a few days when they could not be obtained), the fresh gland from the youngest sheep available being minced and incorporated with gelatine, and half the quantity (that is, a lobe) given night and morning, and so far the results have been most encouraging, for with a diminution in the size of the calves by very nearly an inch, without any general loss of nutrition, there is marked increase of strength, less lordosis (the plumb line now nearly touching the lumbosacral joint), and she can walk upon her feet with the heels touching the ground. I was afraid at first that hope of success might be prejudicing my judgment in this case, and I purposely withheld any expression of opinion until some others had remarked upon the girl's condition. The improvement was first noted by the ward sister, who commented upon the diminished size of the calves, and, later, the child's parents independently expressed their surprise that she was walking and standing so much better. I propose to reserve my remarks upon the other two cases until another occasion, because the one has only been under observation for a few days, and the other has not as yet been able to take the gland with sufficient regularity to render my notes of his condition of any value.

GENERAL LYMPHADENOMA.

Another case which has been interesting me for some time, but which has been less easy to treat upon the lines I have

indicated, is one of general lymphadenoma in a man, aged 62, who was always perfectly healthy prior to an attack of influenza in May, 1891, which seemed to initiate his present illness. (I mention this fact because I believe that the poison of such a disease as influenza may lead to a perversion of the function of some glands, and thus prevent them from exercising their normal controlling influence over the development of certain tissues.) This case had proceeded steadily from bad to worse in spite of all the usual remedies. He was twice under Dr. Carter's care, in the Royal Southern Hospital, for prolonged periods, and was treated with arsenic, phosphorus, iron, and by injection of the glands, but with no appreciable benefit. In January of this year he appeared to be near his end; he was so weak that the slightest movement caused much exhaustion. There was marked and increasing œdema of the thighs, legs, feet, scrotum and penis; there was fluid in both pleural cavities and in the peritoneal cavity, but the amount of the latter was uncertain, the abdomen being so full of hard glandular masses. The subcutaneous tissues of the abdomen and back were markedly œdematous; the lips and cheeks cyanosed. There were purpuric spots on the wrists. He looked extremely anxious and distressed. He was obliged persistently to maintain the sitting posture, any attempt to lie down being followed by suffocation and increased cyanosis. He was passing from 12 to 14 ounces of urine in 24 hours. The breathing was shallow and stridulous, the voice husky, and any attempt to bend the neck forward caused intense stridor, so that he habitually kept the head tilted backwards. The pulse was very compressible, 120. The veins of the neck were distended and tortuous, and there was tortuosity of the vessel over the temples. The tongue was furred, the follicles at its base very prominent. Digestion good. Bowels regular; occasionally he has passed some liquid blood by the bowel. The lymphatic glands of the neck were tremendously enlarged, extending on both sides from the ear to the clavicle and sternum as a continuous mass, for the most part hard, with here and there a softer point. The circumference of the neck at the level of the cricoid cartilage was 23 inches. In the axillæ there were similar huge glandular masses, which prevented the arms being approximated to the chest; on the right side the axillary mass measured 16 inches and on the left side 17 inches in circumference. They were hard, almost cartilaginous, lobulated, and the veins over them were distended. The inguinal glands were also greatly enlarged, and the abdomen was filled centrally with large glandular masses. There was increased hepatic and splenic dulness, merging into that of the glandular swellings. There was anæmia of the mucous membranes, and on percussion or pressure over the sternum there was marked tenderness, but none over the cranial or other flat bones. He was much debilitated, and tended to faint on even slight exertion. Sleep was very bad, and he had not been able to lie down owing to the respiratory difficulty for more than two months. Such are the main features which I have abstracted from my notebook regarding his condition at the end of January. On February 3rd I asked Dr. Carter to see him with me, and he can corroborate the facts as I have stated them, and he expressed the opinion that the end was very near. The question as to his being again taken into hospital being mooted, it was considered that his condition was too hopeless, and the patient himself expressed his despair of any amelioration, and

his desire to die at home. I mentioned to Dr. Carter on this occasion (as I had done many times before in connection with other cases) my theory that in this case there must be some loss of an inhibitory influence which normally controlled the growth of the glandular structures, and although it was beyond me to think where that influence might arise from, still the question came prominently before me, Can anything be added to this man's blood which is now absent, or present in a perverted form, and which could by its presence stay the advance of the disease? And, remembering the circumstance that the bone marrow presents distinct changes in this malady, I determined by way of experiment to feed him upon fresh marrow—a mixture of red and yellow—of which I began to give him a dessertspoonful three times a day on February 9th (the marrow being mixed with a little glycerine and incorporated with gelatine, as in the case of the thymus). No other medicines were given.

On February 12th he began to pass a large quantity of water—40 ounces in twenty-four hours—and on February 17th it began to be apparent that he was improving. He for the first time for many months was able to lie down all night, and he slept for several hours. The pulse was of better tension and had fallen to 80. The œdema had disappeared from the bases of his lungs; he was able to move his neck more freely, and altogether felt stronger.

On February 19th Dr. Carter again saw him with me, and expressed surprise at the manifest improvement. We noted that he was passing more than a quart of urine in twenty-four hours; it was concentrated, deposited urates on cooling, specific gravity 1028, acid, and contained a faint trace of albumen. The œdema had disappeared from the subcutaneous structures, the breath sounds and percussion notes were normal, and there was no evidence of fluid in the peritoneal cavity. He now lay down comfortably, the voice was clear and strong, and he had no stridor. The mobility of his neck had greatly increased, and there was decided softening of many of the glands which had previously been so hard and large. The neck now measured $21\frac{1}{2}$ inches in circumference.

More than a month has passed since this change in the patient's condition began, and he has never relapsed into his former state of danger and misery. Considering the long period during which, week by week, he became worse and worse, and at length appeared to be near death, and the rapid improvement which followed the administration of the marrow, one is tempted to think and to hope that something more than coincidence has accounted for the altered condition in which we now find him. The glands are certainly much softer, and if there has been no actual decrease in their size, they certainly have not increased, either in their number or dimensions, so that something like an arrest in the progress of the disease seems to have taken place.

The extraordinary success which has resulted from the treatment of myxœdema by the thyroid secretion during the past year is, I think, explainable on the same principle which I have laid down as the basis of these remarks. Here it has been proved, both clinically and experimentally, that the absence of the thyroid secretion entails the development of a condition in which there is an excess of mucin not only in the subcutaneous tissues, but also in many other connective tissues. It is well known that mucous tissue is develop-

mentally the normal predecessor of ordinary connective tissue, the white fibres being produced in the jelly-like matrix (according to Rutherford) by the production of a periplast by the cell of the mucous tissue, which elongates, and eventually becomes a white fibre. In myxoedema, therefore, there is an over-production of the rudimentary progenitor of connective tissue, a certain consequence of the loss of a secretion which normally prevents its formation, and it seems a reasonable explanation that the thyroid adds something to the blood which controls the growth of the predecessor of connective tissue, and, therefore, of the fully formed tissue itself. This appears to me to be more probable than the theories which ascribe to it powers which prevent auto-intoxication, and it does not seem to me impossible that the application of this principle may ultimately lead us to treat some local overgrowths of tissues either embryonic or more fully formed, such as sarcoma and carcinoma, by the introduction into the system of materials which may inhibit their production.

The first part of the paper is devoted to a general
discussion of the various methods of determining
the rate of reaction. It is shown that the
method of initial rates is the most reliable
and that the method of half-lives is only
applicable to first-order reactions. The
method of integrated rate laws is also
discussed and it is shown that it is
applicable to reactions of any order.
The paper then discusses the effect of
temperature on the rate of reaction and
shows that the rate constant increases
exponentially with temperature. The
Arrhenius equation is derived and it is
shown that a plot of $\ln k$ versus $1/T$
gives a straight line. The slope of this
line is equal to $-E_a/R$, where E_a is the
activation energy and R is the gas
constant. The paper concludes with a
discussion of the effect of catalysts on
the rate of reaction and shows that they
lower the activation energy and thus
increase the rate constant.



