The Sidney Ringer Memorial Lecture ON THE ADRENAL GLANDS.

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TWENTY years hence the man to whom is given the honour which falls to me to-day of delivering the lecture which has been so generously founded to commemorate the work done by Dr. Sidney Ringer during his long and fruitful years of service to our medical school, may find occasion to review the facts of that great physician's life. Our teachers of the past are soon forgotten, for the full current of life which eddies swiftly and incessantly around all in hospital, teachers and students alike, gives little chance to pause and reflect on bygone history.

To-day such a review is hardly needed, for Ringer's name is still familiar in our ears. The men who worked with him or were trained by him are now the strength of our hospital staff, and from them we hear echoes of his teaching or reminiscent praise of his clinical skill. For Ringer had that forceful character which impressed itself on the manners as well as on the memories of those around him. Consciously or unconsciously they would imitate him, and not a few of the traditions of our school, of which we in this generation are proud, had their birth in the mind of Sidney Ringer.

Much of his strength, like that of Oliver Cromwell, was due to his faith. He believed in the healing powers of his art with a sincerity and vigour that fail to inspire the outlook of physicians in these later days. Hence came the need for the utmost nicety of diagnostic skill—and all of his generation bear witness to the singular refinement of his powers of clinical reasoning. Hence, too, his unrelenting endeavours to win certain knowledge of the action of therapeutic drugs, by observations on man, and by experiments on animals. Medicine to him was not an affair of pathological diagnosis, to be followed by a word of encouragement to the sufferer and by a demonstration to the onlookers. Life, he thought, might be aided in its struggle against the ravages of disease, if happy chance or reasoned wisdom could but find the therapeutic means. Along both paths Ringer sought to achieve this end. On the first every lead was tried; the slenderest fancy was tested; but his sure judgement instantly turned back when the hoped for help proved but a wandering marsh-light. For this scientific workers have termed him an empiricist: justly, and yet with no reproach. The empiricist of the hospital wards was the Euclid of the pharmacological laboratory. Slowly and surely he reasoned out the

elementary propositions of the action of simple salts on living cells, and Ringer's solution is applied by modern analysts to these problems in more than the simply material sense.

For twenty years such questions attracted Ringer, in his few hours of leisure, to the laboratories of University College, and there it chanced one afternoon in 1893, almost at the close of this long period of devotion to research, that he saw the first experiment that gave to physiology her main ideas upon the functions of the adrenal glands.

The story of this discovery has already been told by Sir Edward Schäfer. A former student of our hospital, Dr. George Oliver, had devised apparatus to measure the calibre of the peripheral arteries in man, and he had

observed that when drachm doses of a glycerine extract of the adrenal glands were given by the mouth to his son they made him sick, and his radial artery became constricted. A superficial thinker would have passed this by, and satisfied himself with an explanation on the accepted lines of knowledge from the toxic action which the extract of the glands was already known to possess. Oliver would not do so. Half an explanation is often worse than none, for it may lead to a contented neglect of the new truth that lies hidden beyond. He sought the test of a laboratory experiment. With a little demur at the waste of time in humouring the fancies of a clinician, Schäfer consented to inject some of the extract into a cat, and he and Ringer, with Oliver, then saw that abrupt and amazing rise of blood pressure which occurs as the heart and arteries are stimulated to intense constriction by the active principle. Ringer seems to have taken no deep interest in the matter. Schäfer and Oliver analysed the chief reactions produced in the body by these injections, and subsequent work in the intervening twenty years has discovered what these reactions mean. Physiology is now possessed of half of the secret of these glands, and the knowledge has enlarged her view of the nature of nervous activity in a manner that is bound to be fruitful in discoveries of the near future.

The distribution of the efferent nerves, which the central nervous system supplies to the viscera and blood vessels of our bodies, was first clearly described by Dr. W. H. Gaskell, a man whom we are proud to remember was once a student with Ringer at our hospital. Following up his brilliant generalizations the English school of physiologists has analysed in great detail the intricate networks of these nerves, and Professor Langley's account of the autonomic nervous system is now accepted the wide world over. These nerves to plain or unstriped muscle issue from the central nervous system in three main groups¹—the vagal, the sympathetic, and the pelvic, which histologically cannot be distinguished from one another. The test of adrenalin laid bare a fundamental difference. Adrenalin was found to stimulate all plain muscle or gland cells that were united with the nerves arising

Diagram of the nerves efferent from the central nervous system in the mammal. A, The non-ganglionated ordinary motor nerves to striped muscle, which are distributed segmentally. On the left side these are omitted for simplicity, and only the autonomic or ganglionated visceral nerves to plain muscle are indicated. Of these, B is the cranio-cervical outflow in the vagus, etc.; C, the thoracic-lumbar or sympathetic proper; D, the sacral outflow, or pelvic visceral nerve to the bladder and colon. All these subdivisions contain both motor and inhibitory nerves. C1 is the sympathetic ganglion cell; C2 the paraganglion cell secreting adrenalin, the chief mass of these being concentrated to form the medulla of the adrenal gland, though a few, even in adult life, may be found elsewhere in relation to the various sympathetic ganglia. The black rectangle innervated by the nerves from the cells C1 represents the mass of plain muscle which is also stimulated by adrenalin—that is, by the secretion of the cells C2. Afferent sensory nerves and their posterior root ganglia are all omitted from the diagram. Their course from the viscera is not clearly known.

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in the thoraco-lumbar tract of the spinal cord between the roots of supply to the fore and hind limbs of the body. From no other contractile tissue did it call forth any response. And the reaction of the muscle or gland cell, when excited by this substance, was of precisely the same character as that which it showed in response to excitation of the visceral nerve supplying it. The wall of the stomach was inhibited, its pyloric sphincter contracted, by adrenalin, precisely as by the stimulation of the splanchnic nerves. So, too, with the bowel and its ileo-colic sphincter, with the body of the bladder (in the cat) and its sphincter. From this peculiar reaction it became evident that the thoraco-lumbar set of visceral nerves belong to an entirely different group from the vagal and the pelvic. They form the so-called sympathetic set, an order that in its present function and equally in its past developmental history differs profoundly from the rest.

Next arose the question as to why and how this glandular extract is so intimately related to the activities of a special part of the nervous system.

The adrenal gland is a twofold structure. Its centre is composed of masses of delicate semi-fluid cells, which are richly supplied with sympathetic nerves, and lie enmeshed among thin-walled veins. These contain adrenalin. Intermingled here and there with them, and growing out over the surface of the adrenalin cells so as to form a complete envelope to the medulla, are the cells of the cortex. Their innervation is scanty; they yield no adrenalin or known active principle to extraction, but they are generally laden with a rich store of a peculiar fatty substance.

It will be convenient to review separately what is at present known with regard to the function of each of these masses of glandular cells.

In the first place, it has been proved beyond all doubt that the medullary cells excrete adrenalin directly into the venous blood stream, and that they do this in part automatically, but chiefly in response to a call made through nervous impulses descending by the splanchnic nerves. The experiments of Dreyer and of Tschobolskoff first showed this, and fuller methods of analysis in the last two years have demonstrated the fact completely. I may quote the following experiment which reveals neatly what occurs in the body. The superior cervical ganglion was excised from a cat's neck. This causes the pupil on that side to become smaller from paralysis of the sympathetic nerve, but the iris in a few days acquires an enhanced sensitiveness to adrenalin so that it dilates much more readily than the muscle of the contralateral pupil when small quantities of adrenalin are injected into the circulation. A week later the right and left splanchnic nerves were each divided and prepared for electrical stimulation. On one side the adrenal gland was excised. Stimulation of the splanchnic nerve on the side where the gland remained had then this result: The blood pressure rose in the usual steep curve for 8 to 10 seconds. Suddenly the rise was checked, and was replaced by a smoothly hollowed fall; at the very moment of this turn in the curve the denervated eye as suddenly reacted. Its prolapsed nictitating membrane flashed back, and the iris became dilated to the narrowest rim of yellow around the great black globe. The response of the eye and the secondary fall, not rise, of the blood pressure curve were due to adrenalin that had been excreted from the gland and, after the delay of passage through the lung vessels, had ultimately been distributed through the outflow from the aorta. Stimulation of the other splanchnic nerve, from which the adrenal gland had been removed, caused the blood pressure to rise to the same extent, but there was no secondary fall and no response at a distance in the eye.

I found in cats that in addition to the effect of this transitory stimulus it was easy to recognize a more prolonged excitation through the splanchnic nerves, which in a few hours would discharge the adrenalin until the cells were almost entirely exhausted. This was shown by cutting the nerves on one side, submitting the animal to conditions that were likely to induce exhaustion, and then measuring the amount of adrenalin left in each gland. Prolonged fright emptied the cells. So too did the vaso-motor irritation caused by laceration and haemorrhage in the brain. The mere condition of anaesthesia induced by ether or chloroform for three or four hours led to a rapid exhaustion. But in every case the loss depended upon

excitant nervous impulses, so that the load of adrenalin suffered no loss if the nerves were first divided.

From this it follows that the central nervous system has at its disposal two methods for excitation of the mass of plain muscle that is supplied by the sympathetic nerves. The first is that which has been known for a long time, by the directly applied stimulus of the nervous impulse, which can be accurately restricted to one particular spot and delicately adjusted in its strength. The second is that of which physiology has but recently become aware, by the discharge of adrenalin into the blood stream, whence this powerful stimulus diffuses into every quarter of the body so as to be capable of exciting in one great massed effect all the plain muscle of the sympathetic system.

Morphological workers have proved that these adrenalin cells are related by a common parentage to the ganglion cells of the sympathetic nerves, and I have shown by observations on the result of degenerative section of their nerves that they probably receive their innervation directly from preganglionic fibres. All the secreting glands of which the innervation is known are connected to the spinal cord by nerves of the ordinary visceral type—that is, with the interposition of a ganglion cell on the outward path. Here there does not appear to be such a relay, for the adrenalin cell is not of the peripheral tissue type. It ranks in the higher level of the ganglion cells, lies closer to the spinal cord, and is itself almost a member of the nervous hierarchy. The ganglion cell and the adrenalin cell are as brother and sister to one another, born from the same stock, living for the same end in life, which the one attains by growing out into direct contact with the moving mass of muscle, while the other stays quietly where it was born and exercises its influence from a distance.

Of all the diverse muscles united with the sympathetic nerves the most important and the bulkiest are those of the heart and blood vessels. Vasomotor nerves probably form much the largest fraction of the sympathetic group, and they are the oldest. Gaskell, junior, has traced them down below the vertebrates, and shown how the nerves and the adrenalin cells appear side by side in the worms that have developed a definite circulatory system. Adrenalin cells are present wherever there are blood vessels, even though these be of a very rudimentary type, and, indeed, in some examples they seem to usurp entirely the prerogative of the sympathetic nerves, for the latter cannot be found. Morphology therefore tells the same tale as physiological analysis. The adrenalin cells and the sympathetic nerves belong to a common system, whose first duty is that of sustaining the activities of the circulatory muscles. As the animal develops its muscular efficiency, learns a hundred new functions, and with a constant body temperature becomes independent of its environment, the sympathetic system becomes more and more complex and is split up into manifold possibilities of delicate adjustment. All these are but refinements of means for the one great end—to enable the animal to move more swiftly, to catch its prey, and to fight. Fighting power rises with the rise of blood pressure, reserves of sugar to feed the muscles are hurried up from the liver on the call of the circulating adrenalin, the daily routine of digestion is checked by intestinal inhibition, and the various segments of the bowel are cut off from one another by the closure of the sphincters. Cannon has reiterated this view and, further, shown very neatly how the clotting of blood by adrenalin, which had been observed by myself and others, is a further elaboration to check leakage in any chance wound of the body during action.

By that curious antithesis of the emotions upon which Charles Darwin laid stress, the machinery employed to prepare for fight may, with the cowardice of civilization, be set as powerfully in motion only to express fright. And in this the adrenalin is equally, or perhaps even more, exhausted.

Gazing back over the history and widely over the present functions of the sympathetic musculature, such is the general impression that we receive of the activities displayed by the sympathetic nerves and the adrenalin cells. But another question arises to seize our attention. Why two systems of control, and what is their relation to each other in the fully developed mammal? Removal of each separately will supply some facts upon which an answer may be attempted to these questions. Taking the

nerves first, removal of the thoracico-lumbar extent of the spinal cord interferes with the control of the animal's circulation, but it can still maintain its life. I have removed from a cat the bulk of the peripheral sympathetic ganglia connected with the heart and blood vessels of the viscera. It lived and its blood pressure was tolerably high. Therefore the nerves adjust the pressure and control the direction of the circulation, but upon them does not rest the maintenance of that muscular tone which upholds the pulse of life.

Removal of the adrenal glands, that is of cortex as well as of medulla, brings death. I have succeeded in keeping cats alive for a week or more after this extirpation, and their final condition on the last day before death was always the same. Artificial heat was used to preserve the normal temperature of the body. The muscles of the trunk could be actively used and with good co-ordination. The pelvic nerves were competent for micturition. The vagus could check the heart. But the blood pressure was fallen desperately low, to 20 or 30 mm. of mercury, and no stimulus, whether it were nicotine acting on the ganglion cells or pituitary extract on the muscle, could raise it from this dying level—with the single exception of adrenalin, which temporarily restored it to the normal height. The musculature of the circulation was irresponsible to stimuli, whether nervous or direct, and it was flabby and toneless. Hence the death. But the cervical sympathetic could still dilate the pupil, and other sympathetic nerves had not lost their power. So it is with man in the cold enfeeblement of Addison's disease. In the last day of life his pilomotor muscles will react in a prompt "goose skin" reflex, even though the blood pressure be so low that the pulse is imperceptible at the wrist.

The theory which I at first held to explain these facts was that the nervous stimulus consists in a liberation of adrenalin itself from the ending of the nerve on the muscle. We have seen how the ganglion cell and the adrenalin cell are both derived from what is almost a common cell with power to transmit a nervous impulse or to excrete adrenalin. It is very conceivable that as the nervous cell developed its peculiar outgrowths for the purpose of transmitting and localizing the nervous impulse, it might lose its power of producing adrenalin and come to depend altogether on what could be picked up from the circulating blood and stored in its nerve endings. Removal of the glands would cut off this source of supply, and paralysis of the nerves would result sooner or later in that territory where the nerves had been functionally most active and had consumed their stores.

It is always a pleasure, and therefore a temptation, to accept a theory which harmonizes all the facts into a simple, close-fitting plan. But the evidence at present does not justify us in welcoming this simplification. The paralysis of the splanchnic nerves does not appear until the nerves have lost their tone; and the atonic muscles then fail to react to such stimuli as pituitary extract, which is supposed to affect plain muscle directly. Moreover, removal of the vasomotor nerves does not cause that fatal fall of blood pressure which inevitably succeeds to the removal of the glands. It is therefore unwise to go beyond the bare statement that removal of the cortex and medulla of the adrenal glands causes death because the tone of the circulatory muscles is entirely dependent on the secretion of their cells. That does not rob the relationship of its peculiar interest. Here is a group of nerves which lose their power when the energy of their system runs low. The energy is supplied from the secretion of a separate mass of quasi-glandular cells. Whether it is stored in muscle or nerve is a question of secondary interest.

A comparison has been made which illustrates this view to some extent. Music and the quick clear change from note to note cannot be called from a violin string that is slack. The string must be toned, raised to its proper pitch, for the fingers and bow to play upon it. The muscular tone of the blood vessels is given by the adrenal secretion, and the nervous impulse alters it this way or that in harmony with the body's needs.

Naturally one longs to find examples of a similar mechanism in other parts of the body, to apply this equation of interaction to the problems of nervous activity in the greater departments of the nervous system. The striped skeletal muscles form a homogeneous group which is continually under a tonic influence. This tone is for

the most part derived from direct nervous impulses, but the diseased state of myasthenia gravis proves that the tone is not altogether supplied from the central nervous system. Myasthenia might in the skeletal muscles correspond to the state of Addison's disease in the blood vessels. But this is only a surmise. I have tried in vain to discover an active substance in the muscle plates of striped muscle. And Professor Herring was also disappointed when he examined for this purpose the electrical organs of the skate, which are exaggerated motor plates. The ganglia of other visceral nerves, the auriculo-ventricular bundle of His, the spinal cord itself—all have been extracted and nothing as yet found. But it is hard to forego the belief that such discoveries lie in the lap of the future. Nervous energy may need for its awakening something more material than the subtle interplay of impulses in nervous tissue. That wearisome ailment, neurasthenia, might be curable by some extractive of comparatively simple chemical nature, and those who suffer from it, together with those who must try to alleviate their woes, be both freed from a depressing bondage to uselessness.

From what I have tried to relate it will appear that physiology has a tolerably full knowledge of the nature of the medullary cells of the adrenal glands. Pathology merely confirms this. In many diseases the adrenalin load of the glands is diminished, but not often to what might be looked upon as a really serious state of depletion. The weight of a single normal gland in man is 4 grams, and its adrenalin load is 4 mg. This falls to 1 mg. in many fatal fevers. The greatest exhaustion that I have seen to occur rapidly was not in fevers but in cases in which, with acute cardiac failure and perfect consciousness of his dangerous state, the patient was, so to speak, fighting for life, struggling to keep up his heart. In these the adrenalin load was less than 0.5 mg. I could find no justification for the belief that the adrenalin cells are hypertrophied or more active in diseases associated with persistent increase of blood pressure.

Of the functions of the cortex more might be said than about the medulla, for the usual reason that little is known, and consequently every statement has to be guarded by reservations and contradictions. The cortex in the higher animals forms at least 90 per cent. of the bulk of the gland. Its cells in health are loaded with a doubly refractive fat composed of cholesterol esters and lecithin, and this lipid is just as distinctive of the analogous cells which accompany the adrenalin cells even in animals below the vertebrates. Here, once more, we are dealing with an archaic tissue that has been preserved and, indeed, enlarged in higher animals for the sake of its peculiar properties.

The microscope shows that the chief activity of the cortical cells is directed towards the formation of this special fatty substance. It is particularly abundant in the glands of man, and some quite definite knowledge with regard to it has been accumulated by several pathologists who have studied the adrenals in death from various diseases.

In the first place, it is clear that the cortical lipid bears no immediate relationship to the ordinary fats of the body. Inanition from cancer of the alimentary canal, or the beggarly emaciation of anorexia nervosa, strip all the fat from the body, and yet the cortex has its customary load.

On the other hand, the cortical fat vanishes in a couple of days' acute fever, by which the depôts of body fat are hardly touched. All septic fevers reduce the cortical fat rapidly. The most obvious example of this is in acute pneumonia, where the gland becomes fatless, oedematous, and swollen to twice its natural size. Slow febrile processes, such as that of chronic tuberculosis, cause much less exhaustion. But the removal of the lipid is not determined simply by a physical change in relation to the rise of temperature. In one case which I examined there had for four days been hyperpyrexia rising intermittently to 109°. The cause of the pyrexia was not septic; it was due to cerebellar disease, with internal hydrocephalus and direct derangement of the thermotaxic nervous centres. And in this the cortical lipid was not very much exhausted. Moreover, in several examples of prolonged haemorrhage in chronic gastric ulcer, which recurred with a fatal issue, the lipid was exhausted, though there had been no fever.

It is certain that these changes in the fat load of the cortical cells do not follow those in the adrenalin load of the

medulla. There is no parallelism between the two. The great exhaustion of adrenalin, which has been described in cases of acute cardiac failure with emotional distress, occurred in glands with a full load of cortical fat. Fevers in man reduce the fat to a greater degree than they do the adrenalin. In the experiments which I made to demonstrate the exhaustion of adrenalin in cats, I failed to produce any very manifest alteration in the lipid. Such as did appear was not in any way influenced by section of the splanchnic nerves, so that it seemed to lie outside immediate nervous control; and, indeed, the cortical fat was seen to have an identical distribution in two glands, of which the one was full, while the other was empty of adrenalin.

These, then, are the chief causes of loss of the lipid. Its increase is also manifest in some diseased states. Single large adenomata, masses of cortical cells that are packed with lipid, may occur in any individual and irrespective of any particular illness. But in kidney disease of the arterio-sclerotic form, where the atheromatous change is widely spread through the vessels of the body, the cortex does tend to proliferate in numerous small adenomata, or even to show a general massive hypertrophy. The relation is not to all forms of kidney disease, for I have seen cases of pure interstitial toxic nephritis which were watched in their condition of high blood pressure for a year or more, until at the end they succumbed to a slow uraemia, and yet with these the adrenal glands were not in the least enlarged. In the arterio-sclerotic forms with atheroma, though the cortex may be nearly doubled in bulk, there is no evidence of any increase in the size of the medulla.

These pathological facts, therefore, make it reasonable to regard the cortex in respect of its fat-holding function as a tissue altogether apart from the medulla and the sympathetic nervous system. Some recent work done in St. Petersburg and by Professor Chauffard's school in Paris has illuminated this possible point of view. The Russian pathologists fed rabbits with cholesterol until their blood was laden with excess and atheromatous changes appeared in the intima of the aorta. This was a genuine atheroma, a deposit from the superabundance of cholesterol in the blood, just like the arthritic deposits of sodium urate in the uricaemia of gout. It developed in a few weeks, and simultaneously the cortex of the animal's adrenals was found to be enlarged by an enormous increase in the store of lipid. I have repeated these experiments and confirmed the results at any rate in respect of the increase of size of the adrenal cortex. In Paris routine determinations were made of the percentage of cholesterol in human blood. It was found to be low in acute fevers, and especially in pneumonia, precisely where I found exhaustion of the cortical lipid. It was high in arterio-sclerosis and atheroma. The analyses published by Grigaut² show that these changes correspond directly with the amount of cholesterol contained in the adrenals. From this it follows that the fat load of the cortical cells varies directly with the percentage of cholesterol bodies circulating in the blood, and through them the cortex may be concerned in the general nutrition of the body by facilitating the use in metabolism of the ordinary or of the more specialized fats. This theory may be adapted to contain within its scope all the facts that are known about the cortical cells. But these facts are still so few and ill-defined, that they cannot very well be used for a critical consideration of the theory. It will suffice to name the remainder of them in this connexion.

The cortical cells seem to be essential for the maintenance of life. If one gland is removed from a cat, compensatory hypertrophy takes place in the tissues that are left. When, six months later, the second gland is excised, it may be much hypertrophied. In that case the cat will die in a few days after its removal. The hypertrophy is chiefly of the cortex. But the gland may be but slightly enlarged, and then the animal will live longer, for this means that the loss has stirred to growth the accessory masses which lie along the vein that connects the kidney with the testicles or ovary. These masses are almost entirely cortical, and in one of my cats, though their total bulk was only one-third of the weight of one gland, they enabled the animal to live for two months in fair health until it was deliberately killed. I have not examined the cholesterol content of the blood of cats when dying after the loss of the glands. Certainly they lose weight and

body fat very quickly, but that loss can be attributed to their disinclination to take food. It is not a conspicuous feature of Addison's disease.

The cortical cells are also of importance in the development of man's body during its early periods of life, especially in respect of his brain and sexual attributes. Man is unequalled among the animals in the enormous growth of his cerebral hemispheres during fetal life. Equally distinctive of the human fetus is a great ante-natal hypertrophy of the adrenal cortex. Deformed children are from time to time born without cerebral hemispheres, and in them the adrenals are invariably as small as in the brainless animals. One may suppose that the cortical cells help to supply the fatty bodies that are needed for the architecture of the brain.

As certain as this relationship of brain to gland, and still more mysterious, is that of gland to sex. Maleness appears early, and with exaggerated emphasis, in children whose adrenals are the seat of proliferative tumours. A girl with such a tumour may even lose the physiological features of her sex, and acquire the hairiness and muscular development of a man. So far as I am aware, no pathologist into whose hands such tumours have come has examined their cells for fatty secretion, and doubt remains as to whether this sexual precocity should be ascribed to the lipid or to some other substance. It is most improbable that the fat should be concerned solely with the activation of the sex glands, when that fat is found to be exhausted with such rapidity in septic fevers. Yet, on the other hand, it may well be imagined that a fatty material, which is supposed to be of vital importance in general nutrition, might in virtue of this quality nourish the body to more rapid growth of its sexual attributes—much as the so-called "royal" food used by bees will determine the sexual development of their queen.

The adrenal cortex is derived from a tissue which was the closest neighbour of the sex glands in their old abdominal position. Tiny islets of this tissue lie scattered along the path from the kidney to the descended sex gland, and it is from these vestiges that the accessory glands develop in compensatory hypertrophy. They definitely belong to the adrenal gland group. Embedded in the sex gland itself, either as the interstitial cells of the testis or as the lutein cells of the ovary, are fat-holding cells very similar to those of the adrenal cortex. These also seem to belong to the same group, but placed as direct nurses of the generative cells. If that is their nature, then it must be granted that they have acquired functions somewhat different from those of the adrenal cortex. I have not seen any example of their hypertrophy after removal of the adrenals; nor, conversely, is the adrenal either larger or less in cats that have undergone castration or ovariectomy. Despite these slight difficulties, the morphological evidence is, to my mind, sufficiently weighty to determine the balance in favour of the view that the cortex primarily controls nutritive material in regard of growth and reproduction. Secondly, and now perhaps in the chief degree, it has become associated with cells which are really modified from the special department of the nervous system that governs the circulation. It is not known in which way this association acts. Cortex may feed medulla with some necessary precursor of adrenalin, or provide some adjuvant vaso-constrictor substance, as Abel's recent observations suggest. Or, on the other hand, it may be that the medullary cells are placed near to the cortical cells in order that they may directly stimulate the latter to the performance of their peculiar duties. All that is still uncertain, and all that will surely be determined by future work.

It is necessary to realize very clearly this deep morphological distinction between the cortex and the tiny medulla. Only the latter is of nervous origin, and directly concerned with the functions of a part of the nervous system. Physiology may discover within the nervous system some substance with properties like those of adrenalin to reinforce and maintain the powers of other departments than the sympathetic. But there is not the faintest reason to believe that such substances are prepared in the other ductless glands; that the thyroid, for example, is specially concerned with the activities of the vagal set of nerves. These other ductless glands are not derived from the nervous system, as is the medulla of the adrenal. The thyroid, the adrenal cortex, and the glandular part of the pituitary body belong, as Gaskell has urged, to an old

segmental series of glands which were once related to the genital and excretory apparatus of each segment, and still retain, though greatly modified in each successive gland, the fundamental property of influencing growth and reproduction. How the tissues are affected by the secretion of the thyroid is an enigma. But the fact is certain. For the adrenal cortex even so much as that cannot be said. There is only the conjecture that this fatty substance is essential to a man's strength and manhood. The aboriginal natives of Australia threw boomerangs in curves that long puzzled the wits of the mathematicians of Europe. Their practical instinct seems also to have taught them what the medicine men of civilized life are now slowly reasoning out. To the Australian or "black fellow doctors" the fat above the kidney was magic. If by incantations it could be removed from an enemy as he slept, the victim would surely lose his strength and die.³ We know as much, that there is no warm-blooded life without these glands. Since the first experiment that Ringer watched twenty years ago we have learnt how they sustain the pulse of life, and we look to the future with a great surmise of what will come from an extension of this knowledge. But the chief gift is long delayed. Adrenalin is a more convenient haemostatic than the old-fashioned cobwebs. Apart from that, therapeutics have gained nothing from all this new knowledge, and Ringer's comparative indifference to its birth was a prognosis that, to our regret, has been justified so far as his lifetime extended.

REFERENCES.

- ¹ See diagram, reproduced by permission from *Brain*, vol. xxxv, p. 313, 1913. ² Grigaut, *Le cycle de la cholestérinémie*, Paris, 1913. ³ Howitt, *Native Tribes of South-East Australia*, p. 367, London, 1901.

An Address

ON

SOME CLINICAL ASPECTS OF THE BODY TEMPERATURE IN CHILDHOOD.

DELIVERED BEFORE THE SOUTH-WEST ESSEX DIVISION OF THE BRITISH MEDICAL ASSOCIATION.

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THE vagaries of the body temperature in childhood are frequently perplexing and difficult to understand. In early life the temperature is very variable and uncertain; it may show marked oscillations from slight or trivial causes or rise to a considerable height for no apparent reason. On the other hand, a child may be seriously ill, perhaps with bronchitis or empyema, and the temperature chart will record but little variation from the normal. The heat-regulating centres in childhood, as is the nervous system generally, are in an unstable condition, and may be influenced by emotional or slight physical causes, or they may fail to respond in the way we should naturally expect to a stimulus sufficient to cause a definite amount of fever in the adult. Undue stress, therefore, must not be placed upon the temperature of children. A transitory rise, even though it may be to 102° or 103°, need not necessarily give rise to alarm, although, of course, we should at all times seek for some underlying cause, and especially if the elevation happens to be repeated. In this connexion it is as well to bear in mind that in infants, when once the heat centre has been disturbed, some time may elapse before it regains its equilibrium, and that slight variations in the temperature may persist for a while after the exciting cause has been removed. On the other hand, a temperature which adheres more or less closely to the normal must not lead us to make light of any other physical signs which the child presents.

The most accurate method of taking a child's temperature, and especially that of an infant, is by the rectum. If for any reason this is undesirable, the thermometer may be placed in one groin and the legs held in a crossed position. Axillary temperatures are unreliable in young

children, owing to the difficulty in keeping the child still and retaining the instrument in position, and the same is even more applicable to mouth temperatures, to say nothing of the danger of the instrument being broken when used in this way. Indeed, the mouth should never be used for taking a child's temperature, as even in the case of older children it is often difficult to make them keep the lips closed and breathe through the nose for a sufficiently long time. The presence of adenoids, moreover, may render such a proceeding impossible.

At birth the temperature of a healthy full-term child is normal or a little above. During the first few hours it falls 1°, 2°, or perhaps 3°, as the result of washing and the change to cooler surroundings. In a short time, however, it rises again to normal, and persists with little variation between 98.4° and 99°, though rectal readings may be a little higher still. As a rule, the evening temperature of a healthy child differs but little from that of the morning, but even in health a difference of 2° or 3° may occasionally be found. In premature infants the temperature is usually several degrees below the normal, owing to their feeble powers of heat production and the absence of subcutaneous fat, which allows a rapid radiation of heat from their bodies. For such children artificial heat is a necessity. The child's temperature should be maintained by oiling the skin and wrapping the body in cotton-wool without any clothing except a diaper. The child should then be rolled in blankets and surrounded by hot-water bottles. At the same time the child must not be rendered unduly hot, and its temperature should be taken every four hours. The room should be well heated and kept free from draughts. Washing such children is inadvisable, except in the region of the buttocks after the passage of excreta, but the skin may be cleansed by an application of olive oil every two or three days. When possible, premature children are best kept in an incubator. This consists of a chamber, at the bottom of which is a heating apparatus, generally a water-tank, which is heated by means of a gas flame. Above this is the air-chamber, in the middle of which the bed is fixed. Fresh air enters by an opening below the bed, and is warmed by passing over the hot-water tank. It then circulates upwards, and passes over the bed to an exit in the top. The temperature of the incubator should be kept at about 85° in the case of very young and feeble infants. Care must be taken that the temperature is maintained at a uniform height, and for this purpose the apparatus should always be fitted with a thermometer. Efficient ventilation of the chamber is another important consideration, and an adequate circulation of air may be secured by keeping the room temperature at a moderate level, and not higher than 60°. The proper ventilation of an incubator is always a difficult matter, and for this reason a frequent watch must be kept upon the patient, and a cylinder of oxygen should be at hand for use in the event of the child becoming cyanosed. When in the incubator the infant, as a general rule, need be only lightly clothed, but the amount of protection required will depend upon individual peculiarities. The intake of a sufficient quantity of food further helps to maintain the body temperature of the patient. Weakly infants, who take badly, consequently require, as a rule, a greater amount of artificial heat. Stimulants also are sometimes necessary if the child's powers are very feeble; 10 to 15 minims of brandy, well diluted in 1½ to 2 drachms of water, may be given every three or four hours.

SUBNORMAL TEMPERATURE.

Chart 1 is that of a premature infant, reputed to have been born after only six months and five days' gestation. The temperature at first was almost uniformly between 94° and 95°, but after a few days in the incubator it rose to from 95° to 96.5°, with occasional excursions to normal. A fortnight later the temperature was mainly between 96° and 98°. The child held its own fairly well for a time, but, as not infrequently occurs in such cases, it died suddenly from no apparent cause. The rectal temperature of such infants is usually 1.5° to 5° below the normal, but if it remains constantly below that range, and sometimes it falls as low as 90°, the outlook is very grave. In cases of disease, as, for instance, epidemic gastro-enteritis, a temperature between 93° and 95° is, as a rule, unfavour-