An Address

ON

SOME PROBLEMS IN CONNEXION WITH THE SUPRARENALS.

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GENTLEMEN,—First let me express my sincere gratitude for the high compliment which you have paid me in asking me to give the Address in Medicine. The subject matter of an address in medicine must always be a source of some anxiety to those intrusted with the honour. It may either be on general lines and deal with the history, recent advances, future, and relations of medicine, or it may be more special and deal with a single subject. Each course has its own disadvantages, but after some consideration I have decided on a special subject and I must beg your indulgence for the following review of some problems in connexion with the suprarenal glands.

As is well known the suprarenals are composite glands consisting of two portions which are distinct from a developmental and from a physiological point of view—the cortex derived from coelomic epithelium on the Wolffian ridge and closely related to the genital glands, and the medulla derived from the sympathetic and neuro-ectodermal in origin. These two portions are separated from each other in elasmobranch fishes, the cortical cells forming the single inter-renal gland and the medullary cells a series of paired bodies connected with the sympathetic (Swale Vincent).

THE CORTEX.

The cortex is larger than the medulla and is composed of epithelial cells the structure of which suggests a high degree of functional activity; in Biedl's hands experimental removal of the cortex, the medulla being left intact, was followed by death of the animals; and it is stated that compensatory hypertrophy of accessory suprarenals, when this occurs after excision of the main glands, is solely cortical. These considerations strongly suggest that the cortex has some important function and that it is essential to life, but in what exact way is as yet unknown. The most certain point about the cortex is that it is quite unlike the medulla. Its cells contain fat and lecithin but do not give a green colour with ferric chloride (Vulpian's reaction) or a brown colour with chromic acid as the chromaffine cells of the medulla do. Physiologically extracts of the cortex are quite inactive and do not raise the blood pressure. Our knowledge as to the function of the cortex is very imperfect, but some arguments can be adduced in favour of each of the three following views—namely, that it may be concerned (1) with growth and development, especially of the sexual organs; (2) with neutralising poisons; or (3) in some manner with the internal secretion of the medulla—adrenalin.

1. *The relation of the cortex of the suprarenals to growth and development, especially of the sexual organs.*—It is now known that there is a definite group of cases in young children, the peculiar feature of the cases being that a primary tumour of the suprarenal body (hypernephroma, mesothelioma) (Woolley¹) is associated with excessive development of the organs of generation, hair, and fat. Bulloch and Sequeira² have collected ten cases, all but two under eight years of age, two in males and eight in females, showing this precocious development in association with a hypernephroma which, in some of the cases at any rate, was derived from the cortex of the suprarenal; further researches will naturally be directed to determining whether hypernephromas of cortical origin are, as suggested here, specially associated with exaggerated growth, while hypernephromas arising in the medulla of the suprarenal show no such association. Bulloch

and Sequeira have indeed collected 12 cases of hypernephromas in children who did not show any signs of premature development and in some of these cases the tumours, described as sarcomas or lymphosarcomas, were definitely regarded as arising from the medulla of the gland. It must, however, be noted that in adults cortical hypernephromas, which are probably more often seen in the kidney (renal hypernephromas or "adrenal rest" tumours) than in the main adrenal gland, are not associated with the notable genital development, hirsuties, and obesity seen in children. As rare exceptions to this rule attention may be directed to Thornton's³ case of a woman, aged 36 years, who was covered all over with black silky hair and had to shave her face, and to a somewhat similar case in a female lunatic, aged 32 years (Richards⁴). In passing it is interesting to note the rarity of renal tumours of adrenal origin in children as compared with the incidence of these tumours in adults and with the incidence of hypernephromas in early life. But although excessive genital development and growth of hair in a child should always suggest the existence of a cortical hypernephroma, it must be remembered that these striking signs may exist without any such lesion in the suprarenals (Guthrie and Emery).⁵ As bearing on the connexion between exaggerated cellular growth of the suprarenal cortex and the development of the genital organs, a few cases are on record in which suprarenal hyperplasia has been found in individuals with such excessive size of the clitoris that they were erroneously regarded as males. Further, enlargement of the suprarenals has been noted in animals during periods of sexual activity and pregnancy, and it has appeared to me that there is a close resemblance between the cells of the suprarenal cortex on the one hand and the luteal cells normally found in corpora lutea and exceptionally in luteal cysts on the other hand. This resemblance both histologically and morphologically has been insisted on by Mulon⁶ who, from observations on guinea-pigs, speaks of the corpus luteum of pregnancy as a temporary cortical suprarenal. It is interesting to compare these developmental anomalies accompanying some cortical hypernephromas with acromegaly which is usually associated with hyperplasia or adenomatous change in the anterior lobe of the pituitary gland. For, as Schäfer and Herring⁷ point out, the anterior lobe of the pituitary and the cortex of the adrenal are alike in several particulars—namely, in the glandular character of their epithelium, in the physiological inactivity of their extracts, and in ensheathing collections of neuro-ectodermal cells (the posterior or infundibular lobe, and the adrenal medulla) which, on the contrary, possess extremely active physiological extracts. As bearing in a somewhat remote manner on the relation of the suprarenal cortex to the growth of the body it may be mentioned that evidence is accumulating to show that primary malignant growths of the cortex, like primary carcinomas of the thyroid, have a special tendency to produce metastases in bone (Scudder).⁸ This similarity to the thyroid is of interest in the light of the well-established influence of the thyroid on skeletal growth.

Conversely, hypoplasia of the suprarenals has been found in anencephalous monsters; but the relation between the two developmental abnormalities is doubtful, Zander⁹ regarding the lesion of the nervous system as primary and Alexander¹⁰ considering the suprarenal defect as primary. Very possibly, however, the failure of development is concomitant; in any case this association is not a strong argument in support of the influence of the suprarenal cortex on the growth of the body, for the hypoplasia of the suprarenals appears to affect the cortex and medulla equally and not to be specially marked in the cortex. Hypoplasia of the suprarenals has been met with in a few cases of retarded sexual development, and in their case of osteogenesis imperfecta Lovett and Nichols¹¹ found the internal organs normal with the exception of the small size of the suprarenals. The view has been put forward, but without any

³ Thornton, K.: Transactions of the Clinical Society of London, 1890, vol. xxiii., p. 153.

⁴ Richards, O. W.: Guy's Hospital Reports, 1905, vol. lix., p. 225.

⁵ Guthrie and Emery: Transactions of the Clinical Society of London, 1907, vol. xl.

⁶ Mulon, P.: Comptes Rendus de la Société de Biologie, Paris, 1903, vol. lxi., p. 272.

⁷ Schäfer and Herring: Philosophical Transactions of the Royal Society, London, 1906, vol. excix., p. 27, Series B.

⁸ Scudder, C. L.: Publications of the Massachusetts General Hospital, 1907, vol. i., No. 3, p. 82.

⁹ Zander: Ziegler's Beiträge, 1891, Band xi., S. 145.

¹⁰ Alexander: Ibid., 1890, Band vii., S. 441.

¹¹ Lovett: Brit. Med. Jour., 1906, vol. ii., p. 191.

¹ Woolley: Transactions of the Association of American Physicians, 1902, vol. xvii.

² Bulloch and Sequeira: Transactions of the Pathological Society of London, 1905, vol. lvi., p. 189.

real proof, that mollities ossium is the result of suprarenal inadequacy.

There thus appears to be evidence that in some instances pathological changes in the cortex of the suprarenal glands, whether in the direction of hyperplasia or of imperfect development, are associated with similar conditions of growth generally and especially of the genital organs.

2. *The question whether the suprarenal cortex has the power of neutralising toxins* is a subject about which very little is known and on which it is dangerous though attractive to speculate. It was formerly thought that the suprarenal bodies destroyed effete blood pigment, but this conception has been given up for want of proof. That the cortex may exert antidotal properties is suggested by Myers's¹² observations that cobra poison after being mixed with an emulsion of the suprarenal cortex was no longer toxic, control experiments with emulsions of the suprarenal medulla and of other organs being negative. Experimental infections with various organisms, such as bacillus tuberculosis, slow diphtherial intoxication, and lead poisoning (Gouget¹³), have been found to give rise to hypertrophy of the cortex of the adrenal glands, thus suggesting increased functional activity. It may be mentioned incidentally that, according to Mulon,¹⁴ the histological evidence of over-activity (*hyperépiphrie*) of the cortex is increased pigmentation and diminished fat in its cells.

Adenomas or nodular hyperplasia of the suprarenal cortex are found in a certain number of necropsies. In 6200 necropsies at St. George's Hospital, London, adenomas were present in 11 cases, or 0.2 per cent. (Hodge), and at Guy's Hospital in 0.7 per cent. of necropsies (Richards). They are sometimes found in cases of chronic pulmonary tuberculosis, but special attention has been drawn to the association of cortical adenomas with granular kidneys and high blood pressure, and it has been pointed out that they are rare in cases of chronic nephritis with low blood pressure. There would therefore appear to be some relation between their presence and high arterial blood pressure; as the cortex does not contain any pressor substance it cannot be held that the cortical hyperplasia causes the increased pressure, and it has been suggested that the adenomas are evidence of an attempt on the part of the cortex to neutralise the toxins responsible for the high blood pressure (Aubertin and Ambard¹⁵). As bearing on this it may be mentioned that it is stated that experimental lesions of the kidney lead to hyperplasia of the adrenals (Darré¹⁶). The main interest of the speculation as to the existence of antitoxic function in the cortex of the adrenal glands is in connexion with the pathogenesis of Addison's disease. The low blood pressure and extreme asthenia in that disease can be satisfactorily explained as due to an absence of adrenalin or the pressor substance provided by the medulla, but the vomiting, gastro-intestinal disturbance, and the pigmentation suggest irritation of the sympathetic. This has, in the past, usually been attributed to invasion of the adjacent sympathetic by inflammatory changes and adhesions, or to mechanical stimulation of these nerve plexuses by tuberculous masses in the adrenal glands, but this explanation breaks down for cases in which the adrenals are only atrophied. To meet this objection it has been supposed that the absence of adrenalin leads, by perverted metabolism, to a toxæmic state, and that this toxæmia accounts for the irritative manifestations. On the other hand, Addison's disease might be regarded as the outcome of total suprarenal inadequacy—namely, of (a) medullary inadequacy which, by the absence of adrenalin, accounts for asthenia and low blood pressure, and of (b) cortical inadequacy, which accounts for the irritative symptoms by failure of an antitoxic function exerted by this part of the organ. It is conceivable that, owing to destruction or atrophy of the cortex, there is no longer neutralisation of toxic bodies and that these accumulate and irritate the sympathetic. In this connexion it may be pointed out that the widespread distribution of pigmentation is more readily explained by a general toxæmia than by a local irritation of the sympathetic. It may also be urged in favour of this hypothesis that it explains why suprarenal

extract so commonly fails to cure Addison's disease in the same way that thyroid extract counteracts myxœdema; for although suprarenal extract provides the wanting adrenalin, the extract of the cortex, even when given, is not necessarily the equivalent of the activities of the living cells of that tissue.

3. *That the cortex is in some way concerned with the internal secretion of the medulla.*—Although it does not contain any pressor substance, it is conceivable that the cortex plays an essential part in the early stages of the formation of adrenalin and that the process of elaboration is completed in the medulla, in which part alone the full activity of the secretion is acquired. In favour of this hypothesis Schäfer and Herring¹⁷ point out the analogy between the pituitary and the suprarenal glands. In both, the glandular epithelial parts (anterior lobe and cortex) are inactive, while the neuro-ectodermal parts (infundibular portion and medulla) yield a highly active extract. The close anatomical relation of the epithelial and neuro-ectodermal parts in the two glands suggests that their physiological relation may be equally close.

We have thus seen that three views at least have been put forward as to the function of the cortex: (1) that it is connected with growth, especially of the sexual organs; (2) that it is antitoxic; and (3) that it plays some part in the elaboration of the internal secretion of the medulla. *A priori* it would appear improbable that the cortex discharges all these three functions, but from experiments on animals Marrassini¹⁸ has put forward the view that the three zones of the cortex—zona glomerulosa, zona fasciculata, and zona reticularis—have different functions; this is little more than a suggestion, but it shows the need of waiting for further investigation. The most definite point about the cortex would appear to be that it is co-related with sexual growth.

THE MEDULLA.

The cells of the medulla provide a pressor substance—adrenalin—which acts on the sympathetic nerve endings. These cells, called chromophil or chromaffine from their affinity for chromic acid, are not confined to the medulla of the suprarenal glands but are found elsewhere in contact with the sympathetic, as Zuckerkandl's parasympathetic bodies, the inter-carotid gland which has been described as an accessory medullary adrenal (Mulon¹⁹), Luschka's coccygeal gland, and some collections of cells in the pituitary body. The medulla of the suprarenals therefore forms the most conspicuous part but not the whole of what has been called the hypertensive glandular system. The importance of this conception is that it explains why cases with destruction of the medullary portions of the adrenals do not always manifest the symptoms of Addison's disease, the remainder of the chromaffine system being sufficient to supply the required amount of adrenalin; conversely in some cases of Addison's disease in which the medulla of the suprarenals is not obviously affected, the hypertensive system, as a whole, may conceivably be deficient. The possible pathological relations of the internal secretion of the medulla may be divided into (I.) alteration in quantity, (a) absence, (b) diminution, and (c) excess; and (II.) alteration in quality.

I. *Alteration in quantity.*—(a) Complete absence of the internal secretion is met with in Addison's disease as is proved by the inactive condition of the medulla when tested physiologically. It has also been shown that the suprarenal medulla may be devoid of adrenalin in patients dying from chronic exhausting diseases, and that though there is often obvious naked-eye change in the glands this is not an invariable accompaniment of the loss of functional activity (Mott and Halliburton). As bearing on the interesting question whether there is normally an equilibrium between the pressor or hypertensive internal secretions of the medulla of the suprarenals and of the other collections of chromaffine cells on the one hand and the depressor internal secretion of the thyroid on the other hand, it may be pointed out that in Addison's disease a relative excess of the internal secretion of the thyroid might be expected on account of the absence of adrenalin. There is, however, no evidence of this in Addison's disease; there

¹² Myers, W.: Transactions of the Pathological Society of London, 1898, vol. xlix., p. 368.

¹³ Gouget: Comptes Rendus de la Société de Biologie, Paris, 1903, vol. lv., p. 1659.

¹⁴ Mulon, P.: Ibid., 1907, vol. lxii., p. 905.

¹⁵ Aubertin et Ambard: Mémoire et Bulletin de la Société Médicale des Hôpitaux de Paris, 1904, p. 175.

¹⁶ Darré: Thèse de Paris, 1907, quoted by Beaujard, *emaine Médicale*, Paris, 1907, p. 230.

¹⁷ Schäfer and Herring: Philosophical Transactions of the Royal Society of London, 1906, Series B, vol. cxcix., p. 27.

¹⁸ Marrassini: Archives Italiennes de Biologie, Turin, 1906, vol. xlv., p. 73.

¹⁹ Mulon: Archives Générales de Médecine, Paris, 1904, p. 2543.

are no symptoms resembling those produced by overdoses of thyroid extract or thyroidism, and so far as this goes it would appear that if there be normally a balance between the internal secretions of the suprarenal and thyroid glands, this balance is partially maintained, possibly by diminished thyroid secretion or by some neutralisation of the active thyroid secretion by the tissues of the body, when the internal secretion of adrenalin fails entirely. There is, of course, one manifestation common to Addison's disease and exophthalmic goitre—namely, pigmentation—but it is very difficult, in the present state of our knowledge, to explain this as the result of one and the same process in the two diseases. It is much more likely that in both cases there is over-excitation of the sympathetic nerves, in exophthalmic goitre by an excessive and abnormal thyroid secretion and in Addison's disease by a toxæmia possibly depending on inadequacy of the hypothetical antitoxic function of the cortex of the suprarenals.

(b) Diminution in the amount of adrenalin. This may be considered under the heads of (1) chronic inadequacy; (2) acute inadequacy; and (3) relative inadequacy. (1) Chronic inadequacy. The existence of cases of larval or frustrate myxœdema has now long been recognised; the condition has also been called benign hypothyroidism. The most convincing proof of its existence in a given case is improvement after the administration of thyroid extract. Similarly there is a condition of deficient adrenalin secretion. Possibly in some cases this defect of the adrenalin-secreting cells may be congenital; and it has been suggested that the status lymphaticus and hæmophilia are thus explained (Wiesel). A condition of deficient secretion of adrenalin, or partial medullary inadequacy, is probably more commonly acquired and the result of morbid changes in the medulla. These changes may be due to tuberculous, syphilitic, or cancerous invasion secondary to disease elsewhere in the body; or to toxins conveyed from other parts of the body—for example, the lungs in cases of tuberculosis may so act on the suprarenals as to produce degeneration and fibrosis; or, again, as the result of acute infections, such as staphylococcal or pneumococcal, the suprarenals may be permanently damaged and suprarenal inadequacy be established; this sequence of events is analogous to chronic nephritis after an acute attack of nephritis. To this condition of suprarenal inadequacy the name Addisonism has been applied by Boinet,²⁰ who in 37 cases of pulmonary tuberculosis manifesting Addisonism found the suprarenal bodies fibrosed in 30, infiltrated with small tubercles in four, and with caseous tubercles in three. This conception has some bearing on the pigmentation which so commonly accompanies advanced pulmonary tuberculosis and often raises the question as to the existence of Addison's disease. Everyone is familiar with these cases, but as the symptoms are not sufficiently marked to justify a diagnosis of Addison's disease, the tendency has been rather to put the factor of the suprarenals aside in attempting to explain the melanoderma of advanced pulmonary tuberculosis. Since it has been shown that the suprarenal medulla may be devoid of adrenalin in exhausting diseases (Mott and Halliburton) there appears to be reasonable ground for the view that Addisonism may here be present. Boinet recommends adrenalin in these cases; in order to determine whether there is or is not suprarenal inadequacy the effect of adrenalin on the arterial blood pressure should be estimated, for O. F. Grünbaum²¹ has shown that in healthy persons suprarenal extract has no effect on blood pressure, but that a rise of blood pressure after the administration of suprarenal extract indicates suprarenal inadequacy. This method of diagnosis and treatment deserves further trial. But it must be borne in mind that though low blood-pressure and asthenia may be counteracted by adrenalin, the pigmentation has not been proved to depend on want of the internal secretion of the medulla, and hence it cannot be anticipated that the administration of adrenalin will remove the melanoderma, which may, indeed, depend on a concomitant lesion of the cortex. Just as numerous symptoms have been referred to benign hypothyroidism, so it is not illogical to suppose that various conditions, characterised by low blood-pressure and debility both of the involuntary and voluntary muscles, may depend on an insufficient supply of adrenalin. Thus it has been suggested, but by no means proved, that cyclical albuminuria

and forms of neurasthenia associated with low blood-pressure are manifestations of adrenal insufficiency.

(2) Acute adrenal inadequacy. It occasionally happens that death occurs suddenly in patients suspected to be the subjects of Addison's disease on account of some abnormal pigmentation, but without any definite constitutional symptoms; or that persons previously in fair health and certainly not known to have any disease suddenly become acutely ill, often with convulsions, and die rapidly from collapse. In some of these cases tuberculous disease of the suprarenal bodies is found at the necropsy and death is perhaps certified as due to Addison's disease. Though this conclusion is in the main correct it does not explain the fulminating character of the termination. It is probable that this is due to some form of acute infection attacking the suprarenal glands and leading to suppression of their functional activity, and it can easily be understood that this will occur more readily when the amount of suprarenal medullary substance available has been previously curtailed. In many acute infections, especially in diphtheria, the micro-organisms or toxins produce acute changes, such as cloudy swelling, necrosis, and leucocytic infiltration, in adrenals previously healthy. In some instances the damage is so acute that hæmorrhage occurs into the glands. This acute condition of adrenal hæmorrhage has been specially studied in children, and it has been suggested on the one hand that rapidly fatal hæmorrhagic small-pox explains some of the cases; thus, of ten recorded cases seven were unvaccinated (Riviere²²), and on the other hand that the condition is due to food poisoning or an acute toxæmia of unknown origin and is possibly a distinct disease (Dudgeon²³). Acute adrenal hæmorrhage may also complicate various fevers such as diphtheria, enteric, pneumonia, and erysipelas. The hæmorrhages may be punctate, infiltrating or massive, unilateral or bilateral. The most characteristic symptoms of these adrenal hæmorrhages are sudden onset with fever, violent pain in the hypochondrium radiating to the loins, convulsions, vomiting, diarrhoea, and, later, tympanites, collapse, and death within 48 hours from the onset. No doubt damage is done to the adjacent abdominal sympathetic by the hæmorrhage, and thus clinical manifestations analogous to those of hæmorrhagic pancreatitis are produced. Cutaneous purpura is sometimes associated with hæmorrhage into the adrenals, as in variola, and it would, at any rate at first sight, appear probable that the same underlying cause—toxæmia or bacteriæmia—is responsible for both sets of hæmorrhages. It has, however, been thought that the changes in the adrenals are primary and the purpura secondary (Loeper²⁴), that purpura may stand in the same relation to acute destruction of the suprarenals as pigmentation does to chronic destruction (Dudgeon), and that the proper treatment is to give adrenalin. It is worth while to inquire to what extent the low blood pressure and circulatory failure seen in acute febrile diseases are the result of temporary suprarenal inadequacy, brought about by the action of bacterial toxins on the cells of the medulla of the suprarenal bodies. The action of toxins on the heart muscle cannot be questioned, but it is conceivable that some of the loss of vascular tone in fever is due to a want of adrenalin and that it is not entirely the result of the direct action of toxins on the vascular system. This question is of practical importance as bearing on the advisability of giving adrenalin in acute diseases with threatened failure of the circulation. That the amount of adrenalin in the suprarenal glands may be greatly diminished by acute disease has been shown by testing the glands physiologically (Mott and Halliburton²⁵). The medulla of animals poisoned by diphtheria is devoid of adrenalin, as shown by the colour reaction with chromic acid (Elliott and Tuckett²⁶), and it had previously been found empirically that adrenalin was of great value in the cardiac failure of diphtheria. An obvious objection to the administration of adrenalin in such conditions is that if it increases the peripheral resistance it will of necessity give the failing left ventricle more work to do and so be harmful rather than beneficial. I have, however, for some considerable time been in the habit of

²² Riviere, C.: Transactions of the Pathological Society of London 1902, vol. lli., p. 368.

²³ Dudgeon: American Journal of Medical Science, Philadelphia, 1904, vol. cxxvii., p. 134.

²⁴ Loeper: Cliniques Médicales de l'Hôtel-Dieu, Paris, 1906, tome v., p. 90.

²⁵ Mott and Halliburton: Archives of Neurology, 1907, vol. iii., p. 123.

²⁶ Elliott and Tuckett: Journal of Physiology, London, 1906, vol. xxxiv., p. 332.

²⁰ Boinet: Archives Générales de Médecine, 1904, vol. cxciv., pp 2324, 2525.

²¹ Grünbaum, O. F.: Transactions of the Royal Medical and Chirurgical Society, London, 1907, vol. xc.

giving adrenalin by the mouth in cases of pneumonia in adults and in bronchopneumonia in children, and, I believe, with good results; it has appeared to prevent cardiac failure and has not given rise to any bad symptoms such as œdema of the lungs. Another objection raised against this use of adrenalin is that experimentally it produces arterial degeneration; as bearing on this I have examined the aorta in a few cases in which adrenalin had been given during life and have not found any recent changes. But I do not lay any stress on this for several reasons—my observations are quite insufficient, the amount and duration of the administration of adrenalin were not comparable with those employed in the experimental degeneration, and even if recent changes were found it might be argued that they were due to toxins of the disease responsible for death. While I believe that adrenalin is a valuable circulatory tonic in acute infections, especially pneumonia, I am anxious that this point should be more thoroughly tested, especially as I have found but little increase in the blood pressure of febrile patients showing apparent improvement while taking adrenalin.

(3) Relative inadequacy of the internal secretion of the medulla. By this is meant that if there be normally a balance between the effects of the pressor and depressor glands, any excessive secretion (depressor) of the thyroid should lead, the pressor secretion maintaining the normal mean, to a relative deficiency of the antagonising internal secretion. The question that arises here is whether the symptoms of thyreoidism, of exophthalmic goitre, and the allied toxic manifestations which, as Sir Victor Horsley²⁷ points out, may sometimes be seen in ordinary goitre are in any degree due to a relative deficiency in the secretion of adrenalin. It is clear from Janeway's²⁸ summary that the blood pressure is not low in exophthalmic goitre, as might naturally be expected if the disease be regarded as due to simple hyperthyroidism, and that it may be very considerably raised as the result of psychical excitement. In the few cases in which I have taken the blood pressure with a Riva-Rocci sphygmometer it has been rather above than below the normal. It is true that in some cases of exophthalmic goitre improvement has followed the administration of suprarenal extract; I have seen this myself. But it must be remembered that exophthalmic goitre often improves both spontaneously and after widely different forms of treatment, and that it has not been shown that suprarenal medication is a certain means of counteracting the symptoms of exophthalmic goitre. We have therefore no evidence that an excess of thyroid secretion produces bad effects by means of a relative deficiency in adrenalin.

(c) Excessive secretion of adrenalin. Here, again, very little is known. The excess might conceivably be (1) due to an excessive secretion of adrenalin by the medulla, or absolute excess, or (2) be relative and depend on a diminution in the amount of the thyroid secretion. (1) Since the demonstration that atheroma can be artificially produced in animals by the injection of adrenalin (Josué,²⁹ Pearce and Stanton,³⁰ and others) the question has arisen whether high arterial blood pressure in man and its results—hypertrophy of the left ventricle, arterio-sclerosis, atrophic changes in the kidneys, and so forth—may be due to an excess of adrenalin in the circulation. As it is generally believed that in renal disease a raised blood pressure is, within limits, useful, it might be assumed that this compensatory process is brought about by hyperplasia of the suprarenal medulla. Let us see how the evidence available bears on this question. From some experiments on animals Marrassini³¹ concludes that interference with the renal excretion increases the functional activity of the medulla. A case of parenchymatous nephritis with great hypertrophy of the left ventricle and manifest hyperplasia of the medulla of the suprarenals has been reported (Vaquez and Aubertin)³² and might be taken to support this view. But as regards this special form of renal disease this would appear to be almost an isolated observation. Wiesel³³ has

recorded a number of cases of high blood pressure, arterio-sclerosis, and granular kidney, associated with enlargement of the suprarenal medulla and also of the chromaffine cells in the solar plexus. Here it might at first sight be thought that the suprarenal change was the cause of the high blood pressure and of the structural changes, as in experimental atheroma. It has, it is interesting to note, been suggested (W. Russell)³⁴ that certain foods, especially proteins, may lead to increased secretion of adrenalin. It would thus be possible to construct a hypothesis of dietetic excess, absorption from the intestine of toxic bodies which stimulate the medulla of the suprarenals to increased functional activity followed by hypertrophy, and that subsequently the cardio-vascular changes are produced. But Wiesel believes that the cardiac hypertrophy precedes the hyperplasia of the suprarenal medulla and is not due to it. This relation between the sequence of events must be somewhat difficult to determine and the subject is in need of further study. At present there is no proof of the existence of any disease due to excessive adrenalin secretion and corresponding to exophthalmic goitre in the case of the thyroid, but on this point we must be content to wait for further information.

(2) Relative excess due to a deficiency in the amount of antagonising depressor internal secretion. It is conceivable that, as the result of the atrophy of the thyroid which so commonly accompanies advancing years, the equilibrium normally existing between the internal secretions of the thyroid (depressor) and of the adrenal medulla (pressor) would no longer be maintained and that an excess of adrenalin would therefore accumulate in the circulation and thus induce a correspondingly high arterial pressure. In other words, that the rise of arterial blood pressure as life advances is due to a predominance of the pressor internal secretions. In support of this it might be urged that in myxœdema it is common to find arterio-sclerosis and granular kidney, which may result from long-continued high blood pressure; but too much stress must not be laid on this, for the age of myxœdematous patients approaches that at which vascular degeneration is common, and in a certain number of cases of myxœdema the kidneys are healthy.

To return again to the question whether the hypothetical equilibrium between the depressor and pressor internal secretions may be upset by a deficiency of one, so that the other secretion has a paramount influence, Gioffredi's³⁵ conclusions are to the effect that normally certain organs and tissues—the liver, the blood, and to a less extent the voluntary muscles—transform adrenalin into an inactive product and so protect the body against the toxic results of an excess of adrenalin which might otherwise result. In order to effect this change the blood must be provided with oxygen and be alkaline, but those conditions are not necessary in the case of the liver and voluntary muscles. It is conceivable that such a compensatory mechanism might fail under the same conditions as those under which the thyroid secretion wanes, and that then a relative excess of adrenalin in the circulation would result. These considerations are highly speculative, but they may perhaps be forgiven because they bear in a somewhat remote manner on an important practical point—namely, the prevention and reduction of the rising arterial pressure of advancing years. For they suggest that the administration of thyroid extract might have this desired result and that it may prove to be the routine treatment. Iodides, which are so widely given in clinical medicine in order to lower blood pressure, have been shown to have no depressing effect on the heart or blood pressure (Stockman and Charteris³⁶), but it is conceivable that they eventually lower blood pressure by stimulating the thyroid to an increased secretion.

II. *Alteration in quality.*—Of alterations in the quality of secretions very little is known if we except the gastric juice, but it is reasonable to believe that in the future this factor will attract attention and be shown to have most important pathological bearings. The adenomatous changes in the thyroid in exophthalmic goitre and in the pituitary body in acromegaly may safely be assumed to lead to an altered internal secretion, and so to have a causal bearing on the associated diseases. In the case of the adrenal medulla nothing is known as to any alteration in the quality of the secretion. It is somewhat

²⁷ Horsley: Clinical Journal, 1904, vol. xxiv., p. 29.

²⁸ Janeway, T. C.: The Clinical Study of Blood Pressure, New York, 1904, p. 200.

²⁹ Josué, O.: Presse Médicale, Paris, 1903, p. 798.

³⁰ Pearce and Stanton: Journal of Experimental Medicine, 1906, vol. viii., p. 74.

³¹ Marrassini: Archives Italiennes de Biologie, Turin, 1901, vol. xlv., p. 82.

³² Vaquez et Aubertin: Comptes Rendus de la Société de Biologie, Paris, 1907.

³³ Wiesel: Wiener Medicinische Wochenschrift, 1907, vol. lvii., p. 674.

³⁴ Russell, W.: Brit. Med. Jour., 1904, vol. i., p. 1299.

³⁵ Gioffredi: Archivio di Farmacologia Sperimentale, 1907, p. 145.

³⁶ Stockman and Charteris: Brit. Med. Jour., 1901, vol. ii., p. 1520.

wild speculation, but it may be mentioned for what it is worth, that possibly intestinal toxins may so act on the cells of the adrenal medulla as to produce an internal secretion of such an abnormal character that the normal process of transformation of any excess into an inactive body, as suggested by Gioffredi, cannot be carried out by the tissues. The excess of such an abnormal adrenalin might conceivably cause high arterial pressure, arterio-sclerosis, and the allied morbid changes.

An Address

ON

THE PREVENTION OF MALARIA IN BRITISH POSSESSIONS, EGYPT, AND PARTS OF AMERICA.

Delivered in Section VII. of the Fourteenth International Congress of Hygiene and Demography held at Berlin, September, 1907,

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I.—PRELIMINARY.

ALMOST exactly ten years have now elapsed since the parasite of malaria was first detected in anophelines. This discovery, confirmed and amplified in many countries, suggested many methods for the prevention of the disease; but unfortunately, although science may indicate methods of prevention, local Governments are not always willing to undertake the trouble and expense required for the work. It is very advisable, then, to examine how much various Governments have actually done during this period in several parts of the world to preserve mankind from the vast amount of sickness and mortality occasioned by so widespread a malady and to consider what action may be taken to encourage more energetic efforts in the future. In attempting this task, however, I propose to confine my remarks to those countries in which the progress of events is best known to me—that is, principally to the tropics; but at the same time fear that I must give the history in considerable detail, without which my conclusions will not perhaps be as clear to others as they seem to be to myself.

In 1897–99 I was able to observe in several parts of India that numerous species of anophelines (in two of which I had previously cultivated the crescent-bearing parasites) breed mostly in natural collections of water lying upon the surface of the ground, and not, as many other common varieties of gnats do, in vessels and cisterns.¹ This fact at once suggested the full explanation of the laws known from the time of the ancients—that malaria is generally connected with terrestrial water, and may be reduced by drainage. But at the same time, while it re-established the old prophylaxis by drainage, it rendered it more simple, cheap, and yet precise. No longer driven to the expensive task of draining the whole expanse of a malarious area, we were now able to confine our operations, often with a great saving of money, only to those particular pools which are suitable for the larvæ of the insects, and which in many places I had already observed to be comparatively few and small. Consequently I did not hesitate to advise the Government of India (in a report dated Feb. 16th, 1899) to adopt this important measure in the principal malarious towns and military stations.^{2 3} At the same time, as already empirically known, the use of mosquito nets during sleep was obviously a valuable means of personal prophylaxis. Shortly after writing this report I left India, and a few months later (July, 1899) proceeded with two colleagues, Dr. H. E. Annett and Mr. E. E. Austen, to the British colony of Sierra Leone, where we hoped to indicate more exactly the details of this perfected system of drainage-prophylaxis. We immediately

ascertained by my methods previously elaborated in India that *Pyrethophorus costalis* and *Myzomyia funesta* carry all the species of the parasites of man in that part of Africa; that these mosquitoes breed principally in small but numerous collections of water on the ground; and that it would be a comparatively easy task for the authorities, with all the resources at their disposal, to remove these breeding-places within the city of Freetown and thus to reduce the mosquitoes and the malaria together. In order to help them in this task we indicated for the first time the peculiar attitudes of the anopheline larvæ and adults which enable anyone to recognise them at sight; the special characters of the pools in which they breed; and the exact methods by which these pools should be dealt with; and we furnished them with a complete map of the principal breeding places. Our reports gave the original full exposition of the antimosquito prophylaxis of malaria, which since then has become the basis of all such work in many parts of the world.^{4 5} Not being authorised, however, to undertake the work ourselves, all we could do was to advise, and we then returned to England hoping that the Government would act upon our suggestion.

In the meantime my Indian researches had been followed with enthusiasm in Germany and Italy. In the autumn of 1898 Koch and the Italian observers, who had made so many beautiful studies of the subject, were able to confirm and to extend the original investigations. They immediately suggested another great system of malaria-prophylaxis—that by quinine. It was argued that if all the persons in a community who suffer from malaria are sought out and efficiently treated with quinine the parasites will diminish so greatly within the community that the mosquitoes, however numerous they may be, will no longer become infected, and will so cease to convey the infection to healthy persons. Without delay, the Germans, led by Koch, and the Italians, led by Celli, sought to give practical effect to this logical suggestion. At the same time, Celli especially advocated the general protection of houses by means of screens of wire gauze.

It is not my function to-day to follow the labours of these distinguished workers. The problem in malarious British colonies, which are mostly tropical and inhabited by dark races, is not the same as in Italy—a fact which is often forgotten by academical sanitarians. Such races cannot easily be persuaded to submit to continued medication by quinine and are much too poor to provide screens for their houses, and even Europeans in the tropics frequently reject both measures with obstinacy. On the other hand, drainage-prophylaxis demands no such compliance from the public. As I have frequently pointed out,⁶ local authorities can drain, or otherwise treat, anopheline pools without asking the consent of any one. The people are not required to take any drug for months, or to pay for expensive appliances to their windows. Moreover, mosquito reduction tends to remove yellow fever and filariasis as well as malaria, banishes a source of constant personal irritation, and, no less important, compels local sanitary departments to keep a close watch on all parts of the area in their charge. On the other hand, of course, we cannot expect drainage to be undertaken everywhere, in the open fields or the wilderness; it is principally applicable to towns—that is, to places where the money spent upon it is likely to benefit the largest number of people; for the camp, the farm, the plantation, the isolated house, and the petty hamlet the other measures must frequently be fallen back upon. As a rule, however, for tropical towns mosquito reduction where it is possible has always promised to be the most useful and, in the end, the most economical system of all; and, of course, the other measures may often be adopted, at least partially, in addition. Thus the ideal procedure for towns in the tropics consists (1) in the removal of mosquito-breeding waters; (2) in the treatment of old cases of malaria with quinine; and (3) in the protection, as an additional safeguard, of hospitals, barracks, jails, and as many houses as possible with wire gauze. To these we must add, as insisted upon by Stephens and Christophers, the principle of segregation for Europeans.

But however desirable mosquito reduction seemed to be, my proposals to adopt it were everywhere met at first with

¹ Ross: Instructions for the Prevention of Malarial Fever, Liverpool School of Tropical Medicine, Memoir I., 1899; and Researches on Malaria, Nobel publication, 1902, Stockholm; German translation, Gustav Fischer, Jena.

² Ibid.: Extirpation of Malaria, Indian Medical Gazette, July, 1899.

³ Ibid.: The Possibility of Extirpating Malaria from Certain Localities by a New Method, Brit. Med. Jour., July 1st, 1899.

⁴ Correspondent (Ross): The Malaria Expedition to Sierra Leone, Brit. Med. Jour., Sept. 9th, 16th, and 20th, and Oct. 14th, 1899.

⁵ Ross Annett, Austen: Report of the Malaria Expedition to West Africa, Liverpool School of Tropical Medicine, Memoir II., 1900.

⁶ Ross: Mosquito Brigades. George Philip and Son, London, 1902.