were referred to me by their own doctors on account of the fibroids, the carcinoma of the cervix having been overlooked in each case; had radiation been the recognized treatment for fibroids, the probability is that these growths would have remained undiscovered until a much later period, as the radiologist has no more special training in gynaecological diagnosis than the general practitioner.

Degeneration.

A degenerating fibroid may cause serious symptoms, either from the effect of the degeneration itself as in red degeneration, or because the degenerated tissue has become infected with organisms, or merely from the absorption of the products of degeneration. This last is, I think, much more important than is usually recognized, and accounts for the profound anaemia, often out of all proportion to the amount of blood lost, and the general ill health from which these patients suffer.

Unfortunately not all the specimens in this series were examined in the laboratory, but of those which were, twenty-one were reported as having undergone degeneration—cystic, red, calcareous, etc.; these degenerations occur much more frequently in fibroid uteri after the menopause when the blood supply is much diminished.

How often degeneration occurs in a fibroid after an artificial menopause produced by radiation I cannot say, my personal experience of this method of treatment being very small, but I see no reason to suppose its incidence to be less than in fibroids after a natural menopause, and I have seen one case which required operation six years after an artificial menopause produced by *x* rays. This complication is often overlooked in the papers advocating radiation, as the cases are too recent, and it would be useful to have some of these series reviewed ten or twenty years later.

It is impossible to say what would have happened to all these cases if they had been treated by radiation; I do not suggest all would have ended fatally, though probably some would; and certainly some would have required operation at a later date for urgent symptoms, when the patient's condition would make operation a much more serious matter. This danger is recognized by many radiologists, and the more experienced of them advise all cases of fibroid to be examined by a gynaecologist so as to eliminate degenerations of the tumour; but the great difficulty is to be sure without operation that a tumour is not undergoing degeneration, and the instances must be few in which a competent gynaecologist will take the full responsibility of saying there is no degeneration.

Inflamed Appendages.

This is a complication which precludes treatment by radiation, according to the authorities on this method of treatment. Of course, acute inflammation will usually give rise to acute symptoms which are easily recognized, but there are cases which only come under treatment after the acute symptoms have subsided. In this series there was only one case which could not be included in one or other of the categories, but there were several others with inflamed appendages complicated with degenerating fibroids or with adhesions to rectum or intestines.

Adhesions.

Adhesions firmly binding rectum, bladder, or intestines to the tumour contraindicate the use of radiation, and yet how often do we unexpectedly find these adhesions during an operation! The following case—one of the last in this series—is an instance:

An unmarried woman, aged 49, one year past the menopause, with no previous history of inflammation, was brought to me because of recurring haemorrhage. Examination revealed the presence of a fibroid uterus about the size of an orange, apparently quite mobile; there were no symptoms or signs suggesting degeneration, and it was just the case which would be referred to the radiologist if this form of treatment were used. I opened the abdomen and found both tubes and ovaries firmly adherent to the back of the uterus, but before I could find the tubes and the uterus, I had to separate the rectum and bladder from these organs and from each other. These adhesions were so firm that the rectum had to be cut off from the uterus and appendages, not stripped, as is usually possible.

In all probability these cases with unsuspected adherent rectum and intestines explain the damage to these organs which is occasionally reported after the use of *x* rays. In this series five cases are noted as having adhesions between the uterus and abdominal viscera. Though the number is not very great, the frequent impossibility of diagnosing the presence of adhesions before operation greatly increases their importance.

Retention of Urine.

Seven patients, all about or past the menopause, were operated upon for this condition alone. In each case the uterine fibroid filled the pelvis, and had been allowed to drop into this position through atrophy of the tumour due to the menopause. I cannot say how far *x* rays would have still further diminished the size of the tumours and relieved the symptoms, but their application would have taken some little time, and have necessitated catheter treatment in the meantime. We must also bear in mind the action of radiation upon larger tumours, as the atrophy set up by this treatment may cause a fibroid situated above the brim to descend into the pelvis and set up acute symptoms.

Wrong Diagnosis.

Every gynaecologist knows the difficulty of making a correct diagnosis in these cases of pelvic tumour. This is recognized by the radiologists who have published their work up to this time, and the majority insist upon the necessity of an examination by a gynaecologist before *x*-ray treatment. I doubt whether this will be so in future. Even if a gynaecologist is consulted the risk is not entirely eliminated, and I have to confess to two bad mistakes made during the last two months. In both cases I diagnosed uterine fibroids, and fortunately advised operation, and in both cases the solid tumour proved to be carcinoma of the ovary. In both cases the tumour was not adherent and was removed, so that the patients have a very fair chance of being cured, which they would not have had with *x*-ray treatment.

Conclusions.

1. Small fibroids, not larger than an orange, which are not producing any symptoms may be left alone, but the patient should be kept under observation, as there is a possibility before the menopause of the tumour causing increased haemorrhage or increasing in size, and after the menopause of becoming malignant.

2. If the patient is very anaemic the tumour should be treated by radiation to stop the haemorrhage and allow her general health to improve, but the tumour should be removed later.

3. In all other cases the tumour should be removed by hysterectomy or myomectomy—myomectomy being preferred for women in the child-bearing period who desire a family and when a useful uterus can be left, panhysterectomy for cases with a badly lacerated cervix in addition to the fibroid, and supravaginal hysterectomy for the remainder.

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The Oliver-Sharpey Lectures

ON

THE ACTIVITY OF THE CAPILLARY BLOOD VESSELS,

AND ITS RELATION TO CERTAIN FORMS OF TOXAEMIA.

DELIVERED BEFORE

THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

BY

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LECTURE II.

BEFORE we pass to some of the pathological applications of the knowledge now available concerning the active contractility and tone of the capillary blood vessels, there are a few additional points concerning its normal physiological significance which ought to be passed in review. Professor Richards of Philadelphia has found it possible by means of special lighting arrangements to see the capillaries between the tubules and in the glomeruli of the living frog's

kidney.[1] Dr. Leonard Hill[2] has independently, and for a somewhat different purpose, made observations on the same object. Richards and Wearn have noted the highly active contractile function of the glomerular tufts, some shrinking to small compass while others, previously shrunken, expand so as almost to fill Bowman's capsule. The fact which I have already emphasized, of the varying permeability of the capillary endothelium, with changes in tone of the supporting, contractile cells of Rouget, must surely have some bearing on these pronounced variations of tone in the capillaries of the kidney; but its exact significance remains to be explored.

Since Gaskell's[3] work on the regulation of the blood supply to skeletal muscle the association of vaso-dilatation with functional activity has been clearly known. The work of Chauveau and Kauffmann[4] on the masticatory muscles of the horse demonstrated the same phenomenon. Until recently, however, this dilatation was assumed to concern the arteries alone, and the chief matter of discussion was the relative importance in its production of nervous impulses and of the chemical stimulus of metabolic products. As we have already seen, there can be no doubt now as to the important part played, in this adjustment of blood supply to metabolic requirement, by intrinsic relaxation of the capillaries, or as to the control of the tone of these vessels by nervous impulses. When we come to the question of chemical control the evidence is not yet so clear. On the one hand, it is obvious that the capillaries, with their intimate relation to and constant chemical interchange with the tissues, must be specially exposed to any influence on vascular tonus which the products of metabolism may exert. On the other hand, the particular product of metabolism, carbon dioxide, which, since Gaskell's[5] experiments again, and as the result of repeated confirmation of his results (Bayliss,[6] Hooker,[7] Anrep[8]), has been credited with a potent vaso-dilator action, has not been demonstrated to have a pronounced effect on capillary tonus. Krogh,[9] indeed, as the result of recent experiments, comes to the conclusion that such acidity, due to increased tension of carbon dioxide, as can occur during life, "probably plays no part whatever as a regulator of the capillary circulation." Yet, since the time of Roy and Graham Brown[10] it has been obvious that capillary tone is powerfully depressed by some product of cellular action, which accumulates during brief stoppage of the circulation, so that the capillaries dilate widely when the blood is readmitted, and is formed with abnormal rapidity if the tissue is injured. What can such a product be? It will, I think, be quite obvious, from what I said in the last lecture, that a substance having the histamine type of action would fill the requirements; and the tendency to speculate in this direction is reinforced by the observation that a simple watery extract of almost any tissue in the body contains a substance, or substances, producing this type of effect. At the same time, in the absence of direct chemical evidence—which, it must be admitted, is practically beyond hope of attainment with methods yet available—I think that there is no warrant for the assumption which some have been ready to make, that small quantities of histamine are actually formed in metabolism.

In somewhat closer contact with experimental reality is the evidence as to the factors, other than nervous impulses, concerned in the maintenance of the normal, average tone of the capillaries. You will remember that Richards and I found that the presence of a small proportion of adrenaline in the perfused blood was necessary, in order to enable us to demonstrate the vaso-dilator effect of histamine with an artificial circulation. This suggested to us that a normal function of adrenaline, as continuously secreted into the blood in minute quantities, was the maintenance of a healthy capillary tonus against the dilator effect of metabolic products. The view was supported by an observation of my own,[11] that a cat which has been deprived of its suprarenal glands becomes extraordinarily sensitive to the shock-like effect of histamine, being killed by an injection which, in the normal animal, would produce only an evanescent, vaso-dilator fall of the arterial pressure. My former colleague, Dr. Kellaway, and Dr. Cowell[12] have confirmed this observation, and have given it much greater precision, in studying the effect, on the reaction to histamine, of destroying the medulla of the suprarenal glands in cats, leaving sufficient intact cortex to enable the animals to survive, and to keep in most ways healthy, for weeks or months. They observed in such cats the effects of injecting, into the ear vein, a small dose of histamine, such as in a normal cat produces barely perceptible symptoms, with at most a slight evanescent rise in the corpuscular content, due to temporary loss of plasma from the circulation. In cats lacking the suprarenal medulla such injections of histamine caused pronounced collapse and long persistent rise of the corpuscular content of the blood. But such cats could be rendered for the time being normal, in their response to histamine, by preliminary treatment with hypodermic injections of adrenaline.

There is evidence, then, at least of an antagonism to, or a moderating influence on, the reaction of the capillaries to histamine, produced by the presence of adrenaline in the blood, in such concentrations as do not perceptibly influence the arterial blood pressure. The fact that in many animals the capillaries are under motor control from sympathetic nerves would lead to an expectation of such a tonic influence of adrenaline. Direct evidence, on the other hand, points rather to another hormone as concerned with the chemical maintenance of capillary tone. Krogh and Harrop,[13] in their perfusion experiments on the frog's leg, found evidence of the presence of some substance, not adrenaline, in mammalian blood serum, the presence of which maintained a good tone and normal permeability of the capillaries, while in its absence they became dilated and allowed the escape of fluid into the tissues. Krogh and Rehberg[14] have demonstrated a suggestive similarity, in several properties, between this diffusible substance in serum and an active constituent of the posterior lobe of the pituitary body. They resemble one another in stability, in their solubilities, their diffusion through membranes, and, apart from their tonic action on capillaries, in both showing the dilator action on the melanophores of the frog's skin, which Hogben[15] first observed with the pituitary extract. Finally, it should be noted that Pohle[16] had previously shown that removal of the pituitary gland in frogs was followed by cutaneous oedema. I do not think that the evidence for identification of the substance in serum with the pituitary extract is complete. In view, moreover, of the very wide differences exhibited by the capillaries of different species in their reaction to histamine and other substances, I think that Krogh is wise in deprecating a hasty assumption that all capillaries, in all species, are dependent for the maintenance of normal tone on the presence of traces of the pituitary hormone in the blood. This question of the relation of hormones to the functional condition of the capillaries is, indeed, only just being opened; and it is at least of interest to note that, in the case of both the endocrine glands which have yet been investigated in this connexion, the suprarenal and the pituitary gland, a presumption is already established in favour of their normally exercising an important influence on capillary tonus.

There is an intimate connexion between this question of hormonal control and some puzzling, but highly significant, observations recently made and published by my colleague Dr. Burn.[17] His observations were primarily directed to an entirely different question—that of the relation between the response of the sweat glands to pilocarpine and the integrity of their nerve supply. He found that degeneration of the secretory nerve fibres to the sweat glands of a cat's foot, produced by post-ganglionic section of the sympathetic fibres to the limb, in no wise impaired the sweating caused by pilocarpine. When, on the contrary, the whole of the mixed nerves to the foot were cut, so that sensory as well as sympathetic fibres were divided and degenerated, sooner or later the effect of pilocarpine on the sweat glands of that foot was, in the majority of cases, greatly reduced or obliterated. This was not due to the disappearance of other secretory fibres to the sweat glands, since it was clearly proved that none but those from the sympathetic system exist. A close association, however, was detected between the response of the sweat glands to pilocarpine and the dilator response of the capillaries in the same limb to histamine. When, as after degeneration of the sympathetic fibres only, the sweating response to pilocarpine was

maintained or exaggerated, the dilator response of the vessels to histamine was abnormally pronounced. When, after section of the whole nerve supply, the sweating produced by pilocarpine was reduced or suppressed, the dilator reaction to histamine had disappeared, although the arterial dilator reaction to acetyl-choline was produced as usual. I do not think that the meaning of this change in the capillary reaction, corresponding with the failure of the gland cells to respond to pilocarpine, is yet clear. Burn, adopting a line of argument which Richards and I had used, is inclined to ascribe it to loss of the normal tone of the capillaries. I do not think there is evidence, from the appearance of the skin, that the capillaries are abnormally relaxed. What Burn's results clearly show is that they have lost their normal responsiveness to histamine, and his further experiments bring out the very important point, that the dilator reaction to histamine can be restored, and with it the response of the sweat glands to pilocarpine, if the cat is treated for a few days with daily hypodermic injections of adrenaline. Again, therefore, we have suggestive evidence of an association between a high content of adrenaline in the blood and a satisfactory tone or responsiveness of capillaries, in this case of capillaries deprived of their normal nerve supply. The simultaneous loss of the normal response of the sweat glands, and its restitution by adrenaline, are probably, therefore, to be ascribed to varying states of nutrition of their cells; and this suggestion is confirmed by Burn's further and highly significant observation, that the loss of the dilator reaction to histamine is associated, not only with this depressed response of the sweat glands, but with a generally impaired vitality of the skin of the whole foot. Wherever this is exposed to pressure or friction in walking, the hair is lost, the skin becomes oedematous and loses its normal flexibility, and there is a tendency to ulceration. With the recovery of the reaction to histamine, under the influence of slowly absorbed doses of adrenaline, this malnutrition of the denervated skin disappears, and any ulceration begins to show signs of healing.

This obviously opens up very important questions as to the nature of the trophic changes in the skin following nerve lesions, and particularly of lesions involving the sensory fibres, with their function in relation to vaso-dilator reactions. The case of tabes dorsalis naturally suggests itself, and I believe there are many such conditions in which a systematic investigation of the capillary response to mechanical and chemical stimuli would be highly instructive. The naked skin of the human subject is far more suited to this type of investigation than that of any of the hairy animals usually available for laboratory experiment. The readiness with which the skin capillaries of the normal man react to histamine has been amply demonstrated by Eppinger,[18] and by Sollmann and Pilcher,[19] the latter observers recording the appearance of a capillary flush, followed by an oedematous wheal, when histamine was applied to the very lightly scarified skin, in dilutions as high as one part in 10,000. The modification of this type of reaction by defective innervation of the skin lies open to study, which could not fail, I think, to give instructive results.

There must, I suppose, be some kind of relation between this loss of dilator response, studied by Burn, and the failure of the inflammatory reaction to local irritation, demonstrated some years ago in Hans Meyer's laboratory by Ninian Bruce.[20] Bruce found that the inflammatory hyperaemia and oedema of the conjunctiva, following the application of mustard oil to the eye of a rabbit, was not perceptibly modified by previous section of the roots of the Gasserian ganglion. When the trigeminal nerve was cut peripherally to the ganglion there was no immediate modification of the inflammatory response, but, when time was allowed for degeneration of the sensory fibres with their terminal branchings, the inflammatory reaction to mustard oil was practically abolished. The same depressant effect on the inflammatory response was produced by local anaesthetics. Clearly, then, the reaction was not a central reflex; it persisted without impairment after the connexion with the brain had been broken, but could be abolished by peripheral sensory paralysis, with the central connexion intact. Bruce argued that it must be due to a peripheral reflex of the axon type, through a branching of the sensory fibre to sensory endings, on the one hand, and to the blood vessels on the other, as Bayliss[21] had previously suggested in explanation of the vaso-dilator effect of peripheral stimulation of sensory fibres—the so-called antidromic vaso-dilatation.

Bruce's results were confirmed by Bardy,[22] who only differed from Bruce in that he found that the inflammatory reaction was reduced to small proportions, not altogether abolished, by degeneration or peripheral paralysis of the sensory nerve fibres. Breslauer[23] has more recently found that even the local inflammatory reaction to mustard oil of the human skin fails to appear if the sensory nerves to the area are degenerated, or paralysed by a local anaesthetic. At the time when Bruce and Bardy's observations were published the arteries were still regarded as the only part of the vascular system presenting variations of tone having any significance. Arterial dilatation is, doubtless, a factor of importance in typical inflammation, but it can hardly be doubted, I think, that that of the capillaries is more important still. It is very questionable whether arterial dilatation alone, without relaxation of the capillaries, could produce a condition at all like that seen in inflammation. Axon reflexes to the capillaries are probably at least as important as those acting on the arteries.

In addition to this nervous action we have to take into account a chemical stimulation of the capillaries to dilatation; and this may appear almost immediately if the substance applied has itself such an action on capillaries, or as a later, indirect effect of dilator substances set free from injured or dying tissue cells, directly attacked by the irritant. Obviously the whole reaction, taking into account all these possibilities, may be a very complex one, and in different cases one or other of the various possible factors may be predominant. The whole question of the vasomotor mechanism of inflammation needs a newer and closer analysis, in the light of knowledge, of which some is already available, and much still to be obtained. I think it can hardly be doubted, however, that the result will be to bring active changes of capillary tonus into the centre of the picture.

Discussion of local skin reactions naturally brings to mind a whole series of pathological changes, erythemata and eruptions, with which the dermatologist is familiar, and in the ultimate analysis of which a knowledge of capillary function will obviously play a principal part. I have not the time, if I had the knowledge, to enter upon a consideration of them now. I will merely point to the importance, in this connexion also, of the knowledge, newly accumulating, as to the close similarity in effect upon capillaries of appropriate nervous impulses on the one hand, and chemical stimuli on the other. Dilatation of capillaries, leading to excessive permeability and local oedema, has been experimentally demonstrated as the result of nerve stimulation, and as the result of the action of poisonous substances. There are many instances in which it may be impossible to determine which type of stimulus is at work. Even the correspondence of an eruption with the distribution of particular nerves is not absolutely decisive, if we admit the possibility that a virus or a toxin might descend from the centre to the periphery along the nerves, as the virus of rabies and the toxin of tetanus have been shown to ascend from the periphery to the nerve centres;* or if, on the other hand, we suppose that small centres of capillary dilatation, produced by nervous impulses, may provide points of lowered resistance, where a generally diffused virus can settle, or a toxin accentuate a process already initiated. I indicate such possibilities merely to lay emphasis on the wisdom of avoiding the assumption that, because a phenomenon has some obvious relation to innervation, it is of necessity wholly nervous in origin.

Such considerations lead me naturally to a group of phenomena which have been the subject of much study and discussion during recent years. At the risk of a wearisome insistence, I must recall to you again the complex of symptoms which has received its most detailed analysis in the form in which it is produced by histamine. You will

*For this interesting suggestion I am indebted to Dr. John Brownlee.

remember that it involved a simultaneous stimulation of plain muscle to contraction and of the capillaries to relaxation of their tone. We have considered the effects on the circulation, but have left out of view, up to the present, the equally striking effects produced by contraction of the plain muscle of hollow viscera, and particularly that of the bronchioles. The production of this complex by histamine might excite merely a laboratory curiosity. It becomes of practical interest when we realize that essentially the same combination of plain muscle contraction and loss of capillary tone occurs as the central feature in the action of a large class of protein poisons, and in the so-called anaphylactic shock. In different species, and under different conditions, one or the other feature of the action comes into the forefront of the picture; in the unanaesthetized guinea-pig the conspicuous feature in the action of these poisons, or in the anaphylactic shock, is the constriction of the plain muscle of the bronchioles, causing asphyxial death; in the anaesthetized dog it is relaxation of the capillaries, probably associated with constriction of the hepatic veins, leading to circulatory collapse. But with minor specific and individual variations in the incidence of its component factors, the action produced by this whole group of poisonous agents is fundamentally the same.

The application to human pathology hardly needs indication. It has frequently been discussed in recent years by those more competent than I, and the production, by the same normally or individually toxic agent, of urticaria and subcutaneous oedema in one case, and spasmodic asthma in another, will be very familiar to all of you. There was at one time a tendency, which I hope is dying, to regard the pronouncement of the word "anaphylaxis," whenever this symptom-complex was encountered, as giving absolution from further effort to analyse the condition. Such words are useful when they are used to define, and merely mischievous when they are used to shirk definition. At the same time, it must be admitted that there are points of similarity between the so-called "toxic idiopathies" seen in man, and the acquired specific sensitiveness to a foreign protein, which is properly termed anaphylaxis. I have on several previous occasions maintained, by evidence and arguments which I shall not inflict on you to-day, that the essence of the true anaphylactic condition is the location in the living cells of an antibody of the precipitin type, and that it is the intracellular reaction between this and the antigen which causes the anaphylactic reaction. In the case of the toxic idiopathies, I think it is certain that we have again a cellular sensitiveness, and we must assume that the specifically toxic agent, be it a pollen or an animal epithelium, produces in the sensitive cells changes similar to those which the anaphylactic antigen produces; but we have here but little evidence of the presence of antibodies in the strict sense. Indeed, but few of the substances responsible for these human idiosyncrasies can function experimentally as antigens, and some, such as the simple organic chemicals to which specific sensitiveness occurs—iodoform, antipyrin, etc.—certainly cannot. We cannot assume, then, that whenever a specific reaction of this type occurs an immunity process, involving the presence of an antibody, is at work. All that we can assume is that the protoplasm of an idiopathically sensitive cell has some kind of abnormality, whether due to the presence of a separable antibody or not, which causes it to react to its specific poison by the same kind of change as that with which the anaphylactic cell reacts to its specific antigen, or with which the normal cell reacts to histamine or to a naturally poisonous protein cleavage product.

For the main concern of these lectures the point of chief interest is the location of poisoning of this type, however produced, in the walls of the capillaries and in plain muscle fibres. I take this to mean that all these substances produce, either in all individuals or only in those specifically sensitive, the same kind of physical change in cell protoplasm; and that the predominance of visible response to them in the capillary cells, and in the plain muscle, is due to a special physiological sensitiveness of those structures to this type of change.

When a specific sensitiveness is produced to a normally innocuous substance, this is accompanied, apparently, by a minor degree of enhanced sensitiveness to naturally poisonous substances producing these effects, as shown in some experiments by Dr. Kellaway and myself.[23] This corresponds with the clinical experience that the victim of a toxic idiopathy has capillaries, or bronchial plain muscle, which are to some degree abnormally sensitive to naturally poisonous substances of this class. If this means an enhanced physiological reactivity to a certain type of physical change, it would not be surprising, it would even be expected, that they should also show an abnormal responsiveness to nervous impulses which produce capillary dilatation on the one hand, or constriction of the bronchi on the other. I shall not venture into a discussion of clinical details, which are beyond the scope of an experimental worker. I merely want to emphasize again the fact that there is no experimental warrant for assuming that the two kinds of causation are mutually exclusive. The detection of a neurotic factor does not exclude a toxic one, and vice versa.

I must turn now to conditions in which there is reason to suppose that the whole or a large part of the capillary blood vessels in the body are simultaneously affected by toxic agents. I have given already a brief summary of the conclusions reached, by analysis of the circulatory failure produced by large doses of histamine. Here, again, histamine was chosen simply as a conveniently accessible and accurately measurable representative of a large class of poisons. Sir William Bayliss,[24] in the Oliver-Sharpey lectures a few years ago, gave a full account of the analogous condition of circulatory failure, caused by a general loss of capillary tone, which was studied during the war under the name of secondary wound shock, and attributed to the toxic action of autolytic products from crushed and lacerated tissue. I need only mention, therefore, this special example of what I suspect to be a much larger group of toxaemias resulting in circulatory failure, in which the most serious factor is this loss of capillary tone. A large number of bacterial products exhibit this type of action, including both soluble products and substances liberated only by lysis of the bacteria. In the local, protective, inflammatory reaction to them we probably have a complex of direct dilator action on the capillary walls and reflex dilatation of arterioles through the stimulation of sensory nerve fibres. When poisons like these are formed in such quantities as to be distributed, in effective amounts, through the circulation, so that all or a large proportion of the capillaries simultaneously lose their tonus, there arises the peril of circulatory collapse due to peripheral stagnation of the blood. The most obvious and striking example of such an effect, perhaps, is the cyanotic collapse seen in cholera, where the oligaemia is accentuated by the enormous loss of fluid through the permeable intestinal capillaries. Dr. Esther Harding,[25] who carried out a series of experimental observations in my department, has found evidence of this type of circulatory failure in animals dying rapidly after large doses of diphtheria toxin, and in the early collapse occurring in severe cases of human diphtheria, without respiratory obstruction, and before the toxin had affected the heart muscle. Many years ago Romberg and Pässler[26] put forward the view that the so-called heart failure in septicaemia was not due to defect of the muscular activity of the heart, but to a vasomotor collapse. With the knowledge then available they attributed the result to failure of the vasomotor centre, but, in the light of present knowledge, a direct impairment of capillary tonus suggests itself as a much more probable and sufficient cause of such a condition. Recently Olivecrova[27] has examined this possibility in experimental peritonitis and given definite evidence in favour of a loss of capillary tone as the principal cause of the circulatory defect and of the fatal issue. I believe that the same possibility is well worthy of consideration in the case of all types of acute septicaemia. The condition may be obscured by concomitant poisoning of the heart muscle, but its recognition must have an important influence on scientific treatment. It is obviously useless to stimulate a poisoned and labouring heart if the main cause of its inefficiency is not the weakness of its muscular action, but the failing return of blood by the systemic veins.

One could continue to multiply examples of conditions in which this dangerous complex may arise. Apart from agents directly toxic in themselves, the position is complicated by the fact that, when blood is subjected to injurious influences, as by contact with otherwise inert substances acting as " foreign " surfaces, so that processes are initiated in it which, outside the body, would lead to clotting, it acquires a toxicity of this type. (*Cf.* Novy and De Kruif,[29] Dale and Kellaway.[23])

When you also remember that, apart from dilatation and increase of permeability of the capillaries due to loss of their contractile tone, effects at least superficially similar can probably be produced by substances which directly poison the endothelial wall and disorganize its delicate structure, it will be obvious that there may be difficulty in deciding as to the precise nature of a particular effect. Salvarsan, for example, as an arsenical derivative, may, and in some cases probably does, act as a direct endothelial poison. It is also a colloidal substance which, on injection, may be so precipitated in the blood as to initiate precoagulation changes. Both types of effect probably figure among the toxic effects which salvarsan occasionally produces.

Unfortunately methods of dealing effectively with dilated and permeable capillaries are not easy to find. The action of adrenaline, above mentioned, suggests itself; and there are cases in which it seems to have value. As a prophylactic or a remedy for the immediate, so-called vasomotor, reaction sometimes produced by salvarsan, for example, there seems to be no room for doubt that adrenaline is effective; and its effectiveness supports the suggestion, made on other grounds, that this type of reaction is due to capillary dilatation caused by precoagulation changes in the blood, and not to poisoning of the endothelium. Calcium has had a reputation for reducing the tendency to excessive permeability of the capillary walls. Krogh's recent evidence as to the tonic action of pituitary extract should find some therapeutic application. Experience during the war, however, presented as practically insoluble the problem of restoring the volume of blood in effective currency when once the capillaries had become thoroughly lax and permeable. Saline solutions, gum saline, or even blood itself, often produced but a temporary recovery of volume, the fluid escaping from the vessels, or becoming removed from circulation, almost as fast as it was infused into the veins. In some of Dr. Harding's experiments, in the investigation already mentioned, there could be seen what appeared to be a secondary, and rapidly fatal, accentuation of the toxic collapse, when blood which had lain stagnant in toxaemically dilated capillaries was washed back into circulation by an infusion. The therapeutic problem is a peculiarly difficult and complex one; but the first step towards its rational solution is a clear recognition of the nature of the condition calling for treatment.

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ENDOCRINES, VITAMINS, AND SUBTLETIES.

ABSTRACT OF AN ADDRESS DELIVERED TO THE SUNDERLAND DIVISION OF THE BRITISH MEDICAL ASSOCIATION

BY

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IN no branch of knowledge is it more difficult, certainly in none is it more necessary, than in ours, to get the spirit of the moment into its right perspective. Between the excited welcome accorded to new therapeutic methods on the one hand, and the obstinate impermeability to fresh ideas on the other, the plain man is apt to be bewildered, and it is well that he should occasionally pause to consider on what sort of ground he is standing and whither the pathway seems to be leading. It is with the hope of affording some help in this direction that I have prepared this paper, and such must be my excuse for the very comprehensive title.

I.

In the matter of the first subject, endocrinology, I would like to emphasize at the outset the important fact of the interdependence of the glands which constitute the system. I am fond of comparing them to the eight rowers in an outrigged boat, with the central nervous system as cox. These rowers are all pulling in the same direction; they are, nevertheless, some of them, pulling one against the other. Now, in our clinical dealings with these glands we are much too apt to regard each as an independent entity, instead, as we ought, of considering each as a member of a hierarchy, the whole of which is liable to be deranged when one of the members is seriously affected. As bearing on this generalization, let me indulge in another. It is the evil fashion to speak of " hyper " or " hypo " functioning of certain glands. Such a nomenclature expresses but a part of the truth, and that part a very misleading one. It is no doubt true that in the various degrees of myxoedema, for example, the thyroid is primarily at fault, but the outstanding symptom which brings the patient to the doctor may point insistently to failure of some other gland.

Quite recently a man of 45 came to me complaining of sexual impotence gradually acquired. He turned out to be a case of mild, atypical myxoedema, appropriate treatment for which rapidly restored his sexual capacity. It also restored his domestic peace, which had been seriously impaired by unfounded charges of infidelity.

Now, misleading as it generally is to speak of underaction of a particular gland, it is much more misleading—it is, indeed, generally a misstatement—to speak of overaction of any single gland.

Let us take the thyroid again. It has become a habit with many, who ought by now to know better, to speak of Graves's disease as synonymous with hyperthyroidism. Now, although the thyroid gland may be overactive in Graves's disease, it is so in common with other glands, notably the suprarenal, the pancreas, and the thymus, and the salient symptoms of the disease are due much more to the latter than they are to the thyroid, which, as you know, is frequently not even enlarged. Whatever else it is, or is not, Graves's disease is not a pure hyperthyroidism.

In the matter of underaction it is generally evident that one gland is primarily at fault; in the matter of overaction that is seldom the case, except where there is a definite and local organic irritant, such, for example, as suprarenal and pituitary tumours. The cause of overaction is generally a toxaemia which irritates not one gland only, but many, though in different degrees. In looking for a cause of underaction it is always well to remember the possibility of long-continued toxaemic overaction, leading to exhaustion of the gland or glands in question. This is a frequent cause of thyroid insufficiency, because the thyroid above all others is concerned in combating endogenous toxins. That it is a cause of pituitary insufficiency I hope to show presently. Then again we must always bear in mind that when we have given, say, thyroid extract with success, our good results do not necessarily mean that the patient was lacking in thyroid essence. The good results may mean, and in many cases