effects of central stimulation of the vagus on respiratory activity; and he suggests liberation of this substance in the centres by sensory impulses in the vagus.

CONCLUSION

I can best summarize the account which I have given, of research on the chemical mechanisms for the transmission of nervous stimuli and of its most recent extensions, by putting before you a rough diagram of peripheral synapses and endings of efferent nerves. In each case, where the evidence seems fairly clear, I have indicated a cholinergic mechanism of transmission by the letter C, an adrenergic mechanism by the letter A. (Fig. 5.)

You will see at once that the C's greatly preponderate, just as the later section of my lecture has dealt exclusively with acetylcholine. We get an impression of the cholinergic mechanism as having the more general application in the functions of the nervous system, and probably an earlier origin in evolution, and of the adrenergic mechanism as a more specialized and probably a more recent development. I believe that such a conception would have been congenial to the thought of one of the greatest of British physiologists, and one of the founders of the Cambridge school, the late W. H. Gaskell. You will see that in some places the diagram has notes of interrogation, representing points at which further evidence is required to justify a definite statement. There might have been many more, for the whole field of inquiry is full of unknown details, asking for investigation, and attractive to scientific curiosity. I have tried to show you the main outlines of the map, as they are now beginning to emerge.

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DISEASE AT ITS ONSET

WITH SPECIAL REFERENCE TO OCULAR
MANIFESTATIONS

BY

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Biophysics and biochemistry have taught us that the living body is an admirably equipped laboratory in which Nature is continually performing experiments.¹ These experiments resemble those conducted in every physiological laboratory in so far that some succeed while others fail. When Nature's experiments are successful we are not conscious that anything is happening: everything goes like clockwork, and we feel in good health. When, on the other hand, the experiments fail we become aware of unpleasant sensations, which we have learned to recognize as symptoms of disease. Health, therefore, must be regarded as a dynamic rather than as a passive state. We keep healthy as a result of a perpetual struggle to maintain physiological equilibrium in the reactions constantly taking place between the cells of the body and their nutrient capillaries. Physico-chemical changes, therefore, which originate in the capillary system are, in all probability, the first departure from health, and the cause of the earliest symptoms of disease.

The part played by the capillaries is quite distinct from that played by the heart and other blood vessels. All metabolic changes take place through their walls; consequently they form the most active, purposive, and dynamic part of the vascular system. Their contractility is controlled not only by vasomotor nerves but also by chemical stimuli, the former acting as a coarse and the latter as a fine adjustment. Krogh² has demonstrated that the capillaries are not simply tubes through which blood flows. They do not respond passively to the amplitude of the pulse wave in the arteries. They are really a constituent part of the tissues in which they lie, and their blood circulation is regulated and controlled by the requirements of the individual cells of the structures they supply. All the important business of life is transacted through the walls of the capillaries.

Bryson³ has suggested that in every part of the body the functioning unit and its associated capillaries constitute an organ in miniature. That is a simple, but it is also a most useful, conception. It implies that the health of every organ depends upon the quality and the quantity of the blood circulating in its capillary system. It is to be remembered, however, that in normal circumstances all the capillaries of an organ are not in action at the same time. They work in shifts: while some are open and active, others are closed down and idle. Herring⁴ calls this "the law of fluctuation," and points out that in all living structures the alternation of periods of activity with periods of rest is essential to health.

CIRCULATION IN THE EYE

In the eye, with the help of the ophthalmoscope, a complete circulation—arteries, veins, and capillaries—is exposed to view, and can be studied as an integrated whole, with a completeness quite impossible in any other part of the living body. Thanks to the transparency of the normal retina we can see the blood in the central artery and can follow it into the finest arterioles and, if we make use of Friedenwald's⁵ yellow-green light, we can trace the capillary network in wonderful detail.

From the clinical standpoint the retina, although it is such a very complicated structure, can be conveniently

divided into (1) the conducting portion, and (2) the very highly specialized functioning unit. The former, comprising the ganglion cells and the nerve fibres, receives its capillary supply through the superficial and deep plexuses of the central artery, while the latter, although itself avascular, receives abundant nourishment by transfusion from the choriocapillaris. Both the central artery and the uveal blood vessels, therefore, contribute to supply the retina; and although the capillary supply of the conducting system and that of the functioning unit is distinct anatomically, yet it is strictly comparable physiologically.

In a general sense it may be said that the walls of the capillaries, although freely permeable to crystalloids, water, and gases, are relatively impermeable to colloids. The degree of permeability to colloids varies in different parts of the body, depending upon the special requirements of each particular organ. In every instance there is a biological adaptation of structure to function, and Duke-Elder⁶ has pointed out that in the eye perfect transparency is secured by almost complete impermeability of the intraocular capillaries to colloidal substances. By that means every structure peculiar to the organ of vision is kept optically homogeneous.

Visual function is wholly dependent upon the rate of the circulation of the blood in the capillaries of the retina and in the choriocapillaris; but the retinal circulation must always be considered in its relation to the general circulation. The same principles are observed in the circulation of the blood in the eye as in any other organ of the body; but the intraocular circulation is peculiar in so far as it is modified by the intraocular pressure. The capillary pressure in the eye is higher proportionately than in any other organ of the body in a state of rest, but it is neither a constant nor a measurable quantity. It varies not only in different individuals, but also in the same individual from time to time. It is, however, essential for the health of the eye that an accurate balance be maintained between the capillary pressure and the pressure of the intraocular fluids, because, as Duke-Elder has demonstrated, the intraocular fluids are a dialysate from the capillaries.

TRANSPARENCY OF THE RETINA: AN INDICATION OF HEALTH

The capillaries are very susceptible to every morbid influence, consequently they are peculiarly sensitive to the quality of the blood. Every form of toxæmia causes rapid dilatation, with increased permeability of their walls. It is easy to understand, therefore, how the transparency of the retina becomes impaired by congestion of its capillaries, together with its infiltration with colloidal substances. This abnormal condition of the retina is recognized clinically by a want of translucency in the ophthalmoscopic picture. Here, then, we have a sign of abnormality which is as nearly as possible on the borderland between health and disease. Mackenzie always insisted that the first symptom of disease is a complaint of an unusual sensation, and an additional interest is given to the study of such sensations whenever we can discover an objective cause capable of explaining their occurrence.

We have seen from what has been said (1) that the transparency of the normal retina is due to the impermeability of the walls of the capillaries to the passage of colloidal substances, and (2) that this normal transparency is interfered with by any form of toxæmia, which causes rapid dilatation of the capillaries with increased permeability of their walls. Translucency is the most delicate quality of the ophthalmoscopic picture, and it is reason-

able to assume that any deterioration or loss of this pristine brilliancy is one of the first signs of a departure from health.

In a group of cases I have in mind the only outstanding ocular objective feature is a deepening of the colour and a lack of the normal translucency of the ophthalmoscopic picture. These subtle changes in colour and translucency are somewhat difficult to describe, but they are easily recognized after attention has been directed to them. It is only through physiology that we can approach pathology successfully from the clinician's standpoint; consequently, in dealing with a structure so delicate and sensitive as the retina, its special physiological attributes must be kept in mind. When examining a patient, therefore, in addition to testing his form sense, attention must be given to his appreciation of light and colour.

As a rule, the patients under consideration have little difficulty in reading the test types, but they often say that the letters in the middle of a line are recognized with more conscious effort than those at either end. The symptoms are not relieved by correcting any error of refraction that may be present, for the patients still complain that the eyes feel hot and uncomfortable, and are easily tired. If they persist in reading after the onset of these symptoms they are prone to suffer from a dull neuralgic pain, which radiates from the eye to the forehead and the temple. The print becomes unsteady, and a flicker makes it difficult to read, and more especially to pass easily from one line to the next. Sometimes these symptoms are accompanied by black spots in front of the eyes, by minute flashing lights scintillating in the field of vision, and by occasional sudden attacks of obscuration of sight. The light sense is nearly always disturbed. The patients have difficulty in adapting themselves to changes in the surrounding illumination. They find that their eyes are either easily dazzled by a light, which formerly they could look at without discomfort, or that they now require a much brighter light to enable them to see to work with comfort. These differences in light perception may not be easily measured and charted, but an intelligent and observant patient, assisted by a few well-directed questions, can always give a convincing description of the symptoms.

Slight disorders of the colour sense are even more difficult to detect during an ordinary clinical examination, but careful attention to the patient's description of the difficulties he is having with his sight will usually give a clue to the direction further examination should follow. For example, if a woman is in the habit of working with colours, she is likely to complain of the difficulty she now has in differentiating between varying shades of the same colour. In the group of cases we are specially considering blue is the colour which causes most difficulty. The association of a disordered colour sense for blue with a diminished light minimum at once directs attention to the functioning unit of the retina and to its capillary supply as the sites of origin of the symptoms of which the patient is complaining.

In man the blood supply both to the eye and to the brain comes from the internal carotid artery, and the retinal circulation holds many analogies with the cerebral. As similar tissues behave alike in whatever part of the body they are found, it is reasonable to assume that what can be seen in the eye occurs also, though hidden from view, in the brain. It is not surprising, therefore, that many of the patients complain of nervous symptoms, which are strictly on a par with their visual troubles. Among these may be mentioned want of the power of concentration, and unusual difficulty in remembering what they have just been reading. Many complain that in conversation they are apt to lose the thread of an argu-

ment, and come to a dead stop by forgetting what they meant to say. They are nearly always restless, irritable, impatient, forgetful, depressed, and difficult to live with. The more thoughtful among them are very apt to exaggerate the importance of these symptoms, and to become neurasthenic and hypochondriacal. It is a great help to them when they can be made to understand that both their nervous symptoms and their visual troubles are due to a similar cause, and that both of them are curable.

CAPILLARY CONGESTION IN RETINA AND DISORDERED METABOLISM

Ever since the introduction of the ophthalmoscope there has been recognized to be a close clinical relation between the eye and the kidney. In the one organ as in the other congestion of the capillaries causes impairment of function—diminished light sense in the eye, diminished output of urine in the kidney. One of the characteristic clinical features of the group of cases we are considering is interference with the full activity of the kidney. There is usually not only a diminution in the quantity of urine excreted in twenty-four hours, but also a disturbance in the normal ratio between output and specific gravity. Although the quantity of urine passed in twenty-four hours is considerably reduced, the specific gravity is not increased and is often below normal. A further evidence of an error of metabolism is usually found when a specimen has stood in a urine glass overnight, inasmuch as microscopical examination of the sediment reveals urates, or crystals of uric acid or of oxalate of lime: most characteristic of all is when the field of the microscope shows a very large number of minute oxalate of lime crystals. The frequent clinical association of a defective colour sense for blue with persistent oxaluria strongly suggests that both symptoms are the result of disordered metabolism. In the absence of any complications there is no interference with the normal excretion of urea, and neither sugar nor albumin is likely to be present.

BACTERIAL INFECTION AND THE OPHTHALMOSCOPIC PICTURE

Duke-Elder, in writing of the relation of toxæmia to high blood pressure, says: "A raised blood pressure is an expression of the effect of toxic influences acting over the whole extent of the arterio-capillary bed." Pines⁸ is right, therefore, when he insists on the use of the sphygmomanometer in association with the ophthalmoscope. In the group of cases we are now considering blood pressure is almost invariably above normal, but hæmorrhage from the retinal blood vessels is exceedingly rare. It is now generally admitted that high blood pressure *per se* will not cause rupture, unless there is fragility of the walls of the vessels as a result of previous disease. Persistent hypertension is, however, in all probability a decisive factor in differential diagnosis in its relation to aetiology, prognosis, and treatment. For example, it is well known that capillary congestion of the retina can arise as a result of bacterial infection, and that it is indistinguishable by the use of the ophthalmoscope alone from a similar condition due to metabolic disorder. For obvious reasons it is very important to be able to distinguish the one condition from the other; but any evidence in my possession only warrants me in offering the suggestion that in capillary congestion of the retina search should always be made for a hidden focus of microbic infection in every case in which blood pressure shows little deviation from normal, and when an examination of the urine reveals no evidence of metabolic disturbance. The following case is a good example.

In September, 1928, a man aged 53 began to complain of discomfort in his eyes after reading. He was almost emmetropic, and the spectacles he was using for close work were quite suitable. Nothing was revealed in the examination of the eyes except marked loss of translucency in the ophthalmoscopic picture. It was thought that an error of metabolism was the cause of the symptoms, but the patient did not respond to eliminant treatment. His family doctor reported that he had always found blood pressure and urine to be normal, and that repeated examination had failed to reveal any definite disease. Although the patient never felt well, he was able to attend to his business. No one thought there was anything seriously the matter with him until May 19th, 1930, when he was seized with acute appendicitis. The condition revealed at the operation showed that the local disease must have been present for a very considerable time. Peritonitis and paralysis of the bowel followed, and the patient died within three days after the acute appendicitis had been diagnosed.

Reconsidering this case in the light of the fatal termination I feel very strongly that more attention should have been paid to the fact that urine and blood pressure were persistently normal. Had the significance of that fact been fully appreciated, it is very probable that less attention would have been given to errors of metabolism, and a more diligent search would have been made for a hidden focus of bacterial infection. In medicine intelligent search very often leads to discovery.

In none of these cases is a cure possible until the error of metabolism has been corrected, or until the source of local sepsis has been removed. So long as the exciting cause continues to operate no form of treatment will be effective. When, however, the cause has been removed capillary congestion disappears from the retina, the fundus oculi regains its normal translucency, and the patient is relieved of his general, as well as of his ocular symptoms.

Garrod⁹ has pointed out that injurious influences proceeding from the patient's environment may so disorder normal metabolism as to cause trouble. He also says that the external factor does not affect all alike, but that it discriminates between the different members of the same family. In his clinical investigations into the part played by the home surroundings upon the health of the children, Rowand¹⁰ has found evidence in support of Garrod's research work, and has drawn special attention to a group from 2 to 6 years, all the members of which suffered from slight albuminuria. In almost every one of these children the fundus oculi, owing to loss of translucency, resembled red velvet. The optic disk was well defined in outline, but was of a rose-pink colour as a result of capillary congestion, which was observed to vary in degree from time to time in the same patient. The retinal veins were prominent and somewhat rough in outline, and the light reflex from the walls of the arteries was unusually brilliant. Both eyes were affected equally, consequently the presumption is that capillary congestion was general rather than local, and that the albuminuria was due to dilatation of the capillaries of the kidney, with increased permeability of their walls to colloidal substances, rather than to any definite renal disease. The condition of the retina, therefore, was not due to the state of the kidney, but both in the retina and in the kidney the congested capillaries were the result of general toxæmia, due in all probability to disordered metabolism, and the onset of albuminuria may be regarded as a measure of its severity. In all the children included in this group the glow of health soon returned to the face after careful dieting accompanied, when necessary, with an ample supply of vitamins A and D, with suitable tonics containing iron, and by the free use of eliminants. As soon as the toxins were removed from the blood the muddy complexion cleared, the fundus oculi recovered its normal brilliancy, and the albumin disappeared from the urine. Rowand

has been able to follow up a considerable number of these children, and he reports that all those he has been able to examine have remained in good health.

In conclusion, let me repeat that in all probability the earliest sign of disease is distension and increased permeability of the walls of the capillaries; that this may be recognized clinically by lack of translucency of the ophthalmoscopic picture; that what can be seen in the eye is an index of what is occurring in other parts of the body where the phenomena are hidden from view; and that by means of the ophthalmoscope it is sometimes possible to recognize disease in its earliest stages—that is, at a time when in all likelihood it is easily curable.

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AVERTIN NARCOSIS IN OPERATIONS FOR TOXIC GOITRE

BY

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The operation of partial, or "subtotal," thyroidectomy for toxic goitre is potentially a highly dangerous procedure, and the reasons for this element of danger are plain to see. Many of the patients submitted to operation are acutely ill, and removal of part of the thyroid gland is sometimes undertaken as an emergency or life-saving measure. Even when the patient is not so ill as this, she is often existing on the edge of a precipice, and any disturbance, even of moderate severity, may be enough to push her over, either by the production of "thyroid crisis" or by putting just too much strain on an already overburdened and damaged heart. The degree of strain produced by the operation is bound to be considerable if it is completed in one stage, since it entails a wide dissection of the neck and "dislocation" of the thyroid gland, a sinister-sounding term, which seems to imply some violence. But although the potential danger of the operation is great, the actual danger seems to have been reduced in some hands to an almost negligible amount if figures of operative mortality are to be taken as a reliable indication. It is the purpose of this article to examine briefly the factors responsible for this remarkable change brought about in what was formerly regarded as an exceedingly dangerous procedure, and to support my own belief that the choice of anaesthetic has great importance. It will be illustrated from a consecutive series of 243 operations performed during the last four years on 220 patients.

FACTORS DIMINISHING OPERATIVE RISK

It would be platitudinous at the present time to enlarge upon the improvement wrought in recent years by the use of iodine in preoperative medication. It is well known that a large part of the reduction of the operative mortality has been due to this, and that iodine has its chief value in the preoperative stage, the initial improvement not being maintained if the use of iodine be prolonged. It would be difficult, also, to exaggerate the importance of improvement in the technical skill and in

the judgement of the operator. Thyroidectomy is technically one of the most exacting of operations, and one in which any failure in detail may cost the patient's life. Gentleness and precision, control of haemorrhage, and avoidance of unnecessary delay are all of importance to the patient's safety. It is notorious that the larger the number of thyroid operations in any one clinic the safer are the patients, since frequent practice makes for the establishment of an efficient routine on the part of the team and for the necessary familiarity with operative details on the part of the surgeon. This applies, in some degree, to the performance of all operations, but it is of superlative importance in the performance of partial thyroidectomy for toxic goitre.

Of great importance also is the judgement of the collaborating physician and surgeon as to when the right moment for operation has arrived, and which patients are actually so ill that any operation means certain death—nowadays a vanishing proportion of the whole. Important also is the judgement of the surgeon as to which patients should be treated by operation in two or more stages. Here, again, experience is an important factor, for which there can be no substitute.

It is clearly difficult to disentangle the relative importance of these different factors in the clinical and operative complex. One more remains, however, which I wish to consider in detail, and that is the choice of anaesthetic. A great variety of anaesthetic methods have been used, from the "thyroid-stealing" method of Crile under hypnotic suggestion to the somewhat complicated method presently to be described. Ten years ago ordinary ether anaesthesia was regarded as satisfactory for operations on toxic goitre, though it was found that the inevitable disturbance to the patient from post-anaesthetic coughing and vomiting was distressing, if not directly prejudicial to her prospects; and it may be taken as a rule in dealing with toxic goitre that all disturbance reacts unfavourably on the patient, and is therefore indirectly prejudicial. An effort was accordingly made to eliminate ether anaesthesia, and a phase followed in some clinics of using local analgesia aided only by a preliminary injection of morphine and hyoscine. It was thought necessary to reinforce the effect of the narcotics by elaborate precautions directed towards the removal of external stimuli, such as noise and light—and very difficult it was to do this effectively in a busy hospital ward. The efficacy of morphine and hyoscine, too, is very variable; sometimes these drugs fail to produce adequate narcosis, and occasionally the patient becomes actually excited, the drugs having only produced loss of control without depressing the main centres of consciousness. The use of local analgesia was found to give improved results compared with ether anaesthesia, and its use was continued for some years. The injection technique which I employed was that learnt from Sir Thomas Dunhill, and consisted of local infiltration of the field of operation with 0.5 per cent. novocain solution in normal saline with 1 in 500,000 adrenaline hypochloride. Usually only about 150 c.cm. were used, so that the total amount of novocain injected amounted to 0.75 gram. A field-block of the cervical nerves was added for a short series of patients, but the analgesia appeared to be equally good without it, and it was soon abandoned as superfluous. Considering that the toxic goitre patient would seem, by the nature of her disease, to be pre-eminently unsuited for any operation under local analgesia, the results were remarkably good. Many patients, however, left the operating table with high pulse rates, and the operation entailed a great strain on both patient and surgeon. Any thyroid operation is already sufficiently exacting for the surgeon without the necessity for watching closely the patient's mental reaction throughout the procedure, and for the