THE THEORY OF DISTURBED REFLEXES IN THE PRODUCTION OF SYMPTOMS OF DISEASE.

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WHEN we started the Institute for Clinical Research in St. Andrews we recognized that if success were to attend our efforts we must have a clear comprehension of our object, and a definite idea how that object should be attained. We define our object as the

Prevention of the Diseases that are Common amongst the People.

To understand how disease should be prevented it was necessary to know what are the diseases which are common among the people. On inquiry it was found that, except in a small percentage of cases, this knowledge was nowhere to be obtained.

Here, then, the first step to be taken was to know what the diseases are which we wished to prevent.

The next question was how to proceed to get this knowledge. The great majority of the sick suffered from complaints, and showed signs of ill health, but the disease was unknown. In a few cases the disease could be recognized, because medical knowledge had advanced so far as to

FIG. 1.

FIG. 2.

FIG. 1 represents a disease completely diagnosed, where A is the agent acting injuriously on the tissues and producing reactions or symptoms, which are represented by the circles at the periphery—as typhoid fever, or conjunctivitis due to a foreign body in the eye.

FIG. 2 represents a disease not fully diagnosed, where, while the symptoms are recognized, the injurious agent A has not been recognized, though its nature can be inferred, as in measles.

detect certain signs and symptoms which experience had shown to be due to definite causes. Seeing that the diseases we wished to prevent were for the most part unrecognizable, it would be futile to attempt to prevent them, so that it was manifest an undertaking must start with preliminary inquiry into the nature of the diseases.

Definition of Disease.

In order that our inquiry should be pursued in a logical and systematic manner, we sought to get a clear grasp of what we meant by disease. The definition of an abstract term such as disease would probably be given in different terms, according to the standpoint of the definer. After much consideration and discussion we analysed the phenomena in over 1,000 cases and worked out the following scheme, which revealed the present state of knowledge on the subject, and at the same time afforded a guide for our inquiry.

If we take a simple disease like conjunctivitis, where the cause can be ascertained, we find that the diseased state consists of a foreign body which injuriously affects the tissues, causing certain reactions or symptoms, as pain, lachrymation, redness, blepharospasm. Such a condition may be considered a complete diagnosis and can be represented by the diagram (Fig. 1), where A is the injurious agent and the surrounding circles are the reactions or symptoms.

We found in our inquiry that the complete diagnosis is possible only in a relatively few cases—where the injurious agent has been recognized as due to a foreign body or to a microbe, as in typhoid fever, pneumonia, diphtheria.

In some cases the reactions occur in such definite groups that they can be differentiated, and it can be assumed with

reasonable certainty that the disease is caused also by a microbe which has not yet been identified, as measles, small-pox, rabies, etc. These are represented in Fig. 2, in which the injurious agent is represented by a dotted ring.

There were other cases in which the group of symptoms were also capable of differentiation, but in which the nature of the injurious agent was unknown, or a matter of speculation, as in migraine, epilepsy, diabetes, etc. This is represented in Fig. 3, where a point of interrogation represents the injurious agent.

The bulk of patients suffer from diseases in which, so far, it has been found impossible either to recognize the agent or to arrange the symptoms into groups that permit of their clear differentiation from others that they resemble. The nomenclature of such conditions is usually based on the presence of a dominant symptom or of a number of symptoms associated with some organ, such as anaemia, neuralgia, neurasthenia, debility, disordered action of the heart, indigestion. The knowledge of the disease in those cases may be represented diagrammatically (Fig. 4) as a confused heap of symptoms in which it is not possible to obtain a suggestion as to their relation to a common cause.

To the latter group belong probably all chronic diseases, even though the ill health is definitely due to damaged organs which can be recognized by physical signs—as arterio-sclerosis; chronic heart disease, chronic kidney disease, and even consumption and cancer. The reason for including these is that they are probably secondary diseases, the original cause not being capable of recognition.

FIG. 3.

FIG. 3 represents a disease with a well-defined group of symptoms, but where the nature of the agent is not recognized—as migraine, convulsions.

FIG. 4 represents the vast majority of diseases, where a number of unco-ordinated symptoms are present with no recognizable cause.

The Relation of Symptoms to Disease.

This method of looking upon disease reveals not only the state of our knowledge of diagnosis, but gives a guide in research. It shows that disease is only revealed by the symptoms it produces, and that even in the few diseases where the nature of the agent is understood it can only be identified in the human body by its symptoms.

A consideration of the history of the recognizable diseases shows that the first step in research is to recognize the symptoms. The next step is to group them together, so that one group can be clearly differentiated from those that resemble it. By this method the clinical observer differentiates the disease, it may be, without recognizing the cause. Having reached this stage, he can present a clear-cut problem to, for example, the bacteriologist, who may complete the diagnosis by discovering the injurious agent. The symptoms of the majority of diseases have not yet been clearly differentiated, and there is little prospect of progress being made until this has been done.

This brief review of our present knowledge of disease shows that the chief aim of medical science—the prevention of disease—can never be achieved till we are able to recognize the diseases. Where success has been achieved and disease prevented, it was due in the first instance to the recognition of the symptoms. The clinical observer who obtained this knowledge succeeded because the symptoms were striking in character and easily recognized—as by the presence of a rash or eruption or other sign. It is reasonable to conclude that if we had a better understanding of the mechanism by which less obtrusive symptoms are produced we would get nearer to the detection of the agent producing them. When a person falls ill, the fact is made evident only by the symptoms,

so that the only way in which the disease can be detected is by the recognition of symptoms.

The study of symptoms has been carried on since the dawn of medicine, and from the early days additions have continually been made to their numbers, until to-day the number is so great that no one individual can recognize more than a fraction of them, and methods are ever being invented for the discovery of new symptoms. If our enterprise were but to seek for new symptoms, it would be in vain, for the addition of new symptoms would but add to the confusion of a subject already far too chaotic.

The Evolution of a Science.

All subjects that have attained the position of a science have passed through stages of which the collection of facts was the first. So long as these facts were unco-ordinated their accumulation tended to confusion, and there came to be recognized the need for an ordered arrangement based upon a law of nature.

The history of chemistry is an illustration. The appreciation of Dalton's atomic theory gradually enabled the mass of detail to be classified according to a law of nature. Not only this, but it opened up possibilities and gave guidance to further research, and so enabled the science of chemistry to make remarkable progress.

Symptomatology is in the same confused state as chemistry was before the recognition of the atomic theory; and it calls as urgently for a classification based upon some law of nature that reveals the mechanism of the production of symptoms.

The Classification of Symptoms.

Hitherto there has been no clear conception of the nature of symptoms, and the classifications that have been made have hampered progress and misdirected the course of research. Thus symptoms are usually described from the standpoint of the organ giving rise to them, and specialists devote themselves to the study of the symptoms of individual organs or systems. When a person falls ill nearly every organ of the body may be disturbed, and each specialist has no difficulty in detecting symptoms belonging to his particular branch. In consequence of this we find that confusion of diagnoses which results when a patient consults a number of specialists.

Another source of error arises from the fact that when one organ is diseased its impaired function is revealed not by the organ at fault but by its effects upon the other organs of the body.

It is now many years since I saw the need for a knowledge of the mechanism by which symptoms were produced. I have steadily pursued the subject, and several years ago I dimly recognized that there was some definite law governing this mechanism. I attempted a classification and I was able to group a number of symptoms according to their mechanism, such as a *structural group*, recognized by a physical sign, a *functional group* due to interference with the functions of an organ, and a *reflex group*, due to a peculiar stimulus setting up definite reactions. But there remained a large group, which I recognized somehow or other belonged to the last group, but their mechanism was not clear.

This was the state of knowledge when we began our inquiry. We recognized that it was useless to attempt a research into any particular disease until we had acquired a knowledge of the laws that underlay the production of symptoms, and to that end our chief endeavour was given. We met twice a week; at one meeting we discussed the nature of one particular symptom, and sought for an explanation in the daily routine of examining patients. At the other weekly meeting we discussed in detail the symptoms of individual patients.

The Law Governing the Production of Symptoms.

As time went on we got a better insight into one symptom after another, and we felt we were getting nearer the law of which we were in search, and gradually its recognition dawned upon us. At first we scarcely recognized it when it was put before us because of its extreme simplicity, for we found the law to be that the vast majority of the symptoms of disease are disturbances of normal reflexes.

I know quite well that no one who reads this will accept at present the view that this theory will do for clinical medicine what the atomic theory did for chemistry, but

I know equally well that when the method of applying it is understood its significance will be appreciated, and it will have a very far-reaching influence on the progress of medicine.

How the Theory was Discovered.

The discovery of this law is the outcome of a long and painstaking search with a definite object in view.

Shortly after entering general practice, over forty years ago, I was impressed with my ignorance of the diseases from which my patients suffered. In the majority the evidence of ill health was confined to the patient's sensations, which I could not interpret. Realizing this, I resolved to see if I could not improve my knowledge, and began to pay more attention to such signs as I could detect, and the principal sensations of which the patient complained. I had not gone far when I realized that these signs and symptoms were so numerous that I could only hope to investigate a limited number. But even when I had selected a few for particular observation I did not know what method to pursue. On reflection I decided upon concentrating my attention on two aspects: (1) *The mechanism by which a symptom was produced*; and (2) *the bearing the cause of the symptom had on the patient's future*.

Of these aspects the latter is, of course, of the utmost practical value to a doctor, and although under the term "prognosis" it has received perfunctory attention, I found that neither the manner in which the subject should be studied nor the individual whose opportunities fitted him for the task had been realized; but with that I do not deal here.

The study of the mechanism by which symptoms were produced led me into several different fields. There was, for instance, the pulsatile movements in the jugular veins and the liver, the movements of the heart in health and disease, and the mechanism of irregular heart action to be considered. I devoted several years to finding out the mechanism of these signs, and the results were an ample reward for the labour and time spent, and helped to make that revolution which has made of human cardiology a totally different subject from what it was when these researches were begun.

The study of the sensations of the patient was much more difficult. I began with the most clamant of all—pain. Hilton's book on *Rest and Pain* was the furthest step that had been taken, but valuable as it was it did not go to the root of the matter. For some years I made little progress—collecting isolated facts but unable to see any reasonable explanation for their causation. In 1888 Dr. James Ross published his article on referred pain, and I at once recognized that he had provided a hypothesis which not only helped to explain much that was obscure but gave a guide for carrying the subject further. In this paper he stated that pain, when arising in an organ, was felt in two ways—first by a pain in the organ itself, and second by a pain felt in the external body wall at a place remote from the organ. The first of these he called *splanchnic* and the second he called *somatic*.

I had already gone so far in my inquiry that I recognized the significance of his somatic or referred pain, but I was doubtful of his splanchnic, considering that it also was really referred. He used as an illustration the pain of gastric ulcer when limited to the epigastrium as being a splanchnic pain, but when I examined a patient with a gastric ulcer I found that on a deep inspiration, while the stomach descended, the pain remained fixed.

Though suggestive this was far from convincing, and I sought diligently for other signs, and in 1891 I found a sign which threw much light upon the matter. This was finding a large area of hyperalgesia of the skin over the liver in a patient after an attack of gall-stone colic. This led me to seek for cutaneous hyperalgesia in other cases, and I soon found that it was of frequent occurrence, particularly in affections of abdominal organs. It required, however, a long training to acquire the skill to detect it in many cases.

Shortly after this another sign was recognized—namely, the contraction of the muscles of the abdominal wall, due to disease of an abdominal organ. It had been recognized before, and spoken of as "protective rigidity," but its real nature and significance had never been understood. I watched how portions of the muscle wall of the abdomen would become hard and resistant during the course of a

disease, such as gastric ulcer, appendicitis, gall-stone disease, cholecystitis. I observed it disappear with improvement, until it was not evident, and I could recall it by gently rubbing over it. I noted in patients the sudden contraction of muscle that ensued under certain conditions. Thus, some of my patients described that on the onset of an attack of renal colic the testicle would be dragged up (by contraction of the cremaster muscle).

I described these symptoms of pain and hyperalgesia in consequence of disease of the viscera as a *viscero-sensory reflex*, and the contraction of the muscle as a *viscero-motor reflex*.

There was a large group of symptoms which occurred when patients fell ill from some obscure cause (as infection), such as the feeling of exhaustion, loss of appetite, breathlessness on exertion, palpitation, vomiting, mental depression. These had been vaguely described as toxic symptoms, and I had indeed described them as due to a hypersensitiveness of certain parts of the central nervous system, but I did not clearly realize the mechanism which produced them; this was the stage reached when we started the Clinical Institute, and the matter was summarized in an address I gave on the "Soldier's heart and war neurosis: a study in symptomatology."¹

The Application of the Theory.

In the description of the theory and its application which follows, some simple observations are given to show the manner in which certain reflexes are disturbed; while we have found it already of value in the interpretation of our patients' symptoms, we recognize that there is required a much better knowledge of reflexes before the theory can be used in a systematic manner. The illustrations therefore are merely to indicate how it may become of use.

While the stimulus and response parts of a reflex may often be recognized, the mechanism of that part of the reflex in the central nervous system is not yet quite clear. Consequently the diagrams of this part of the reflex do not pretend to represent the actual mechanism.

In attempting so to explain the theory that symptoms arise from disturbed reflexes as to carry conviction we recognize that we are handicapped in that what we take to be facts may not be accepted as facts by the reader, and it would take up too much space and time to give our reasons. When, for instance, I state that exhaustion of heart muscle produces pain and proceed to develop the argument in which that statement is accepted as a fact, the reader may not accept the statement. The observations on which that statement is based have been carried on for many years, during which patients have been watched and the circumstances provoking the pain have been considered, the gradual progress of the case observed, and the conditions at the *post-mortem* examination carefully noted. Another long series of observations have been made to discover the laws that govern the production of pain in all muscular organs—a research, indeed, in which we are still engaged, and which every day tends to confirm the view advanced here. In like manner, when I take it as a fact that exhaustion is due to a disturbance of a vasomotor reflex, it is not possible to give the long series of observations on which the statement is based.

Until we are able to publish the researches into these and other matters involved in this description, I would ask

the reader to assume that our facts are proven, so that the explanation of this theory may be understood.

FIG. 5.—Diagram of a simple reflex arc. The stimulus affects the receptor A, from which a nerve passes to a nerve cell at B, where it joins another cell which sends an efferent fibre to C—the effector or structure which gives the response.

Description of a Reflex Arc.

In the reflex arc we recognize the following parts (Fig. 5). A, The receptor or place where the reflex is initiated. An afferent nerve fibre conducts the stimulus to B, the nerve centre. Here the afferent nerve ends in a synapse with one or more nerve cells—the actual number and relationship varying in complexity. The nerve centre in turn sends an efferent fibre to C—the effector or structure, be it muscle or gland or centre of

consciousness, which gives the ultimate response characteristic of the reflex.

The whole of this arc is necessary for the production of a simple reflex. Symptoms, or, in other words, alterations in the reflex, may be referable to causes acting upon any part of the arc, but in practice they are found to be mainly confined to alteration in A, the receptor; B, the nerve centre; or C, the effector.

The Part of the Reflex in Life.

The whole economy of the body is built up of a system of organs whose activities depend on reflexes. A flood of stimuli is continually being poured into the system through the skin and special senses, and each stimulus produces a definite reflex on some part of the body. In the deeper tissues of the body stimuli are continually arising and being sent to different organs, which respond by some modification of their activity.

The sources of stimulation, therefore, arise in every part of the body. Organs that at one time are the source of stimulation become at other times the effectors. Thus, when pain is felt, the source (A part of the reflex) may be the peripheral distribution of any sensory nerve, while the brain is the organ which responds (the C part of the reflex). The different organs of the body during periods of activity and quiescence send out stimuli-producing reflexes which modify the activities of other organs—as the heart when it increases its activity in responding to a call for more blood, or decreases its activity in a cessation of effort.

The interplay of these reflexes results in the harmonious action of the organs of the body which we recognize as "health." The disturbance of one or more of these reflexes results in a disharmony which we recognize as symptoms of disease.

Methods by which Disturbed Reflexes are Produced.

There are two ways in which reflexes may be disturbed:

1. By the nature of the stimulus acting on the A part of the reflex arc, the impulse entering through the nervous system.
2. By altering in a positive or negative sense the receptivity of the B and C parts of the reflex, the agent (chemical or thermic) entering through the blood stream.

Disturbance of Reflexes due to the Stimulus Entering through the Nervous System.

The following observations sufficiently illustrate the mechanism by which this kind of disturbed reflex is produced.

Many years ago I had shown that the only serous membrane in which a sensation of pain could be produced was the visceral layer of the tunica vaginalis.

Observation 1.

Dr. Orr, in tapping a hydrocele, tested this statement and noted the sensitiveness of the parietal and visceral layers of the tunica vaginalis. He found he could scratch the parietal layer and the patient feel nothing, but when he touched the visceral layer with the trocar the patient (1) drew back, (2) felt severe pain, (3) became pale, (4) nauseated, and (5) collapsed.

Observation 2.

A man was seized with an attack of renal colic and suffered violent pain in the left side of the abdomen, with contraction of the muscles. He became pale, and sweat poured out; he vomited, and the pulse became soft, and he felt faint.

In Observation 1 the touching of the visceral layer of the tunica vaginalis was the stimulus at the receptive or A part of the reflex. Then followed a variety of responses or effects on the C part of the reflex: (1) A muscular response in the sudden drawing back of the body; (2) the sensation of pain—the centre of consciousness being the response part of the reflex; (3) pallor—a cardiac reflex—due to a stimulation of the vagus, which also probably caused (4) the nausea, and (5) collapse, due to a vasomotor reaction. In Observation 2 we have a similar series of reflexes, these being in addition, the vasomotor reflex causing the sweating, and the vomiting reflex.

Alteration of the Receptivity of the B and C Parts of the Reflex Arc.

The other method, by altering the B and C portions of the reflex arc, comes about through the circulation in the blood of certain agents which affect parts of the arc in a negative or positive way—that is, either increasing or

diminishing the intensity of the impulses during their passage from A to C.

The demonstration of the disturbance of the reflexes through the nervous system is readily understood from such observations as 1 and 2. The demonstration of the circulatory—chemical or toxic—influences is not so easy. Perhaps the best way is to consider the effects of certain drugs whose effects have been sufficiently observed.

Observation 3.—The Effect of Atropine.

An individual who receives a certain quantity of atropine may complain of impaired vision and palpitation. When examined he is found to have a dilated pupil and an increased heart rate, which is abnormally increased on effort.

Each of these effects is due to the drug blocking the passage of normal impulses at c. The pupil of the eye is maintained in an ever-varying balance between dilatation and contraction, responding with great sensitiveness to the stimulus of light. This is because of two reflexes, one presiding over the dilator muscles of the pupil and the other over the sphincter muscles. The atropine blocks the passage of the normal impulses to the sphincter at c and the balance is upset. The heart's activity is regulated in the same way by two sets of nerves, acceleration of rate by the sympathetic, and slowing of rate by the vagus. The heart is like the pupil, ever ready to respond to a demand for more or less blood from the tissues, according to their ever-varying activity. The atropine acts by paralyzing the peripheral end of the vagus, or by depressing the c end of the reflex arc, and the uncontrolled sympathetic fibres cause the increased rate.

Observation 4.—The Action of Strychnine.

In the reflex action of muscles in causing the movement of a joint there occurs normally at the same time as the contraction of the muscles a relaxation of the opposing muscles. Thus in

FIG. 6.—Diagram of a muscular reflex. The stimulus from A passes to B, where it affects the nerve cells supplying the muscles C and C'. In response to the stimulus the muscle at C contracts, while the muscle at C' relaxes. The signs + and - indicate the different actions.

FIG. 7.—Diagram illustrating the effects of strychnine. The response from the stimulus arising at A affects the cells at B differently, so that while the muscle at C contracts the muscle at C' does not relax, but also contracts. This is shown by the - sign in Fig. 6 being now a + sign.

strychnine poisoning. It is to be noted that neither the strychnine nor the toxin in rabies can by themselves initiate a stimulus for the production of a reflex—this arises always from some part of the body through the A portion of the reflex arc, as at the skin. This fact shows that the drug does not cause convulsions, but only modifies the reflex in such a way that the stimulus from A produces the convulsions.

These methods of action probably explain the action of all drugs or toxins which are supposed to act on centres. A great number of drugs are credited with causing vomiting for instance, but the manner in which they act is to render the B or C portion of the arc more susceptible to a stimulus so that a normal stimulus passing into the nervous system affects certain reflexes which have been rendered unduly sensitive.

The following observation shows how a normal act can affect the reflex at B when it is rendered hypersensitive by an agent such as a drug.

Observation 5.

A man with a regular heart, after I had given digitalis, showed irregularities which a graphic record demonstrated to be due to the dropping out of ventricular systoles, the auricular rhythm being unaffected. The digitalis was stopped, and in a few days the heart's rhythm became quite regular, the ventricular systoles having ceased to drop out. Commenting on this fact to the patient, he said he could bring the irregularity back, and I asked him how, and he replied, "By swallowing." I requested him to swallow, which he did, and a ventricular systole dropped out. I took a long tracing, and when he did not swallow the rhythm was regular, but as soon as he swallowed a beat was missed. This was repeated a great number of times. Four days later the heart was quite regular, and swallowing had no effect upon the heart's rate.

Observation 6.

A woman, aged 52, experiences attacks in which she becomes prostrated, suffers severe pain in the head, and vomits. If she lies quite still she does not vomit, but if she is startled by a noise—such as the banging of a door or ringing of a bell—or if she smells tobacco or cooking, vomiting occurs.

In this condition there is manifestly a hypersensitive condition of the B part of the reflex arc, but it is to be observed that vomiting occurs from a stimulus from the periphery, just as the convulsion in rabies and strychnine poisoning.

The Added or Reinforced Stimulation.

In the production of reflexes in disease the reflex often takes place with unusual ease or facility, a slight stimulus producing an exaggerated reflex or calling into play an unusual reflex, as in Observation 5. The reason for this is that the disease disturbs some parts of the reflex arc rendering them more or less susceptible to stimulation. This may happen in several ways.

In certain forms of visceral disease certain areas of the skin or other tissues of the external body wall show an increased susceptibility to stimulation. Thus, when pressure is applied to the skin of such a strength that in the unaffected part it produces only the sensation of touch or pressure, it produces in these hyperalgesic areas the sensation of pain. The explanation of this disturbance of the normal reflex is that already a stimulus is affecting the arc from the diseased organ A, and the added stimulus of pressure A' is sufficient to produce pain (Fig. 8).

The contraction of the muscles of the abdominal wall in disease of abdominal organs (the "viscero-motor reflex") is but an exaggeration of the normal reflex which maintains the tone of these muscles. If the gradual disappearance of these contractions be observed it will be found to merge into that state of resistance which we recognize as tone in these muscles, so that the contraction in visceral diseases is but an exaggeration of the normal tone.

The increased sensitiveness which is shown by hyperalgesia of the tissues of the external body wall is capable of giving rise to pain from a stimulus reaching the central parts of the arc.

Observation 7.

A man with advanced aortic disease suffered from attacks of angina pectoris. He had a diseased tooth, which caused a slight degree of pain. During the attacks of angina pectoris, in addition to the pain in the chest and left arm he had pain along the jaw, but the pain was always most severe around the diseased tooth.

In this instance the diseased tooth kept up a continual irritation of the A part of the sensory reflex, and the pain would become more severe when pressure was made on it in chewing, the reflex arc being disturbed by an increase of the stimuli at A. During the attacks of angina pectoris pain was felt along the jaw—where there was already a disturbed reflex—this additional stimulus reaching the arc at B produced an increase of the pain, or, in other words an increased response, at C.

FIG. 8.—Diagram to illustrate an added or reinforced stimulus. The presence of disease at A (say gastric ulcer, a diseased tooth) keeps up a persistent irritation at B, so that a stimulus from A' (the skin or other organ) not sufficient to cause pain by itself, affects the irritated cells at B and produces pain (see also Observations 5, 6, 7).

Observation 8.

A man suffered from jaundice with severe attacks of gall-stone colic for several days. The skin of the upper part of the abdomen on the right side was very tender on pressure (hyperalgesia). The pains suddenly ceased and a gall stone the size of a bean was passed by the bowel. The hyperalgesia of the skin persisted, but he suffered pain over the hyperalgesic region on taking food. When the hyperalgesia disappeared he suffered no pain on taking food.

Here, as in Observation 5, a normal stimulus (resulting from the taking of food) on entrance into the central nervous system affected a hypersensitive part of a reflex.

Balanced Reflexes.

There are a great many different kinds of reflexes, some so obscure that their mechanism is not clear. There is one form which from its simplicity illustrates the theory of disturbed reflexes as the basis of symptoms. This is the kind which might be called balanced reflexes, where two systems of reflexes mutually react. This was seen in the description of the reflex contraction of muscles, when at the same time one set of muscles contracts another set relaxes, where strychnine and the toxins of rabies and of tetanus disturb this balance (Figs. 6 and 7). It is also shown in the pupil, where normally the movements of the pupil are exquisitely balanced by the nerves supplying the dilator and sphincter fibres, and where atropine upsets this balance by paralyzing the sphincter fibres. It also occurs in the heart, where the play between the accelerator and depressor nerves of the heart results in the delicate regulation of the heart's activity in response to stimuli from the other organs of the body.

In many illnesses the balanced reflex is upset, so that we find the pulse rate a valuable indication of the patient's state. In most toxic cases the rate is increased, possibly by the excitation of the accelerator (sympathetic) part of the reflex. In some cases the toxin stimulates the depressor part, as in typhoid fever, and the effect upon this part of the balanced reflex is seen in certain diseases where the heart's rate becomes very slow, as in the following observation.

Observation 9.

A man 50 years of age began to suffer from sudden attacks of loss of consciousness of brief duration. His pulse was found to be slow, and records—graphic and electrographic—showed that his ventricle was responding only to every second auricular beat. As this is typical of one kind of an over-action of the vagus, an attempt was made to remove this by atropine, which paralyzes the peripheral end of the vagus. A hypodermic injection of one-fiftieth of a grain of atropine was followed in ten minutes by the appearance of more beats, and in thirty-five minutes the ventricle responded to every auricular systole.

In this instance the disturbed reflex was due to an over-action of one part of the balanced reflex (the vagus) and the removal of this over-activity at the c portion of the arc by the atropine restored the heart to its normal rhythm.

An example of the disturbance of the balanced reflex, which not only illustrates the mechanism but throws light on a matter of real importance in practice, is afforded by the variation in the heart rate occasioned by the act of respiration. In differentiating the different forms of heart irregularity I recognized one form common in the young, which I called the youthful type of irregularity, and demonstrated that it was produced by the breathing; the heart increased in rate during inspiration and decreased during expiration. This variation was more marked if the individual breathed slowly and deeply.

On inquiring into the significance of this form of irregularity I found it present in young people in perfect health. I found it disappeared when any febrile illness caused an increase in the heart's rate, and it returned when the fever fell and the rate returned to normal. I have used this irregularity for over twenty years as a guide in doubtful cases after recovery from illness, looking upon its presence as a proof that the disease had departed, and that the heart was free from any active process. This view is now justified. Under ordinary circumstances the balance between the accelerator and depressor nerves is so even that a stimulus such as breathing disturbs the balance. The presence of a toxic agent affects the reflex, causing an increase in the rate, so that the slight stimulation from the act of breathing no longer has any effect, and hence the reappearance of the irregularity at the termination of a febrile illness.

The Disturbed Part of the Response.

The tendency to heart-block by stimulating the vagus (as by the use of digitalis) is more apt to occur when the bundle connecting the auricle and ventricle is damaged, and the question arises, Is the effect at c which produces heart-block due to an increase of the vagal activity or an increased susceptibility of the responding organ—that is, the auriculo-ventricular bundle? That the reflex may be impaired by the diminished susceptibility of the recipient organ at c can be inferred from the following observation:

Observation 10.

A man 68 years of age consulted me because he had found that on making a considerable effort, as running upstairs, his pulse, in place of increasing in rate, fell to nearly one-half its rate. I tested him, and found that this was so; I considered that the bundle which conveys the stimulus from auricle to ventricle was damaged, so that while the damaged bundle could convey a stimulus at the rate of 60 or 70 times a minute, it failed to do so when the rate became higher. Subsequent records, graphic and electrographic, confirmed this view.

In this instance the normal balance of the reflex between the augmenting and inhibiting nerves to the heart is disturbed by the damage to the recipient organ.

Multiple Stimuli and Multiple Responses.

The response at c may be due to stimuli originating at different places and in different ways. Thus an abdominal muscle may contract in response to a stimulus from the brain, or from the skin, or from the movements of respiration, or from the movements of the body, or from a visceral stimulus, as in Observation 2.

A single stimulus can give rise to a number of responses—indeed, most stimuli do; we have seen that a cutaneous reflex giving rise to a movement of a joint does so by the contraction of one group of muscles and the inhibition of another group, while Observations 1 and 2 showed that in response to a stimulus a number of reflexes followed.

Multiple Reflexes.

During ill health the patient may complain of a number of symptoms, and the doctor may detect a number of signs. This is due to the fact that the agent which causes ill health disturbs a great many reflexes. To look at these signs and symptoms, each one recorded as an isolated fact, presents such a confused picture that a coherent description of the patient's condition cannot be given. When the individual reflexes are recognized, then the symptoms can be grouped upon a rational principle.

This plan of analysis can be employed in studying the reflexes produced by the impaired functions of organs, or by the specific reaction to the toxins of disease, as well as to drugs, in the manner already described.

The Disturbed Reflexes due to Organic Disease.

One essential question in cases of diseased organs is their functional efficiency. When all the organs are functioning in a normal manner the reflexes pass unnoticed by the individual. When a failure of function takes place the reflexes are disturbed and symptoms appear. It is difficult to recognize the real source of a reflex, for many organs when they fail to function in a normal fashion do not themselves show the signs of failure, but the signs are shown by other organs that are deprived of the material the erring organ contributes to the economy.

While the failure of each organ will give rise to different reflexes the fundamental principles governing the production of the symptom will be the same.

The Disturbed Reflexes due to Heart Failure.

The symptoms produced by heart failure offer a good illustration, as they have been worked out in some detail.

When a healthy individual engages in violent physical effort he will in time produce exhaustion of the heart, so that it no longer supplies sufficient blood to the organs and tissues, and the individual suffers distress. The same thing happens when an individual with a diseased heart undergoes an effort which leads to exhaustion, only in the second instance the amount of effort is less. The signs of heart failure are those of distress and are not to be found by the examination of the heart but by effects of an insufficient supply of blood to other organs. This is well recognized in advanced heart failure when there are

in addition to distress on effort, the physical signs of dropsy and an enlarged liver.

In the great majority of people who suffer from heart failure these physical signs never appear. In them the heart failure is made manifest by a limitation in their response to effort; they are pulled up by distress in some effort they were wont to perform in comfort. This is because of certain reflexes that are set up by organs which suffer from an insufficient supply of blood. The reflexes are of a nature that produce distress of such a clamant kind that cessation of effort is called for. They are mainly of two kinds—the distress associated with (1) breathlessness and (2) pain in a distinctive region.

In healthy people the most frequent evidence of heart exhaustion (as in running) is breathlessness and the accompanying sensation of tightness at the throat and a sense of suffocation. Occasionally there is also a sensation of constriction of the chest with pain across the chest.

What happens in a healthy person is also what happens in one with a weak and diseased heart, one difference being that less effort produces the distress in the latter case and another that pain is a fairly frequent cause of distress.

The mechanism of these two reflexes is quite distinct. Respiratory distress is the outcome of a disturbance of the respiratory reflex on account of the heart being unable to supply purified blood to some part of the respiratory system. I do not discuss further this mechanism here, as it would lead us too far, but everyone recognizes that breathlessness is a sign of heart exhaustion and that it is due to a disturbed reflex.

The other reflex, of which pain is the dominant feature, is a reflex arising from exhaustion of the heart muscle itself. The pain is often accompanied by other reflex signs, as contraction of the intercostal muscles producing the constriction of the chest—sometimes of such extreme violence as to be more dreaded than the pain. Sometimes the mouth fills with saliva, and the pain may be felt not only in the chest but in the arms and along the jaw (Observation 7). These are multiple reflexes comparable with that described in Observation 2.

Observation 11.

A man 68 years of age complains of breathlessness on going up a hill or stairs. Also of pain across the chest, on effort under certain conditions, such as walking out on a cold day or after a full meal. The pain across the chest is preceded by a sense of tightness, or constriction, such as used to pull him up when running a race in boyhood. These signs of limitation have come on gradually, and he noticed his limitation fifteen years ago. There are no physical signs of disease, except some arterial degeneration.

This account is one common to a great many people, in whom the coronary arteries become diseased so that the heart muscle does not receive an adequate supply of blood.

In this case the heart in supplying the active muscles of the legs fails to supply other parts with enough blood, and amongst others the respiratory system is affected, and gives rise to the complex reflex which is called breathlessness. At other times the heart muscle does not receive a sufficient supply of blood, and it gives rise to its peculiar reflex—pain and contraction of the muscles of the chest wall.

In heart exhaustion, then, we have two prominent reflexes—the one arising from a deficient supply of blood to the respiratory organs, and the other arising from exhaustion of the heart muscle. Which of these reflexes first appears on heart exhaustion depends on whether the respiratory or cardiac reflex is first called into play. In the case quoted, under certain circumstances it was the respiratory, and under others it was pain. Occasionally they may both appear.

In certain cases the respiratory reflex is readily produced, as in auricular fibrillation—a condition in which pain is infrequent and rarely severe, while in diseases which limit the supply of blood to the heart muscles pain is readily induced. In the following instance the reaction of the reflex to the different heart states is brought out.

Observation 12.

A man 66 years of age consulted me for pain on walking. The pain at first was only produced by walking, and only on certain occasions—mostly on walking after a meal. The pain was situated across the chest, and was accompanied by a gripping sensation. As years passed the pain became so easily provoked that walking under any circumstances would cause it. The

heart was normal in size and the rhythm of the heart normal. One day, when 72 years of age, he called to see me, and said that until recently he could walk 200 yards before the pain compelled him to stop. Now he can only walk 100 yards when he is pulled up, not by pain but by breathlessness. Indeed, since this breathlessness occurred he had not suffered from pain. On examination I found the heart was irregular in its action, the irregularity being characteristic of that due to auricular fibrillation.

This is not an isolated instance, as I have had several cases with a somewhat similar history, but explains an observation I made many years ago, that people with auricular fibrillation do not suffer from severe attacks of angina pectoris.

The Effects of Drugs.

It has already been shown that drugs act by causing a disturbance of reflexes. This way of looking at the action of drugs explains much that is obscure in pharmacology, as the following observation shows.

For a long time it was recognized that digitalis acted in a remarkable manner in some cases of rapid pulse in reducing the rate, while it had no effect in other cases. It was never understood why there should be this difference. I found out about fifteen years ago that in the cases in which it had this slowing effect the heart was regulated by abnormal rhythms—mainly that abnormal rhythm due to the condition now recognized as auricular fibrillation. I have attempted many times to reduce the increased rate of the heart when the rhythm was normal, and invariably failed. I speculated for a long time as to the cause of this difference, but never understood it till the theory of disturbed reflexes made the matter plain.

In infectious diseases—as pneumonia, measles, etc.—the balanced reflex that moderates the heart's action is disturbed by the toxins of the causal agent of disease, so that the rate of the whole heart is increased.

In auricular fibrillation this reflex is not disturbed. When the rhythm is normal the ventricle contracts only to the stimulus that arises from an auricular systole. In auricular fibrillation there is no rhythmic contraction of the auricle, but a continuous fibrillary twitching of the muscle, so that in place of the regular stimulus from the contracting auricle there is a shower of weak stimuli which assail the conducting system between auricle and ventricle, and cause the rapid ventricular rate. Not only is there this difference in the cause of the increased rate, but there is a difference in the condition of the cardiac reflex. In rapid pulse with the normal rhythm the reflex is disturbed by the toxins of the diseased state, so that the digitalis can produce no effect. In auricular fibrillation the reflex is unaffected, so that the digitalis can act upon the vagus portion, and in doing so depresses the conducting mechanism to the ventricle and renders it not so susceptible to the numerous stimuli from the auricle.

The Analysis of Symptoms.

In many diseases all the symptoms on which a diagnosis is based are reflex in origin—in some the reflexes are disturbed by the entrance of the stimulus through the nervous system, and in others the disturbance is through the circulation. To the former belong the symptoms of such diseases as gastric ulcer, renal calculus, gall-stone disease, where the symptoms are of the type described in Observation 2. The symptoms in infections are due to the disturbance of the reflexes through the circulation, as influenza, malaria, typhoid and typhus fevers, measles, and abscess formation, apart from the swelling.

In some diseases we get a mixture of both kinds of reflexes, as in appendicitis, where there is not only the local pain and tenderness of the tissues of the external body wall, with contraction of the muscles of the abdomen, but the feeling of exhaustion, rapid pulse, tendency to vomit. In cholecystitis we get a similar complex.

The need for the more accurate recognition of symptoms is seen when it is considered how difficult it is to diagnose even such seemingly simple affections as gastric ulcer and appendicitis. Though surgeons have been operating for these complaints for many years, the most experienced recognize that in many cases they find they have been mistaken in their diagnosis. This is due in a great measure to the fact that the nature and mechanism of the symptoms of these diseases have never been understood, and the symptoms were never clearly differentiated from those of other diseases which they resemble.

It will thus be seen that symptomatology is like chemistry, where the combination of elements results in the production of a great number of compounds bewildering in their variety. Nevertheless, as in chemistry, when they are subjected to strict analysis they can be resolved into their component elements. When the analysis of symptoms is studied as fully as the analysis of chemical compounds have been studied, then it will be possible to group the disturbed reflexes in an orderly manner. The next step then will be to find out the agents capable of provoking the different reflexes, so that we get nearer to the immediate cause of disease.

The employment of this method of investigation is but a return to those methods of clinical research which were so fruitful in their results in the past, especially during the early half of the nineteenth century. To realize how great the progress was during that period we have to consider the discoveries associated with the names of Addison, Bright, Graves, Adams, Stokes, Cheyne, Paget, Hodgkin, and Jenner. These observers employed the most useful of all weapons in research—the trained senses. What we aim at is to recognize the methods which these great observers employed, and by improving and refining their methods restore clinical medicine to the van of research.

Structural and Functional Symptoms.

A certain number of symptoms are due to structural changes and functional derangements. These are generally shown by physical signs, and are due to departures from the normal in various ways, as in alteration in the size and shape and consistence of organs, changes in the colour, as pallor, modification of the sounds of the heart and lungs. These are not dealt with here, but will have to be reconsidered in view of this theory of disturbed reflexes, because many apparently structural and functional signs are really disturbed reflexes, or are produced by disturbed reflexes.

A Preliminary Note

ON

THE HISTO-PATHOLOGY OF EPIDEMIC (LETHARGIC) ENCEPHALITIS.*

(With Special Plate.)

BY

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INTRODUCTORY.

IN a previous communication on the same subject published in collaboration with Miss Helen Ingleby, M.B., mention was made of a granular, pigment-like material occurring in the nerve cells of regions of the central nervous system where brown or black pigment is not usually found. It was also pointed out that in certain nerve cells small round or oval bodies had been detected, in the middle of which a granule could be seen. The optical impression of such an appearance, when present in Bielschowsky or Nissl preparations, was that of a sort of whitish halo surrounding each granule.

When that note was written no more detailed description of these pictures was given, both because it was meant to be only a short comment on a demonstration of preparations and because I was still uncertain as to the significance of such appearances. It was only later on that a careful examination of a great number of specimens convinced me that I had under observation something not, as far as I knew, hitherto described either in epidemic encephalitis or in other diseases of the central nervous system. As, however, the doubt of an optical illusion could not be entirely dispelled, no further communication was made on the subject, and I waited for an opportunity of somehow strengthening my conviction. This presented itself under the form of a few preparations I was able to obtain recently in Paris through the kindness of Dr. H. Durand, Chef de laboratoire of Professor Netter of the Hôpital Trousseau, and of Dr. Trétiakoff, Chef de laboratoire of Professor P. Marie at La Salpêtrière.

Though many of my doubts are still present, the new

facts observed are, in my opinion, such as to require control from those interested in the pathology of epidemic encephalitis. I propose, therefore, to give now a brief description of the already mentioned appearances and of the more recently observed facts, reserving any further discussion about the occurrence of the granular, pigment-like material for another paper.

FIRST HISTO-PATHOLOGICAL FINDINGS.

A fairly good idea of the appearances to be described is given by Fig. 1 (special plate), which is a photographic reproduction of a coloured drawing† made from a toluidine blue preparation of material fixed in alcohol and embedded in celloidin.

This large nerve cell was seen in the lower part of the medulla oblongata, near the middle line, a little ventrally to the nucleus of the hypoglossus, of the first case of epidemic encephalitis published in collaboration with H. Ingleby. As clearly shown in the figure, the Nissl substance has undergone an almost complete process of chromatolysis, all that remains of it being still visible at the edges of the cytoplasm and near the nucleus, which, though retaining its form, has become shifted to the periphery of the cell body. The whole of the cell body is beset with a great number of granules easily distinguished in the preparation because of their blue stain contrasting with the purple of the fundamental cytoplasmic framework. The granules are found in the deep as well as in the superficial parts of the cytoplasm, and nearly all of them are surrounded by a minute light area which under moderate magnification looks like a halo, but under very high power and proper illumination appears as a very delicate, though sufficiently well defined, body, whitish or slightly bluish in colour, and irregularly round or oval in form. As a rule there is one granule in each body, though in some of them two granules, arranged like diplococci, can be observed. Most of the bodies are discrete, and only a few appear united in dumbbell-shaped forms. The granules measure about $0.4\ \mu$, their surrounding light areas from 1.4 to $1.8\ \mu$ in diameter.

These are the appearances which repeatedly attracted my attention. For the sake of brevity they will henceforth be spoken of as "minute bodies," comprising in this term also the granules which appear to occupy their centre. It must be pointed out here that specimens as plain as that shown in Fig. 1 are very rare. In most instances the "bodies" are seen in altered nerve cells, together with a variable quantity of granular material which becomes stained by toluidine and polychrome-methylene blue in various shades of green. This is mentioned both because it may help other investigators in their search for the "bodies," and because it shows that their recognition is not hampered by the presence, within the nerve cells, of a granular material with which they seem, however, to have some relation.

A good instance of this is given in Figs. 2 and 3, which are likewise photographic reproductions of coloured drawings, the former being made from a toluidine blue, the latter from a polychrome-methylene blue preparation. The large nerve cell shown in Fig. 2 was found in the reticular formation of another section of the same medulla oblongata from which Fig. 1 was drawn. The diseased condition of the cell is clearly proved by the advanced chromatolysis, deformation, and peripheral shifting of the rather opaque and dark nucleus. The middle parts of the cytoplasm are occupied by a number of granules which in the preparation were stained a yellowish-green. Some of them appear here and there surrounded by a very small light area which, up to a point, imparts to them an aspect similar to that of the "minute bodies" which are particularly noticeable in the peripheral portions of the cytoplasm. These do not differ as regards form, staining properties, and situation, from those shown in Fig. 1. Outside the nerve cell two other "bodies," identical with those situated within it, can be recognized on the top of small fragments of protoplasmic material the exact nature of which could not be ascertained. In the same Fig. 2 another nerve cell has been drawn, showing for the purpose of comparison a common process of vacuolization.

The two nerve cells shown in Fig. 3 were drawn from the layer of small pyramids of a section of the first frontal

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† All figures illustrating this paper were drawn by Mr. W. Pilgrim with the help of the Abbe-Zeiss camera lucida, comp. oc. 8 K, obj. 2 mm. Z., drawing sheet at the level of the microscopic table.