An Address ON CLINICAL RESEARCH.

DELIVERED AT THE OPENING OF THE ST. ANDREWS
INSTITUTE FOR CLINICAL RESEARCH,

BY
SIR JAMES MACKENZIE, M.D., F.R.S., ETC.,
DIRECTOR OF THE INSTITUTE.

INTRODUCTION.

In proposing to start an Institute for Medical Research we have to answer the inquiry, "Is there need for such an institute?" In all civilized countries there have been institutes established specially devoted to medical research, some of them endowed financially with great liberality, furnished with all the appliances of the most recent scientific discovery, and directed by men of distinction specially trained for the purpose of investigation. There are, moreover, the teaching schools in which research is carried on in innumerable laboratories and hospital wards. What justification can there be for starting an institute in an out of the way place like St. Andrews, seemingly deficient alike in equipment and material for observation?

Certainly our enterprise needs justification, and it is my purpose to-day to give you the reasons for an enterprise of the sort we are about to start, and to show to you how a place like St. Andrews is specially suited for this purpose.

THE SCIENCE OF MEDICINE.

There have been many stumbling-blocks in the path of medical progress. They are mainly due to the lack of understanding of the distinctive character of the science of medicine. The knowledge of disease is so incomplete that we do not yet even know what steps should be taken to advance our knowledge. It has been assumed that the methods which are suitable for various branches of science—as chemistry and physics—should be applied to medical investigation, but the methods of these sciences are not applicable to the investigation of the most important phenomena of disease. The methods which have helped some sections of medicine—as physiology and bacteriology—are not applicable by themselves to the wider fields of clinical medicine.

The present-day conception takes too narrow a view of the field with which medical science has to deal. It assumes that instrumental methods are of necessity the only scientific methods. It has been assumed that because recording and measuring instruments and other methods have greatly advanced such limited fields of medicine as physiology, bacteriology, and chemistry, that therefore clinical medicine should adopt the same methods. In medicine there are phenomena which the scientific instruments of to-day, however delicate, can neither register nor measure, and there are methods necessary for the investigation of disease which no laboratory experience can supply.

As an outcome of this misunderstanding, large fields for investigation which are essential to the progress of medicine have been ignored, methods and principles have been unrecognized or imperfectly applied, while the appropriate investigator has been neither trained nor encouraged to do the work which he alone has the opportunity to perform. Our scheme is not antagonistic to the investigation in other fields of research, nor do we wish to substitute our scheme for others. What we contend is that there are fields essential to the progress of medicine which have been neglected, and it is to some of these fields we intend to devote ourselves, and to use the methods which are suitable for the purpose.

THE AIM OF MEDICAL RESEARCH.

In undertaking any enterprise the first essential is to grasp clearly the objects at which we aim. In medical research the object is mainly the prevention and cure of disease. While that is the chief claim of the medical profession for its existence, much of its endeavour is, however, diverted to the relief of suffering, which is not quite the same thing.

The immediate call for the relief of suffering is so urgent that it absorbs the great bulk of the time and endeavour of

the profession, not only in the attempt to give relief, but also in the search for means to afford relief. Our object indirectly aims at the same result, but by a different method—that is, in the prevention of disease and therefore of suffering.

We must, from the outset, keep clearly in view that the goal of our endeavour is the prevention and cure of disease. This aim is, no doubt, the chief motive in all medical research institutes, but its accomplishment has been hampered because research has hitherto been restricted by the limited experience of the investigator, so that the opportunity has been wanting for that broad outlook which is necessary to see the subject as a whole. The bacteriologist, for instance, has undoubtedly greatly increased our knowledge of the tubercle bacillus, but his work does not help in the discovery of those signs of phthisis which reveal the early stages of the disease when the possibility of recovery is at its best. I am in no sense ignoring or depreciating the great advances that have been made by the different sections of medicine, and our institute is in no sense to be considered either as a rival to these or as a substitute for them. Our work is to be supplementary, and we will employ their methods and discoveries, as well as those that are peculiar to our special needs.

THE BASIS OF OUR SCHEME.

We must grasp the principles we should employ to achieve our object. Common sense as well as worldly experience tell us that if we should try to solve a difficult problem the first step should be to make ourselves familiar with all its aspects. The means for solving a problem or overcoming a difficulty can best be found by knowing what the difficulty is and so coming to understand its nature. Applying this principle to our contemplated endeavour, we find that our problem being the prevention of disease, we require a complete knowledge of disease in all its aspects before we can take steps to prevent its occurrence.

The first principle I wish to lay down is that as *disease is made manifest to us only by the symptoms it produces, it is imperative that the first step should be to understand the nature and significance of symptoms.*

It may be helpful if we consider shortly the stage which the study of symptoms has reached, so that by understanding clearly where our knowledge is defective, we may obtain a direction which will guide us to a subject for profitable investigation. Medicine as a science is slowly emerging from a confused state, and has attained a certain degree of precision with the development of knowledge of structure (anatomy) and with the knowledge of function (physiology). To these have been added more precise knowledge of morbid structure and disordered function (pathology). The knowledge acquired from these branches has been assimilated and put into practice by the physician, who recognizes in the living gross changes due to altered structure and function by what is called "physical signs." The later development of bacteriology has revealed the causes of a great many diseases, and its discoveries have been so striking that for the time being it dominates the field of medical research. Its power for good is greatly restricted, however, by the fact that the attention given to the study of bacteria as they behave in the laboratory has diverted attention from their reaction in the human body—that is, in their production of symptoms.

It is obvious that the stage of disease when it has caused structural damage has been fairly well studied, and in the pathological institutes and hospital wards the damaged tissues have received due attention, while the study of the microbes of disease outside the human body is well provided for.

What of the early stages of disease, the symptoms first provoked by the derangement of function or by the entrance of the microbe into the body? This is the stage where there are no gross physical signs, for the structure of the organs has not been damaged, and consequently no mechanical aid to diagnosis can reveal them. What of the stage that precedes the onset of the disease when the patient is rendered vulnerable by some inherent defect or by the condition of his environment? It is manifest that the surroundings in which research is carried on to-day in laboratories or hospital wards do not provide the opportunities for discovering either the early stage or the predisposing stage of disease.

If, then, we desire to prevent or cure disease, it is

essential that the investigation should be carried on in those places where the early stages can be seen and the conditions that predispose to disease can be detected. That, shortly, is the object of our institute and the justification for our enterprise.

THE EARLY STAGE OF DISEASE.

The question arises, Are there not symptoms provoked before damage is done? We who have had experience in general practice know quite well that the vast majority of patients complain of ill health long before there is any physical sign or signs detectable by mechanical aids. Chief among these symptoms are the feelings of the patients—a consciousness of ill-being produced by some sensations, or by the absence of the indefinable sense of well-being, or by the presence of symptoms perceptible only to the unaided senses of the doctor.

Health may be defined as the harmonious working of all the organs. Ill health occurs when there is some discord in the working of the organs. Disease upsets the harmonious working of the organs and gives rise to the consciousness of ill health. The first symptoms, then, of invasion by disease is invariably a consciousness of some impairment, and the vast majority of patients are conscious of something that tells them all is not well. Now, while this consciousness of ill health or absence of well-being—however it may be described—is often the first sign of invasion by disease, as is admitted on all hands, it is universally supposed to be of such an indeterminate nature as to be of little value in the detection of the disease. Certainly to the superficial observer the patient's description often lends colour to this supposition, but if we seek to analyse the sensations produced by ill health it is remarkable how much information can be gleaned when we are trained to obtain from the patient a description of his sensations. But this is a point I want to impress upon you: it requires a long training to enable you to ask the appropriate questions, and a long experience before you can interpret the answers.

NATURE OF THE PREDISPOSING CONDITIONS.

Medical knowledge has advanced so far as to recognize that a great many diseases which impair the health are secondary diseases—that is, they are grafted on a body which has been weakened by some other diseases of slighter virulence. A great many people suffer from slightly impaired health due to some seemingly trivial cause, from which there is no danger to life, but this impaired health lowers the normal resistant powers of the body so that it is rendered vulnerable to more virulent diseases.

The condition that lowers this resistance may not be disease, but be due to the environment, deficient nourishment, the kind of work, or other circumstances.

It is manifest that, to find out these predisposing conditions, opportunity must be had of seeing the patient while these conditions are in operation, and before the onset of the more virulent disease. The period at which the early symptoms are recognized being nearer the time of onset naturally gives a better opportunity for finding out the predisposing conditions than the study of the later stages, when the time of onset may be forgotten.

The investigator must therefore be one who has the opportunity for seeing the early stages, for seeing the patient when still only affected by the predisposing disease, and for finding out the circumstances of his life.

THE NEGLECT OF SYMPTOMS.

As the basis of our scheme is to obtain a thorough knowledge of disease by the study of the symptoms it produces, it is essential you should clearly realize the necessity for such a study, for it is manifest that if you do not, you will fail to understand the methods necessary for the successful pursuit of our object.

While we are all aware that there are defects in medical knowledge, it is not easy to understand what they are. Yet it is manifest that before we attempt to make good the defect we must realize where the defect lies. When I say we must begin with the study of symptoms, it will be said that this subject has been studied by every physician and surgeon from time immemorial. Indeed, it is stated by some authorities that the study has reached a stage where all the knowledge to be got from symptoms has already been acquired, and if any further knowledge is to be gained it must be by the use of methods not yet invented.

So far from that being the case, it can be said that the knowledge which symptoms can yield is so far from having been acquired that the kind of knowledge which they yield is not recognized, and in consequence the steps necessary to obtain this knowledge cannot be undertaken.

In making this statement I am not reflecting upon the intelligence of the physicians and surgeons in the past, any more than that it would be a reflection on the great surgeons before Lister's day to say that they did not know how to find out the cause of suppuration in wounds. It merely shows that medical knowledge has not advanced so far as to reveal its defects. A clear perception of the defect is the first step to make the defect good.

While I could illustrate this point from the study of almost any symptom, let me give some illustrations from our recent war experiences, where the defect has been demonstrated in a striking manner, but where the demonstration has passed unrecognized.

During the war large numbers of healthy men were rejected for the army because the examining doctors detected a murmur in the heart. Why was that? Because there is a widespread belief that a heart with a murmur is an impaired heart, and although it is also recognized that many murmurs are not of serious moment, yet the absence of a knowledge of which murmurs are serious and which are innocent has not been recognized. In other words, the knowledge of how to assess the value of murmurs is lacking.

Here, then, is a matter essential to the knowledge of symptoms which was found lacking, and this defect of our knowledge gravely affected the interests of the State at a time of crisis; yet the conception of medical knowledge by our military and educational authorities did not permit them to recognize the nature of the defect. To take another example—life insurance examiners, whose duty it is to assess the value of symptoms, have not yet awakened to the fact that the methods they employ are but a species of guesswork, and they have not yet realized that accurate knowledge of this kind is absolutely necessary to the progress of medicine.

Deplorable as was the effects of a lack of knowledge of the significance of a murmur during the war, it was nothing to be compared with the results of a similar defect in regard to other symptoms.

When the stress upon the nation became greater and it was found necessary to introduce conscription, those with impaired health and of older age were called up for military duty. The authorities recognized that many of the recruits would be unfit for full military work, and they set themselves the task of devising some method by which the impaired could be given work equal to their strength. They produced the scheme of placing men in different categories, grading them according to the amount of physical work they were supposed to be fit for. On paper this scheme seemed all right, provided that there was the knowledge necessary to recognize the man's degree of impairment. This, every one will recognize, is an essential requirement to the success of such a scheme, and this is just where it broke down—no one possessed this knowledge. It meant that the ordinary doctor should not only be able to recognize the signs of disease, but able to say how much work a man with a given impairment should be able to perform. This is a kind of knowledge which nowhere exists.

It is not necessary to dwell at length on the complete failure which followed the introduction of this method. While many healthy people were rejected, large numbers of people with impaired health were placed in categories which required of them effort for which they were unfitted, with the result that many broke down, some died, others were crippled and spent most of their time, while in the army, in hospital. So great was the outcry that Parliament had to intervene, and attempts were made to mitigate the evil effects of the system.

The reason I call attention to this is that here, before the eyes of the world, was a revelation of great significance of a defect in our knowledge of symptoms, and yet so backward is the state of medicine that the real cause of the failure is unrecognized.

THE TEST OF EXPERIENCE.

The path of medical progress is strewn with derelict schemes and projects. What reason is there for assuming that our endeavours shall not share this unkindly fate?

While it would be ungracious to dwell upon the unhappy lot of many attempts, for each represents a laudable idea followed by energy wasted and hopes unfulfilled, yet a consideration of their procedures may throw a light which will warn us of the dangers ahead. Without going into details one can see that the failures resulted from the fact that the nature of the problem had not been clearly realized, so that the steps taken to solve it were inadequate for the purpose. One of the great causes of failure has been that the lines which guided the attempts were based upon theoretical considerations, and were not the outcome of experience. If one turns to those instances where research has been rewarded, as in the discovery of the cause of suppuration and of certain microbial diseases, it will be seen what long and careful study, with testing of methods and training of the observers, preceded the successful issue. The principles on which antiseptic surgery is based seem now so simple that the younger students have no difficulty in comprehending them. When Lister began his researches the state of medical knowledge was so backward that he had to spend strenuous years in acquiring a knowledge that would qualify him for the pursuit of his quest. After that there were many years full of trials and failures to be endured before success at last crowned his efforts.

A hundred years ago no one man nor body of men understood the principles which should guide to the discovery of the cause of suppuration. Before Lister could make headway he had, with much toil, to discover those principles. Once these were discovered progress was comparatively easy.

That which hampered Lister at the outset of his investigations hampers medical research to-day—mainly an absence of a knowledge of the principles that should guide research. We must recognize that the principles which may guide research to a successful issue in certain limited fields of medicine are not applicable to the wider field which is to be the object of our endeavours. Before we enter upon our enterprise we must be satisfied that our methods have been tested. For that purpose I cite a few experiences which, when you have grasped their significance, will be a justification for our proposal.

I have referred to certain experiences during the war which revealed like a flash of lightning certain defects in medical knowledge. One of these was the inability to assess the value of murmurs or their prognostic significance. This defect was forced upon me early in my career as a general practitioner, as I was constantly being called upon to decide whether the presence of murmurs called for treatment, or rendered the patient unfit for work that entailed effort, or made him unsuitable for life insurance. A study of textbooks gave no light on the subject, and I slowly realized that the knowledge did not exist. Here was a matter essential to intelligent practice which required clearing up, and I resolved to try my "prentice hand" at its solution. For a long time I did not know how to proceed, and, looking back now, I perceive that the principles of clinical research were so imperfectly understood that though the lack of knowledge was manifest to everyone who gave the matter consideration—no one understood how to set about acquiring the knowledge. You will see in such an instance what a short distance medicine had travelled on the road to become a science when a matter of such urgent importance was looked upon as insoluble. Thus Sir William Gairdner, one of the most capable physicians, about this time frankly confessed that the basis on which such signs as murmurs and irregularities were assessed for life insurance was a matter of guesswork—the insurance examiners had no clear conception of any principle to guide them. It occurred to me that the only method was to follow the individuals through life to see what became of those who had murmurs. I started to keep records of my patients and watch their behaviour through the varied circumstances of life—the behaviour of the heart when the patient led a strenuous life, during illness, and in women during the pregnant state and all that it involved.

But I was soon held up by the consciousness that I did not know what to watch. I spent some years noting the different modifications of sounds and the regions into which murmurs were propagated. But I found this led nowhere; and, indeed, when you look back upon the history of auscultation, you will realize that it has not

advanced during the last fifty years, simply because it has never been understood how to make use of the method for the advancement of medicine. Time and energy have been wasted in meticulous study of the sounds and their modifications, or in modifying the stethoscope.

Recognizing that my path was blocked, I tried many ways to get a better insight into the problem till it occurred to me to ask the question, What is there to be afraid of in the detection of a murmur? After consideration I found the reply was "Heart failure." What did I know of heart failure and what were its symptoms? Put in this way I had to confess my ignorance, except when heart failure had advanced so far as to produce dropsy and dyspnoea. Again I turned to my textbook, but found that neither physician, pathologist, nor physiologist could explain heart failure nor give the symptoms except in the extreme degrees.

It was evident, then, that I could not hope to assess the value of murmurs until I understood the symptoms of heart failure and how they were brought about. I therefore set about educating myself by watching the onset and progress of heart failure in my patients, and after some years at last acquired a sufficient knowledge to permit me carrying on the inquiry into the significance of murmurs. I achieved a measure of success so that it was possible to lay down certain principles of a simple and easily understood kind, which guide to a sure prognosis in the great majority of cases. There are still some murmurs (as those due to aortic regurgitation) which require further study, as there are factors present in the production of heart failure in aortic regurgitation which I do not yet understand.

Turning to another field of clinical research—the discovery of conditions that lead to ill health. Those who have followed intelligently the more recent developments of cardiology acknowledge that the recognition of the condition now called auricular fibrillation and all the phenomena connected with it has altered the outlook of the profession towards many forms of dangerous heart failure. The manner in which this condition was discovered arose in this way: There had been long recognized, in a confused sort of way, a class of patient with extreme heart failure with an irregular heart. But there was no accurate knowledge as to its significance, nor were its symptoms clearly defined to separate it from other conditions. In my investigations into irregular action of the heart I had recognized this peculiar condition, but for a long time was unable to account for its occurrence and its relation to heart failure. As it was frequently associated with a history of rheumatic fever I followed for years cases with mitral stenosis, taking note of all associated phenomena. One patient whom I had watched for seventeen years suddenly became ill from heart failure, and I found that this coincided with the disappearance of all signs of auricular activity, with the onset of a rapid and irregular action of the heart. The clue being thus given I was able to detect the phenomena peculiar to the condition, and to recognize it as a distinct clinical entity; and by the study of thousands of cases to demonstrate that at least 80 per cent. of all cases with extreme heart failure, as shown by dropsy and orthopnoea, were either due to this abnormal rhythm or had the heart failure greatly aggravated by its occurrence. Moreover, with this knowledge I studied the treatment of these cases, and found certain principles which helped to the discovery of a very satisfactory method, which is now being recognized and generally adopted.

Take a third field of clinical research, that of remedies. In my examination of patients generally, and in those with heart failure in particular, in noting their symptoms I also kept a note of the effect of drugs in modifying the symptoms or in producing new symptoms. In this way I discovered that the action of cardiac drugs could be studied with a fullness and a precision obtainable in no other way. After many years' observation I was able to show that the action of digitalis was not the same on healthy hearts as on diseased hearts, and that of diseased hearts there were many on which it had no effect, while it acted differently in different forms of disease. After much study I was able to lay down principles for the administration of this drug, and to show clearly the cases in which it could safely be given and with benefit, and the cases in which it was of no use. While this subject is far from exhausted, both clinical and experimental

investigation in the action of cardiac remedies are now directed by these observations.

My purpose in citing a few of the results of the application of the principles peculiar to clinical medicine is not to exaggerate their importance, but to demonstrate the principles which achieved such a limited success, so that we may have a guide in our prosecution of medical research. These principles I shall describe to you, and you will see that they are of such a simple and self-evident kind that you will not be surprised that many people consider that they have been recognized and practised from time immemorial. Indeed, you will find them embodied in many eloquent addresses dealing with medical knowledge. But though they are simple and self-evident, no one has thought of putting them into practice with that systematic application which is necessary for the discovery of their real value. For instance, those who have given consideration to my work recognize that the prognosis of heart murmurs has been laid on a sound basis, that the application of these principles was the means of detecting clinically the condition now called auricular fibrillation, with its chief symptoms and its susceptibility to digitalis, long before it was experimentally demonstrated to be due to fibrillation of the auricles. The application of these principles also led to the recognition of the principles of digitalis reaction on the diseased human heart.

When you reflect that these objects had been studied and investigated by great numbers of physicians, as well as physiologists and pharmacologists, who had every conceivable means of assistance, yet their discovery was effected by a general practitioner untrained in methods and lacking in all the accessories supposed to be necessary for research, you naturally wonder how it came about. A little consideration will reveal that it was due to nothing more nor less than the putting into systematic practice certain principles which are essential and peculiar to clinical medicine.

When I place before you the principles on which our scheme of research is based you will see nothing original in them. Indeed, you will recognize them as those which guided the research of the great physicians and surgeons who have done so much in bringing to light the knowledge of disease as it is recognized to-day. You will find, for instance, that these principles were used by the greatest of all clinical investigators—John Hunter. He made himself familiar with the symptoms of the diseased condition, and then by experiment sought the solution. He not only did not restrict himself to the bedside or the laboratory, but he used both, being trained first as a clinical observer before he attempted research. Moreover, he did not restrict himself to a speciality; though called a surgeon, he was in reality a general practitioner, and his writings to-day are as instructive to the physician as to the surgeon. He was the first, for instance, to describe that peculiar form of breathing which later Cheyne and Stokes described, and which now goes by their name.

The great physician of the past had not that restricted experience which the physician of to-day has perforce to put up with. They were all practically general practitioners, many of them also pathologists and physiologists, so that they had that wide outlook upon medicine which to-day is only to be found in the ranks of the general practitioner. The difference between our work and theirs is that, benefiting by their experience, we can now see clearly the principles by which they made progress, and we can now organize research by the systematic application of these principles. To them we owe the methods for finding out the morbid conditions which caused the physical signs of disease and the knowledge of the later stages of disease. We, strengthened by the knowledge they have given us, turn the other way and look towards the origin of disease by the study of its earliest signs.

THE CHOICE OF THE GENERAL PRACTITIONER AS INVESTIGATOR.

During the past year at the hospital we have been having weekly meetings, and I have demonstrated to you the presence of symptoms usually overlooked or misunderstood, and have shown how little we know of the essential matters connected with symptoms. This was done for the purpose of impressing you with a particular defect in our knowledge, so that you might value the need for an

investigation into disease in a manner not yet systematically pursued.

One of the greatest difficulties I have had in getting physicians and other medical men to understand what I am driving at is, that I have been looking at the subject for thirty years from a point of view they have never seen; for the investigation of disease as it presents itself to the general practitioner has led me to see the symptoms of disease from an aspect different from investigators in other fields. The elementary principles of research in disease have therefore, to me, a meaning different from that which is usually accepted.

Before I recognized this fact I felt somewhat disappointed at the neglect of the work I had done and the misunderstanding of my results. Moreover, I found that the young qualified men, many of whom had been trained in laboratories, could not understand the principles which guided me, and I found in later years, when they recorded their own observations, that they had not grasped the significance of my teaching.

I now recognize that my ideas were the result of over thirty years' observation and study; and while they seemed to me clear and simple, yet those who had not a similar experience could not grasp my point of view. Recognizing this, I saw that I must look for assistance to those who had undergone experiences similar to my own, and it is for this reason I seek the help of the general practitioner in this research.

The reason, therefore, I have asked you to join in the investigation is because you have the opportunity of seeing disease in the human subject in all its phases. As family doctors you have the opportunity of knowing the individuals before they become stricken with disease, of seeing their surroundings and their mode of life. You are consulted at the first appearance of ill health, and you see the patient through the whole course of his illness.

You have from experience had forced upon you the great defect in medical knowledge, and you have gained some experience in the significance of symptoms. You have therefore taken the first step to qualify yourselves as investigators in that you have recognized that there is a problem to be solved. Your vocation as general practitioners has been to solve the problem, and in your attempt to do so you have been faced with the difficulties that lie in the way of solution. Your experience has given you some insight, so that you can appreciate ways and methods which hold out a reasonable expectation for accomplishing the object of medical research. This is a matter of very great importance, because to-day investigators do not see the problem as you see it, and therefore do not take the steps which will lead to a solution.

THE TRAINING OF THE OBSERVER.

I want you to grasp fully what is required of a trained clinical observer, because to-day the essential qualities to a great extent have been lost sight of. This has arisen through an imperfect conception of the requirements for clinical observation. Methods that have been found suitable and necessary for other sciences have been introduced, and have been substituted for those that are essential and peculiar to clinical medicine. Men are now recommended to go into laboratories devoted to one or other of the branches into which medicine is split up, and are trained in methods that are supposed to be more exact and scientific than the clinical methods. This view is the one dominant to-day, so that we find preference given to men trained in this way in all matters concerned with research, and even in the teaching of medicine. This practice is based upon a misunderstanding of what clinical observation requires and what clinical research means, and it leads directly to incompetence of the laboratory trained man as a clinical observer and as a clinical investigator.

A very brief consideration will render this apparent. Take the physiological laboratory, which is assumed to be the most scientific of all our branches. An experiment is performed which produces a reaction which an instrument can record. This record is carefully studied, and certain conclusions—it may be of value—are drawn. From a great many experiments of this kind a large increase of valuable knowledge has been obtained. The success and usefulness of this method is undoubted, but its success has blinded people to its limitations as a method to be applied in clinical medicine. Each of these experiments produced a great many more reactions than the one recorded, but as

these reactions were not capable of being recorded by an instrument, they were ignored. The result is that a laboratory-trained observer cannot recognize any sign except those of a grosser kind, while the subtler and more elusive signs pass unrecognized. It therefore happens that the result of every experiment is only partly recognized. The clinical observer is like the physiologist in this respect, that both are searching for a reaction to a stimulus. In physiology the stimulus is artificial, in clinical medicine it is natural or the result of disease. In both cases a variety of reactions follow the stimulus. The grosser reactions are only noted by the physiologist, and he has no means of detecting the subtler. In clinical medicine the grosser kinds have also to be detected, and the laboratory-trained observer can detect them, but his training has not enabled him to detect the subtler reactions, and hence he fails to attain that skill in observation which is essential to the clinician.

I have already referred to the fact that the bulk of the most instructive phenomena produced by disease are incapable of detection by mechanical aids. Many valuable signs are only perceptible to the trained eye or the trained ear or the trained finger. Still more valuable signs are only revealed by the sensations experienced by the patient. To interpret these requires a training that can only be acquired by many years of patient observation, during which the mind is stored by the experiences of the past, by methods which are peculiar to medicine. These methods can never be acquired by a laboratory-trained observer, and it is because of this that men trained in the laboratory fail as clinical investigators, however distinguished they may be as physiologists, chemists, or bacteriologists.

Before we can make progress towards the solution of any problem there are certain preliminary steps to be taken. The first is the perfecting of the instruments to be used. Before a man shaves he first sharpens his razor. Before we undertake an investigation we must see we have the appropriate implements. One implement essential to the success of our enterprise is a trained observer. It is scarcely realized what a difference there is between a doctor who has systematically trained himself to observe, and another who has perfunctorily examined his patients without attempting to improve his powers of observation. This can be shown in a simple matter like the feeling of the pulse. Many experienced doctors fail to detect irregularities except when very marked. Some physicians will recognize every beat in an irregular pulse; others will fail to detect a large proportion of the beats. Indeed, so common is the inability to count the beats in certain cases that I view many observations with a good deal of suspicion. Certain steps are necessary to train an observer so that he can acquire the ability to detect the peculiarities of the pulse, and to recognize their significance. He must, for instance, have seen a large number of cases, and studied them with great care, so as to correlate the sensations of his fingers with the result of observations made by his other senses. Thus he must correlate the pulse peculiarities with the sounds of the heart, with the movements of the apex and of the jugular veins, and with the character of the sphygmogram. The significance of the pulse can only be recognized by watching the patient for long periods to ascertain what happens to him, and the variations that take place in the pulse and in the other symptoms as the case progresses have to be observed.

The same methods are necessary to train the other senses. A glance at the face will often reveal a great amount of information to the trained observer. Consider the years of study and observation that has been necessary to acquire that knowledge—a kind of knowledge essential to medical investigation, and impossible to acquire by the use of instruments however scientific.

I have referred to the well recognized fact that the symptoms provoked in the early stages of disease are mainly subjective. There are a number of these sensations, and it is evident that, if the early stages of disease are ever to be recognized, the nature and significance of these sensations will have to be understood. There is, unfortunately, a widespread belief that all the information that the patients can yield is easily acquired, and it is generally supposed that the information is often so misleading as to be of little value. Moreover, the belief has obtained that abnormal signs revealed by an examination of the patient, especially by the use of an instrument, are

of much greater importance, so that practically all the instruction at the schools is devoted to the study of physical signs. This is a great mistake, and is the chief reason the knowledge of the early stages of disease is so defective.

To bring this aspect of medicine before you, consider for a moment some of the sensations which indicate the onset of disease. Most patients, when they fall into ill health, become conscious of it by the fact that they are easily exhausted—exertion which they used to undertake with ease and comfort now renders them tired. The questions that arise are: "What is exhaustion? and what is the mechanism of its production?" Put in that way you will recognize at once how little we know of this important symptom. An inquiry which I have been making for a number of years has led to a limited knowledge, and I can recognize that this sensation can arise from a number of causes, and where the condition of the patient is carefully investigated it will be found that this sensation of exhaustion can be divided into a number of different kinds.

The same careful training is necessary for the investigation of the most clamant of all symptoms, that of pain. To understand the full significance of pain in any case, we have to know a great many matters which are still hidden from us. The tissues capable of producing pain, the nerves in whose distribution the pain is felt, the manner in which the pain spreads, and the laws governing the spread of pain; the character of the pain itself; the manner of its onset and its variations, and the phenomena with which it is associated, are all matters which it is necessary to understand before we are qualified to undertake an investigation into disease. So with all other sensations.

It is manifest that before a patient's sensations are understood the doctor must have a knowledge of the mechanism of their production and of their significance. As a rule, the patient is merely concerned with detailing the sensation which troubles him most. It rests with the doctor to obtain by means of judicious questions the particulars of the different sensations. But the doctor cannot ask the proper questions unless he has sufficient experience and a knowledge of the nature of the sensations.

You will gather from this that the physician who would undertake the investigation of the early stages of disease must not only be a man of very wide experience, but must have trained himself to observe on lines that have hitherto received little attention. The training, amongst other things, must have included the watching of patients for long periods to see the outcome of the complaint. If you grasp my meaning you will understand how vain it is to expect the early stages to be revealed in hospitals, where the custom is to hand the out-patient department over to the junior physician, who lacks that experience which should make him a competent examiner. I have for many years been calling attention to this error in education and showing how it hampers practice and research.

To qualify a man to be a skilled investigator in bacteriology, in physiology, and in chemistry, many years of special training are necessary. If it be realized that before a man is qualified to undertake on the lines laid down an investigation for the prevention and cure of disease—the real object of medical research—he must have a knowledge of symptoms, it will be seen that a training is required which is bound to take a great many years. It is curious that men see the necessity for this in bacteriological, physiological, and chemical research, and will undergo the training, but so far the necessity has not been recognized for such a training before undertaking research in clinical medicine.

I dwell upon this so that we may recognize that to make ourselves competent observers we must ever be learning. When we are face to face with our patients and are unable to detect the nature of their ill health, we must not say to ourselves that the disease is not capable of recognition, but rather say that the signs of disease are there, but we are incapable of detecting or understanding them. This is a humiliating confession but a salutary one, and its recognition will direct attention to the sources of failure.

PRINCIPLES OF INVESTIGATION.

While the methods hitherto used in the examination of patients will be employed, other methods which are peculiar to clinical medicine, but which have been imperfectly

understood and only partially used, will be systematically employed. These methods will include certain simple principles which I have found useful in conducting observations on disease. These principles are but provisional, but they will be our guide until the knowledge they reveal is exhausted, by which time we will have gained such an insight into research and what is wanted that they will either be added to or supplanted. We must all recognize that in this work we are but learners, and while the steps we are taking to-day may seem very important and our discoveries may bulk largely in our visions, as time goes on their place in the perspective may be very small. First steps are always feeble and uncertain, but they are a necessary prelude to the vigour of full achievement.

As I have said, the principles that I am about to place before you have been in use during the whole history of medicine, only they have been so imperfectly appreciated and applied that their significance has been overlooked.

These principles are, first, the clear differentiation of symptoms; second, the classification of symptoms; third, the employment of the recognition of a new fact as a foothold for further advance (the law of progression); and fourth, the search for other symptoms (the law of associated phenomena).

DIFFERENTIATION.

Having detected a symptom, whether subjective or objective, it is necessary to separate it clearly from all others that it resembles. This proposition is so self-evident that it seems unnecessary to dwell upon it, yet its significance has not been appreciated. The importance of this step was forced upon me many years ago when I began an inquiry into the significance of irregular heart action. I had not gone far in the study of the subject before I recognized that there were different kinds of irregularity, and though others had also, no doubt, recognized this, no one had attempted to differentiate them with any degree of accuracy on a rational basis. This inquiry I undertook, and was able to found a differentiation based upon the mechanism of their production.

But in this inquiry I found that differentiation means more than the mere recognition of the mechanism of production. A differentiation based on the mechanism rarely leads to a recognition of the significance of a symptom. We know, for instance, that physicians have for long differentiated the murmurs of the heart on the basis of the mechanism of their production, but not knowing how to carry the inquiry further they left the matter there, and a misunderstanding of the significance of the murmurs has resulted. We know to-day how widespread is the misinterpretation of the significance of murmurs, and what injury has been and is being done to the individual patients and to the progress of medicine because of this limited differentiation.

Medicine calls imperatively for a further differentiation—one based upon the significance of the sign in its relation to the progress of the disease that produces it. A murmur may be differentiated according to the valve orifice at which it arises, but it is necessary that it should also be differentiated by the effect its cause has upon the functional efficiency of the heart. This you will at once see is of the first importance, not only in the practice of medicine but also in the pursuit of all kinds of research in which the heart is concerned.

Some years after I had begun the investigation of irregular heart action, other investigators took the matter up and helped greatly to determine the mechanism by which they were produced; but I was struck by the fact that they all stopped there, and practically no one but myself undertook the far more difficult task of differentiating them so as to determine their significance. This could only be done by applying certain principles of investigation which are essential to medical research; I will describe them to you later.

It is necessary to insist that we should always keep in mind that not only have we to detect the symptoms of disease, but we must differentiate them clearly on two principles—one on the basis of the mechanism of their production, the other on the bearing they have on the patient's future.

CLASSIFICATION.

The accumulation of symptoms is so bewildering in their numbers and complexity that it seems impossible

to obtain a clear and simple comprehension of their significance. So long as what is called research is but the addition of new symptoms and of new methods for their detection, it can safely be said that little progress will be made in our knowledge of the fundamental principles of research.

A classification based upon nature's laws tends towards simplicity and a fuller understanding. Such a classification I have attempted, and although I am far from stating that it fulfils all the requirements, it is nevertheless of distinct practical use, and as it is based upon natural laws it leads us to clearer understanding of symptoms. In this classification, symptoms can be divided into three groups according to the mechanism of their production, namely:

1. A *Structural group*, shown by a physical sign the result of a structural change in the tissues.
2. A *Functional group*, due to the disturbance of function.
3. A *Reflex group*, arising from a stimulation of the central nervous system.

I pointed out in dealing with differentiation that, in addition to a differentiation due to the mechanism of a symptom, another sort of differentiation is required showing the significance of the symptom. For instance, when we recognize a sign due to a structural alteration, whether it be a change in the size or shape of the organ or a modified sound of the heart due to a deformed valve, it should be recognized that the knowledge obtained from the mere recognition is extremely limited. What it is required to know is what effect has the cause of the sign upon the patient's future? This question, which can be applied to the consideration of every symptom, cannot be answered by the study of the symptom, so we look for other signs, being guided in our search by the natural question, whether the functional efficiency of the organ is affected. Thus we are guided to seek for evidence of the second group of symptoms.

There are a great many diseases in which we fail to detect any structural sign or any functional impairment, yet we can recognize the disease with great accuracy. Most cases of gastric ulcer are recognized by such signs as pain, tenderness of the skin of the epigastrium, and hardness of the upper part of the recti muscles. There may be no structural sign nor sign of functional disturbance. Such symptoms are produced by an irritation of a limited portion of the central nervous system in a reflex manner, the source of irritation being in the ulcer.

While these groups form the basis of a classification, there are combinations of symptoms which give occasion for further grouping and subdivision, which we will discover in the course of our inquiry.

LAW OF PROGRESSION.

For many years no advance has been made in the use of many methods, such as the thermometer or the stethoscope. These and many other instruments are of the greatest use in clinical medicine, but it has been assumed that the limits of their usefulness have been reached. As a matter of fact, the clinical significance of the information which they yield has only been partially understood.

This restricted use has arisen because the laws governing research have not been understood. There has been a desire to improve a method, but it has not been recognized how it could be done. This has usually taken the form of modifying the instrument, as in the different forms of stethoscope that have been evolved. No doubt much benefit has resulted by perfecting the x-ray methods and laboratory methods generally, but the progress has rarely been commensurate to the time and trouble spent, because it has not been guided by an understanding of the principles of clinical investigation.

The discovery of a new fact or a new method must not be the end of the inquiry which has revealed it. Rather must it be looked upon as a means to an end, a stepping-stone to help a further advance. Medicine has failed fully to appreciate this aspect, chiefly because it was not understood how progress should be made. If the path had been clearly indicated, a forward movement would have been made in many instances where our knowledge has stood still, as in the signs discovered by the stethoscope.

The chief causes that have hampered progress are the failure to recognize the necessity for understanding the prognostic significance of symptoms, and the lack of understanding of the principles of investigation.

THE LAW OF ASSOCIATED PHENOMENA.

One principle of supreme importance for the advance of medicine is the law of associated phenomena. This law is based on the fact that ill health is always accompanied by a number of symptoms, and in every case it is incumbent upon us to search for other symptoms besides those which are most prominent. When, for instance, we detect a structural symptom, we must recognize the limited knowledge it reveals and we must extend our observation and seek for signs of functional derangement. If we detect a sign and recognize it as the product of reflex stimulation, we are at once given a suggestion for further inquiry, and we must search for other signs which will lead us to the area of stimulation. The discovery of this area will lead us to the organ at fault, and it may be to the nature of the condition that provokes the reflex, and thus we get nearer the actual disease.

A very little study will soon bring conviction of the necessity for constantly keeping this law in mind. From the simplest complaint, a headache or a cough, to the most obvious physical sign indicating gross changes, the due appreciation of the case will depend on the application of this law.

THE SIGNIFICANCE OF SYMPTOMS (PROGNOSIS).

The law of associated phenomena is necessary to the understanding of another of our main objectives. We intend to find out the effect the cause of a symptom has on the patient's future—that is, we intend to study prognosis, a part of medical science which lies at the foundation of the intelligent practice of medicine. To do this we must keep in contact with the patient, and follow him during the remainder of his life or for the duration of his ill health, and in doing this we must ever be on the look-out for the modification of the symptom and the development of new symptoms—that is, by the detection of all associated phenomena. This, indeed, is a necessary part of our work, and we must formulate a plan by which it can be carried out. We will have from time to time, as experience ripens our judgement, to alter or modify such a plan.

It is by this part of our work that we hope to detect the early stages of disease. At first we may have no true conception of the cause of a symptom we may detect in an individual, but in course of time, as the disease develops, we may be able to recognize it. By referring back to our notes we will see how the symptoms were developed, and thus acquire a knowledge of the early stages. By finding similar symptoms in other patients later we may be able to detect the disease earlier, and so back to the beginning.

THE USE OF LABORATORY METHODS.

The principle on which we will work is that we recognize the symptoms of disease, then endeavour to find out the agents producing the disease. Many of the symptoms will not be recognizable by the unaided senses, so in applying the law of associated phenomena we will use mechanical and other laboratory methods to assist us. We start with a chemical laboratory and an x-ray department, and we will continually resort to these departments for assistance.

So many diseases arise from bacterial invasion that no method of research into the cause of disease would be complete without a skilled bacteriologist, and we have arranged for a bacteriological department. At the outset our endeavour will be to find out the nature of the symptom provoked by the different bacteria. We recognize by the clinical symptoms the occurrence of a great many infectious diseases, where the specific microbe has been discovered, as typhoid fever and pneumonia. The recognition of other diseases is dependent entirely on the clinical symptoms, as measles and scarlet fever. We infer that the symptoms produced by other infections may give rise to specific symptoms, and we will use this idea as a guide in one field of research. It is manifest that bacteriology must be greatly hampered until the symptoms of invasion are related to the infective agent causing the ill health.

THE CLASS OF PATIENTS.

It may seem to you that St. Andrews with its population of about 10,000 people is too small a centre for the purpose of research, and that large towns would afford greater opportunities, not only in numbers but in variety. There are various reasons why a town of small size is better

adapted for our purpose. As a rule the inhabitants are less migratory, and we can more easily keep in contact with them and so have the opportunity of acquiring a knowledge of the significance of symptoms. We can acquaint ourselves more readily with their environment and with the conditions that preceded their ill health.

Thus we have the opportunity for this particular kind of research. It is not our intention to inquire into the rarer forms of disease, but to study those that are most common, and as St. Andrews is far from exempt we will have plenty of material of the sort we want. Indeed, I must warn you against attempting too much. Far more knowledge is to be acquired by the thorough study of a few than by noting the more prominent symptoms of a large number of patients. We hope by this method gradually to lay the basis of a symptomatology that will be available for those who have perforce to see a large number of patients, and who have not the time and opportunity which will be afforded us.

The class of patient we propose to study, while including patients with different kinds of disease at all stages, will chiefly be those at the very earliest stage of their illness. For this purpose the patients that come to you in your ordinary practice complaining of ill health with no definite physical signs will receive our special consideration. Not only will careful note be taken of their complaints, but we will endeavour, as far as possible, to discover the cause and the mechanism by which their symptoms are produced, while special arrangements will be made for finding the outcome of their ill health.

EXPECTATION OF RESULTS.

I must warn you against any immediate expectation of achieving the chief aim in medicine, the prevention and cure of disease. A long and weary road has to be travelled, and many of us will fall out before that is achieved. As I have said, we have first to train ourselves in the detection of symptoms. Our immediate object, after training ourselves, is to find out the nature of the symptoms of disease, on the lines I have indicated, by discovering their mechanism, and by watching individuals to see what happens. It may be we may detect in this way the onset of some diseases. After that we will have to search for those who show the early signs of a particular disease, and recognizing these signs, seek then for the cause and the factors that favour its onset.

Such a contemplation of our work seems discouraging, for we all like to see the fruits of our endeavours. But it must be borne in mind that all great enterprises are based on work that has been done by individuals whose part is lost in oblivion. Someone has to do the obscure but necessary work of digging a foundation, and if it falls to our part we must be content with the knowledge that we are playing a necessary part in a great enterprise.

POINTS IN THE EARLY DIAGNOSIS OF PULMONARY TUBERCULOSIS.*

BY

THOMAS BEATTIE, M.D., F.R.C.P.,

PROFESSOR OF THERAPEUTICS, UNIVERSITY OF DURHAM COLLEGE OF MEDICINE; SENIOR PHYSICIAN, ROYAL VICTORIA INFIRMARY, NEWCASTLE-ON-TYNE.

I MAY remind you first of all of a few generalizations concerning pulmonary tuberculosis. Nature is curing tuberculosis of the lungs daily all around you, and the pathological statistics of the world reveal the startling fact that 65 per cent. of the population, especially those of large cities, have definite evidence of having had tuberculous infection of the lung. Some of them, even in advanced stages, become arrested and they die from some entirely fortuitous cause. You must be prepared to find on physical examination tuberculous cicatrices, fibrosed areas, scars, tubercle that has long since been arrested and is no longer active. To put it in another way, more than every second person you meet has to your knowledge tubercle in his lungs which has become arrested, and you therefore may find in some of your patients evidences of arrested tuberculous foci and may be misled into advocating active remedial measures where nothing more was necessary

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