

SIR JAMES MACKENZIE AND CELLULAR PATHOLOGY

by

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INTRODUCTION

MANY practitioners who graduated before 1925 can recall the great prestige which the name of James Mackenzie enjoyed; and they may be surprised to find that more than 100 years have passed since his birth. It is just fifty years since his sudden rise to fame in British medicine—on the publication of his book *Diseases of the Heart*. At that time he was already past middle age, having been a general practitioner for twenty-eight years in Burnley, Lancs.¹

Until the last few years, Mackenzie's name seemed doomed to oblivion. But the College of General Practitioners has enshrined his name in an annual lecture in order that it may not die. When I was a student in the early twenties, I was told during physiology lectures about the Mackenzie polygraph which took simultaneous tracings of the radial and the jugular pulse. And I was told, too, of Mackenzie's views on referred pain, which he related to an irritable focus in the cord. Apart from these references, I heard little of his name. When he died in 1925 I was ignorant of the event. But I well remember when, shortly after I graduated, one of my teachers told me to get *Symptoms and Their Interpretation* and to read it. I secured the book and glanced through it, but I was not impressed. As his chief motif, Mackenzie emphasized again and again the deficiencies of the orthodox medical training;² and I, an unfinished product of the system, can scarcely be blamed for failing to perceive the deficiencies in my own schooling.

A dozen years later, however, after ten years in country practice, I had become dimly aware that I was ignorant of the symptoms which more than half of my patients complained of. I had looked in the text-books for these and had not found them. Once again I happened to pick up *Symptoms and Their Interpretation*, and this time I found the book intensely interesting. It was a new and stimulating experience to be told that every symptom had its meaning, which we could learn if we observed it patiently enough. After this I read everything of Mackenzie's that I could find; and it was like an interesting detective story, one article or letter leading to another in the *British Medical Journal* or the *Lancet*. Only a few articles had appeared in any journals before 1903, when Mackenzie had been in practice for twenty-four years.³

STUDIES ON THE HEART

Soon after entering practice in 1879 Mackenzie began to wonder about the meaning of the common symptoms encountered in practice—especially about

their prognostic value.⁴ He consulted the text-books and an encyclopaedia of medicine and got no help. But he was impressed from the beginning with the prognostic powers of his senior partner, Dr. Briggs;⁵ and, with characteristic humility, Mackenzie blamed himself for his own deficiencies. In 1883—entirely for his own improvement and never dreaming of research—he began to keep careful records of the symptoms his patients complained of.⁶ He wondered night and day about the irregularities of the heart—which ones were unimportant and which of serious import? He took tracings of the pulse and, after a time, of the jugular veins. He consulted the leading physiologists, who had never heard of jugular tracings; so—quite unwillingly—he set about interpreting them himself. Later he hit on the idea of combining the jugular and radial tracings on the same drum;⁷ and later again (in 1890) it dawned on him that the instrument could tell him what the different chambers of the heart were doing.⁸

In 1892 Mackenzie demonstrated that the auricles did not contract during an extrasystole, though the ventricles did.⁹ In 1897 a patient who had had mitral stenosis for many years developed an irregularly irregular pulse.¹⁰ Mackenzie called it paralysis of the auricle; the presystolic murmur had disappeared, and with it the auricular tracing in the polygraph. He wrote a number of papers and sent them to the medical journals, but many were rejected.³ In 1902 he published his first book—*The Study of the Pulse*.¹¹ In this he differentiated the serious from the less serious irregularities, and pointed out that sinus arrhythmia and extrasystoles were unimportant.

In 1903 some European physicians inquired for Mackenzie at a medical meeting, but he was not there.¹² So they then visited him at Burnley, where they found him working at his general practice. In 1906 he was invited to address a meeting at Toronto, and during the Atlantic crossing British physicians became aware that a genius was aboard; Mackenzie was always in the centre of a knot of distinguished visitors.¹³

But in England he could not achieve recognition while he remained in general practice; so in 1907 he left Burnley and went to practise in London, where his first year's takings were £114. Then his book *Diseases of the Heart* was published, and in a few months he was famous. Honours were showered on him—F.R.S.; Knighthood; Mackenzie school of cardiology at the London Hospital; an enormous consultant practice. It was not unusual for correspondents to the *British Medical Journal* to ask his opinion on any unsolved problem.¹⁴ During World War I he was Army consultant in heart diseases; at the end of the war he was at the pinnacle of his greatness.

RETREAT TO ST. ANDREWS

When he was at the top of his fame, Mackenzie did what seemed to be a crazy thing; he suddenly abandoned London and returned to general practice in the country. He was sixty-five years old; he had had angina pectoris since 1907 and it was getting worse;¹⁵ he had achieved in a few years more than three average men could achieve in a lifetime. Surely, his friends thought, he had

earned a life of ease and a peaceful retirement! But they had misjudged him; he was not at all content with his achievements.

Mackenzie set up at St. Andrews his Institute of Clinical Research, whose chief object was the study of symptoms. He had a small band of helpers associated with the University, and he had the help of the general practitioners of the town.¹⁶ He hoped to do on a larger scale what he had done at Burnley—keep a record of the symptoms of the inhabitants from youth to old age. He hoped to inspire others to follow in his footsteps; but after six years his heart got worse and he had to retire. Then he returned to London to write a summary of his findings.¹⁷ Observant as ever, he measured the progress of his coronary disease by his symptoms on the golf course. For a time he could play thirty-six holes without distress. Then he could do only eighteen holes; then nine, and finally only one or two slowly.¹⁸ He wrote a masterly treatise on angina pectoris in which his own (Cast 28) was studied in detail.¹⁹ He gave instructions that his heart should be examined at autopsy, and his friend Sir Thomas Lewis found sclerosis of his coronary arteries, with a recent infarction and evidence of several old ones.¹⁵ After his death, the St. Andrews Institute for Clinical Research was renamed the James Mackenzie Institute for Clinical Research.²⁰ It carried on through the 'thirties; but it was closed through lack of staff early in World War II.²¹

THE VALUE OF GENERAL PRACTICE

Even when honoured as a great specialist, Mackenzie remained a general practitioner. The unsolved problems of medicine were before his mind every minute; he had a gift for what Sir Francis Walshe has called 'the unresting contemplation of the facts of observation'.²² *Symptoms and their Interpretation*, written in general practice, takes the whole range of human ills for its field. His research on the heart, Mackenzie insisted, was but an example of the traditional clinical method which should be applied to every aspect of medicine.²³ Though he introduced technical methods into the study of the heart, he discarded them when they had served his purpose.

During his pioneer days in general practice, Mackenzie saw clearly this fundamental truth: medicine is a special branch of science, dealing with a special group of phenomena, to which the clinical investigator must apply the methods especially suited for his purpose.²⁴ The patient provides us with symptoms—usually abnormal sensations with few or no physical signs. In the elucidation of symptoms, therefore, the patient's sensations are all-important; he is aware that he feels ill long before any physical signs can be demonstrated by chemical or mechanical methods.

Mackenzie kept repeating, almost *ad nauseam*, that the future of medicine lay with general practice and not with specialization.^{25, 26} He knew that great technical advances would come through the perfection of laboratory methods, but he pointed out that these did nothing to solve the basic problem, the nature of disease. 'Laboratory workers', he wrote²⁷ 'now get a limited view of disease, and we must recognize that their opportunities permit them to see but a very

small part of the field of medicine'. He insisted that it was wrong to teach students to look for signs whose meaning and mechanism were not understood, and at the same time to disregard symptoms which might be important.

The example of Mackenzie is a permanent inspiration to the general practitioner, because he did not believe that daily practice was dull. Many a graduate soon after commencing practice begins to feel a sense of frustration; the self-confidence of the young man versed in book-lore should give way to humility when he realizes the depth of his ignorance of the causes of disease. When his patients are sick he cannot tell them why they are sick. The young doctor who had wished to give his best to the service of others, finds his ideals being shattered. His energies begin to find outlets in other directions; and the practice of medicine becomes a routine. The study of most of the common diseases is a lifelong task which can be undertaken only by general practitioners who watch their patients for a quarter of a century.

A promising young American cardiologist, after spending a day with Mackenzie, asked: 'What line of research would you advise me to take up when I return home?' Mackenzie replied: 'I would advise you to go into general practice and to stay there for ten years.' The visitor was bewildered and taken aback.²⁸ He had not trodden the hard road Mackenzie had chosen, and therefore he could not see that the general practitioner was 'the only individual in the medical community who has a broad outlook on medicine, whose life-work gives him the opportunity of seeing all parts of medicine in their true perspective.'²⁷

THE ART OF PROGNOSIS

James Orr,²⁹ who worked at St. Andrews, pointed out that Mackenzie never once allowed himself to lose sight of the primary aim of his work—the elucidation of the prognostic significance of the symptoms of disease. On prognosis he had written:³⁰

Prognosis is the judgement of the significance of symptoms as indicating the future course of the patient's complaint. A knowledge of this branch of medicine is absolutely essential to the intelligent practice of medicine. . . . A knowledge of prognosis can only be acquired by the detection of symptoms, and by the ability to recognize whether these symptoms are the expression of a diseased state or a variation of the normal.

Mackenzie's only pride was that he had freed a large number of people from fear. Previously, all irregularities of the heart had been called dangerous; every patient with a murmur was given a gloomy prognosis and told to rest. All of Mackenzie's efforts with the polygraph were directed to a single end—the distinguishing of dangerous from innocent types of irregularity. The polygraph and the tracings in themselves meant little to Mackenzie; their only value was that they helped him to foretell the future. When he was praised as the inventor of the polygraph, he compared himself to an explorer who, on his voyages to a great polar continent, had been helped by a new kind of rubber boot. On his return he found himself famous as the inventor of a boot and not as the

discoverer of a continent!³¹ This error is still made, even in the highest quarters. Thus Mackenzie was recently called the 'indefatigable exponent of the sphygmograph . . . a keen but stubborn physician equipped with inadequate methods'.³²

The following remarks could be applied to medical practice today:³³

At a time when every aspect of disease is apparently being investigated with a degree of thoroughness hitherto unequalled, when intensive researches are being made into a great many complaints, and when innumerable investigators, equipped with all the apparatus of modern medicine, and indeed of modern science, are busy with the different problems of illness, the problem of the nature of illness seems to have been left untouched. . . . This truth was, I think, dimly apprehended by me a few years after I entered practice. I realized then that I did not understand the fundamental nature of a single complaint nor the mechanism of a single one of the signs which I was accustomed to detect while examining a patient. It lay beyond my power to understand how the remedies I employed—even those which were beneficial—exercised their effects. Further, a careful and patient perusal of text-books failed to supply the kind of information I wanted. Thus it was forced upon me that there existed a body of medical knowledge necessary to intelligent practice, the underlying principles of which were not clearly understood.

AURICULAR FIBRILLATION AND FLUTTER

Mackenzie's views on these arrhythmias did not remain static.^{33a} In the third edition of *Diseases of the Heart* he had not suppressed his outmoded views. But he completely rewrote the fourth edition,³⁴ and he had nearly completed the preface when his fatal seizure occurred; Lady Mackenzie wrote the last few lines.

When Thomas Lewis³⁵ had demonstrated with the electrocardiograph that a supposedly paralysed auricle was in reality fibrillating, Mackenzie was not convinced; though he adopted the term auricular fibrillation.³⁶ But he rejected Lewis's circus movement theory as meaningless;³⁷ it did not tell him where the impulse originated. Mackenzie said:³⁸

'There are quite definite signs that the auriculo-ventricular bundle is carrying on, so far as possible, the function of the lost sino-auricular node.' And of auricular flutter he wrote:³⁹

We are, therefore, bound to conclude that, between the sino-auricular node and the auricle, there lies a structure which, when the sino-auricular node ceases to exercise its function, takes up in this peculiar manner the function of starting and controlling the contraction of the auricle. The probability is that this structure, which has not yet been detected anatomically, is a portion of the genetic [conducting] system normally concerned in conducting the impulses from the sino-auricular node to the auricle.

Lately, the circus theory has been put out of date by Prinzmetal⁴⁰ and other workers.⁴¹ They used motion-picture methods of high-speed X-ray photography and observed the heart-beats in slow-motion; simultaneously they recorded the electrical activity of the auricles with the cathode ray oscillograph. Both fibrillation⁴⁰ and flutter,⁴¹ they have clearly shown, are due to impulses discharging from an ectopic focus at a rate too rapid to permit adequate recovery in the ventricles. This is the structure which (Mackenzie said) had not been detected anatomically. Yet nobody was listening and the whole world was

running after the electrocardiograph and the circus theory. The distinguished medical historian³² who wrote: 'Mackenzie had no idea of the concept of block in the conduction system', was probably unfamiliar with the last ten years of his work.

Mackenzie was disappointed when the use of the electrocardiograph led to the formation of a 'Mackenzie School of Neo-cardiology' founded on mechanical methods, in which the patient was put in the background.³⁶ The electrocardiograph told him little more than he had known already about auricular fibrillation, and it gave no help in prognosis. He disagreed with the methods pursued by Lewis, and the fourth edition of *Diseases of the Heart*³⁴ comprises a reasoned protest. But Mackenzie died, and his book was scarcely noticed.

THE SEARCH FOR THE LAWS OF NATURE

Early in his career, Mackenzie had formulated a fundamental principle: disease is merely a reversal of one of the laws of nature. In the physical world the laws of nature had been incomprehensible until increasing knowledge demonstrated that they were based on an essentially simple atomic table. A like simplicity, he argued, would be found to apply to the physiological laws governing the bodily functions; therefore the laws governing symptoms would prove to be simple. At St. Andrews he pursued the task of discovering these laws; and he has left us a record of them in the introductory chapters of the last edition of *Diseases of the Heart*,³⁴ and in the little book entitled *The Basis of Vital Activity*,³³ which was completed forty-eight hours before his death. This book finished with the following words:⁴²

We are anxious to avoid dogmatic assertions of any kind. It is manifestly too early to make positive statements or to suggest that the principles described above are all-sufficient. We fully recognize that these principles may require to be modified or actually superseded, but even in the last event, our labour has not, we believe, been in vain. At least we have done what we could to direct attention to the need of a truer conception of the aims of medical research. The definition of a want is the first step towards supplying it.

These last words of Mackenzie exemplify his humility and his practicality. He was never wedded to any special theory and was ready to abandon it as soon as he came across one fact which contradicted it. This is a characteristic of the really great mind; it is never settled and never certain of its conclusions. It was a quality of John Hunter⁴³ and of Joseph Lister^{43a} which bewildered their friends until they could follow no longer, and left them always surrounded by a retinue of young men.

THE HISTORICAL OUTLOOK

Though Mackenzie was not a historian of medicine, he was steeped in history,⁷ and he judged all medical questions both from the scientific and the historical viewpoint. He had not only historical knowledge but he had 'the better art to know the good from bad'.⁴⁴ He looked back and perceived from

what direction medical progress had come, and he looked forward and judged accordingly the future path of progress. He carefully separated technical medical achievements, which were great in his day, from progress in the true understanding of the nature of disease.²⁷

The discovery of the bacterial origin of many diseases had not carried medical science any farther in its search for the meaning of symptoms and the nature of disease. A great technical achievement often hinders true progress, because it catches everyone's attention and diverts it from the right goal.

The gradual unfolding of medical truth is like a detective story. There are so many false clues; multitudes have been sidetracked many times. Thus the bacterial origin of many diseases was discovered just after Virchow had propounded his cellular doctrine. Virchow was not greatly impressed, because he saw that the germ theory did not solve any fundamental question.⁴⁵ But scientists in great numbers went off in all directions looking for the bacterial origin of nearly all diseases. And many of them got lost and are but now returning to the straight and narrow path.⁴⁶

And even when there was no suggestion of a bacterial origin, many argued by false analogy in attempting to explain diseases whose causes were unknown.⁴⁷ Hence the word *toxaemia*; from the analogy of bacterial products toxins were invented which had never been seen.

Von Behring went on from the bacterial theory to the science of immunology and a great new structure arose, often based on false analogy; allergy was the child of this.⁴⁸ And all the while the possibilities of the cellular theory were not being exploited. Many were deflected to the minuter examination of changes in the blood, despite Virchow's warning:⁴⁹

If the blood be considered as a whole in contradistinction to other parts, the most dangerous thing we can do is to assume what at all times has created the greatest confusion, namely, that we have in it to deal with a fluid in itself independent, but upon which the great mass of tissues more or less depend. The greater number of the humoropathological doctrines are based on the supposition that certain changes which have taken place in the blood are more or less persistent; and just in the very instance where these doctrines have practically exercised the greatest influence, in the theory, namely of chronic dyscrasias, it is usually conceived that the change is continuous, and that by inheritance peculiar alterations in the blood may be transmitted from generation to generation, and be perpetuated.

This is, I think, the fundamental mistake of the humoralists, the real hinge upon which their errors turn. Not that I doubt at all that a change in the composition of the blood may pertinaciously continue, or that it may propagate itself from generation to generation, but I do not believe that it can be propagated in the blood itself and there persist, and that the blood is the real seat of the dyscrasia.

* * * *

The essential point, therefore, is to search for the local origin of the different dyscrasia, to discover the definite tissues or organs from which this derangement in the constitution of the blood proceeds.

Virchow said further that we should search for local (cellular) origins for general diseases. His prophecies have been right many times; thus diabetes

was found to depend on a few cells in the pancreas and pernicious anaemia on certain cells in the liver. A new term 'internal secretion' gained strength from the pancreatic discovery and gave rise to a new specialty—endocrinology. This departure failed to recognize that all cells have their internal secretions. The internal secretion in the liver, which controls the blood, was not called endocrine; instead it gave rise to still another specialty of haematology, cut off from the main body of medicine. Virchow would not have approved.

CLINGING TO CELLULAR THEORY

Mackenzie instinctively clung to the truth of the cellular doctrine and accepted the article of faith that all diseases are due to disorders of cells. Almost miraculously he was preserved from error as he clung to this straight and narrow path. But he was anxious to develop the cellular theory; to carry on from where Virchow had left it.

Very few new developments had in fact taken place. Before 1880 the structure of nearly every organ was known as thoroughly as it is known today. But pathology had stopped in its tracks and no longer asked any significant questions. The morphology and behaviour of every cell in every tissue was well known and freely discussed. But nobody wondered: firstly, how do cells in an organ affect each other? Secondly, how do different organs affect each other? Fundamental pathology has advanced little farther today and the great majority of us are completely incurious about these vital questions. Mackenzie wrote:⁵⁰

No one can understand how any particular organ functions unless he knows with some degree of exactitude how other organs affect it, and how it affects other organs, and the same rule applies in a slightly different way to the special study of diseases.

CELLULAR DOCTRINE AND NERVOUS SYSTEM

By 1890 the medical world was convinced about the cellular nature of all tissues except the nervous system, which was still thought to be granular or reticular.⁵¹ Nerve fibres, whose degeneration had been studied by Waller⁵² and Ranvier,⁵³ were known to convey impulses;^{53a} but their cellular origin had not been established. Waldeyer in 1891 was largely responsible for the concept of the neurone, which immediately met with general acceptance.⁵⁴

The chief advance in histology since 1880 is the ability to stain the finest nerve fibrils.⁵⁵ In the rat, Ranson⁵⁶ counted the neurones in a spinal ganglion and the nerve fibres in its posterior root. The cells outnumbered the fibres and Ranson argued that many fibres were so small that they could not be recognized. Histology has gradually progressed, and today every fibre in a posterior nerve root can be identified.⁵⁷ In the tissues, however, nerves from posterior roots divide and become smaller and smaller until they can no longer be recognized. These have been called free nerve endings; but many believe now that there are no free nerve endings—that every fibril strives to end on or in the

body of a cell.^{58, 59} Bodian⁶⁰ says that fibrils can be identified in every tissue—visually in most and electrically in the few where the microscope has been unsuccessful.

Virchow believed that many tissues were not influenced by the nervous system.⁶¹ In some (e.g. cartilage) he could not identify nerve fibrils and concluded that they were not there. But finer and finer filaments have been found, until at last it is recognized that no tissue is without them.⁶⁰ Now Weiss⁶² has shown that embryonic tissues early in development make permanent connexions with the nervous system, so that they influence and are influenced by them in an association which is never dissolved.

Mackenzie laid down the fundamental principle—life is a special form of energy which cannot be described in terms of electricity, or heat, or chemical products.⁶³ Heat and electricity are by-products; but it happens that the electricity is easier to record in nerve cells than the heat produced. By Mackenzie's day the cellular nature of the nervous system was accepted but the full implications of the doctrine had not been generally adopted. Physiology schools had been set in motion which emphasized the impulse⁶⁴ or its chemical transmission,⁶⁵ to the disrepute of the neurone as a whole.

GENERAL PROPERTIES OF CELLS

But we have travelled too fast, and must now pause to meditate on some of the fundamental qualities of cells in general. Physiology and anatomy have concentrated chiefly on their morphology and their secretory functions. All embryonic cells have the following faculties:⁶⁶

1. Stimulation (initiate impulses).
2. Receptivity (respond to impulses from other cells).
3. Conductivity (transmit impulses from one cell to another).
4. Mobility (move or alter shape).
5. Secretion (fluid or particles).
6. Sensation (respond to mechanical and chemical stimuli).
7. Absorption or phagocytic activity.
8. Growth and reproduction.

The last five qualities are well known and studied in most cells and tissues, by biochemical and microscopic methods. As each cell specializes it loses most of its potentialities and concentrates on one (motion, sensation, secretion, absorption, etc.). But even the most specialized cells possess the remaining attributes in rudimentary degree. Connective tissue cells retain most of the potentialities,⁷⁶ and fibroblasts in healing wounds are like embryonic cells.⁶⁸

Nerve cells have concentrated on stimulation, receptivity and conductivity, though they have minor secretory powers,⁶⁹ and the terminations of their axonic processes are continually changing shape.^{70, 71} The cell-bodies do not grow, but a stream of new protoplasm flows continuously down the axon to replace the terminations which are dying and renewing themselves.⁷¹ Because

it is so readily detected in the axon, there is a general impression that the impulse is electric and a special quality of the neurone. It is not true, however; every cell discharges an impulse at the same time that it performs its peculiar function.⁷² The impulses can be detected electrically in muscle cells, and doubtless could in all other cells but for difficulties in technique.

In vegetables⁷³ and lower animal forms,^{73a} where there is no central nervous system, coordination of function takes place through neuroid transmission (conduction of the impulse from cell to cell). Mackenzie studied this phenomenon in the hair on the leaves of the Sundew (*Drosera rotundifolia*):⁷⁴

When an appropriate stimulus is applied, such as a fly alighting upon the leaf, the hair bends down until its points or tip rest on the fly. In this bending movement there are shown those forms of vital activity usually spoken of as stimulation, conduction and contraction. These are shown by the cells engaged in bending the hair. Further, since the cells situated on the reverse side of the hair oppose no resistance to the bending, it is manifest that an influence must be exerted on them also. This influence is usually called inhibition.

Mackenzie analysed this common phenomenon and showed what an essential part impulses from ordinary cells play in every form of activity.⁷⁵ Thus the orderly movement of cilia in ciliated epithelium is coordinated by intercellular communications and is not related to the nervous system. Fasciculation ('fibrillation') which occurs in a denervated muscle is coordinated by non-neural transmission of impulses from cell to cell.⁷⁶

THE BASIS OF VITAL ACTIVITY

The fundamental laws of vital activity may be stated briefly as follows:⁷⁷

1. The cellular law of vital activity.
2. The law of fluctuation.
3. The principle of control.
4. The law of associated phenomena.
5. The principle of the reflex arc.
6. Symptoms (a) definition.
(b) classification.

*Cellular Law of Vital Activity*⁷⁸

- (i) All vital activities are due to the functioning of living cells.
- (ii) Living cells are never at rest; they are either discharging energy or renewing it.
- (iii) Cells, in discharging energy, exhibit their peculiar function (e.g. contraction, secretion, sensation, absorption) and at the same time discharge an impulse, which exerts an influence on neighbouring cells.
- (iv) The cell impulse is a distinct form of energy, totally unlike electricity or any other known form. As it passes through tissues it generates heat, electricity and other kinds of energy.

*Fluctuation*⁷⁹

- (i) Living cells are continuously discharging energy or renewing it.
- (ii) The discharge of energy takes but a moment; the time occupied in the renewal of energy is variable.
- (iii) Cell activity can be modified only by hastening or delaying the renewal of energy.
- (iv) When cells are grouped to form an organ or a structure, the law of fluctuation applies to the whole organ, whose activity is regulated and controlled.

*Control*⁸⁰

- (i) Certain cells or organs (e.g. sino-auricular node; nerve cells) exercise a controlling influence on other cells or organs.
- (ii) The functional activity of organs is regulated and controlled by structures other than their own cells.
- (iii) The nature of control cannot be properly appreciated until it has been lost (e.g. auricular fibrillation; denervated muscle; trophic changes in fat and skin).

*Associated Phenomena*⁸¹

- (i) No one can understand how any particular organ functions until he knows how other organs affect it, and how it affects other organs.
- (ii) The function of every organ is susceptible of influence by other organs.
- (iii) In disease there is no limit to the number of physical signs which may be detected, as technical methods are developed for recording them in each organ.

*Reflex Arc*⁸²

- (i) The activity of an organ is controlled by structures other than its own cells.
- (ii) These other structures, with the organ, constitute the elements of a reflex arc.
- (iii) Symptoms are due to a disturbance of some element of the reflex arc.

*Symptoms*⁸³

- (i) A symptom is the exhibition of the abnormal or unusual activity of living cells (organ), caused by a disturbance of the reflex arc.
- (ii) Such disturbances result in
 - (a) an increase, or
 - (b) decrease in the number of impulses reaching the organ, or
 - (c) in interference with the generation or conduction of impulses.

*Classification of Symptoms*⁸⁴

- (i) Those depending on increased activity of an organ.
- (ii) Those depending on decreased activity.
- (iii) Ill-regulated activity or its complete cessation, giving rise to disorderly function.

Sir James Mackenzie and Cellular Pathology

At first glance Mackenzie's fundamental principles do not appear very new or very profound. When we think them over it is easy to tell ourselves that we knew them all the time. Mackenzie's greatness lay in his being able to see through the confusing fog of detail and to state the problem in the simplest terms. They are truths which are self-evident only when stated. But in the perceiving of them true genius lies.

THE ACCEPTANCE OF MEDICAL TRUTH

Mackenzie said that there were three stages in the history of the acceptance of every medical truth.⁸⁵

First, people say it is not true. Then when they see it is true, they say it is not important. Then, when its importance has become sufficiently obvious, they say it is not new. Mackenzie often over-estimated the eagerness of other people for knowledge; he made the error of judging them by himself. Few of us are prepared to live in a perpetual atmosphere of questioning and doubt; most of us are satisfied when we have got a few solid facts to hang on to. But Mackenzie was never content. Thomas Lewis wrote of him:⁸⁶

Diagnosis—the affixing of a contemporary label—gave him little satisfaction. His mind could not rest on the known, but turned incessantly, and at each hour of the day, to the unknown, and in perceiving and defining the unknown he displayed a masterly power.

An anonymous friend wrote as follows in a preface to *The Basis of Vital Activity*:⁸⁷

These pages are his best work, his ultimate contribution to the science of medicine. . . . They represent the profound convictions of a mind which never, at any time, lost its keenness, and the observations of an eye which overlooked no detail of the picture of health or disease. The reader may be warned that in their apparent simplicity is hidden an entirely new conception of medicine.

But nobody was left with the force to propagate the new principles, and medical scientists were more interested in the latest technical method or biochemical advance. Osler commented more than once that advance in the theory of medicine is always slower than advance in technique.⁸⁸ A new method of treatment or prevention of disease, if valuable, is quickly adopted. But a new development of thought must influence a generation before it can be adopted; and, during the whole of this time there is the danger of reverse through the death of its sponsor, or through a wave of fashion in another direction.

From 1850 to 1900 a holist interpretation of many inflammatory diseases, including rheumatism, had been widely adopted throughout Europe and North America.^{89, 90} But it was swept aside by the germ theory; everyone believed for a generation that the cause of rheumatism was bacterial and its discovery was at hand.⁹¹

The most recent thinker in this direction is Speransky, who had adapted the 'Relationspathologie' of Gustav Ricker, and proved by experiments on animals

that disease of the nervous system induces disease of the tissues. He demands a unified theory of medicine and protests against the exaltation of biochemistry:⁹²

It is not surprising that chemists have calmly assumed the leadership, but it is strange that the physicians have not only become reconciled to it but seem to be convinced that this position is inevitable.

CONCLUSION

The rapidity of Mackenzie's rise to fame seems the more extraordinary when we realize that he did not begin to study medicine until he was twenty-one.⁹³ He practised for a while as a chemist; and he wrote a novel and collaborated in a play; in Burnley he commenced another novel. This might be called wasted effort; but these efforts no doubt led him to trust his own intelligence, and to develop that vigorous prose which finally convinced his opponents.

Macnair Wilson has given us an entertaining account of Mackenzie's life; but I suspect that he has over-dramatized the struggle and too sharply contrasted Mackenzie with the 'giants' whom he had to assail. For the story of Mackenzie is the story of every innovator in medicine. First he is disregarded; then he is thought a nuisance; only after the prophet has convinced the world is he honoured in his own country. Even then he will not be honoured if he has not inspired affection. Providentially, the struggle usually brings out the finest qualities of character, for such a one can succeed only through a buoyant temperament, coupled with untiring industry and a large measure of human understanding. Mackenzie had all of these qualities, wedded to an innate mental fearlessness which compelled him to rest his doctrine on his own observations and not on authority.

The twenty-five years of contemplation and reading were necessary to his full cultural development. He did not claim to be a medical historian, but nearly everything which he wrote was imbued with the historical outlook.⁷ Such discerning judgment as he possessed on any medical subject implied that all knowledge had been sifted in his mind. Mackenzie possessed that rare balance which enabled him to choose unerringly the true and to reject the false. Even his admirers, however, were unable to follow him in his last search for the uttermost truth. But the *British Medical Journal*⁹⁴ uttered a warning which may yet prove prophetic:

He may have been right or he may have been wrong about his new principles; but Mackenzie had in the past an uncanny knack of being right. His earlier work was ignored for many years, and it is to be hoped that English workers will not ignore this later work, and will not leave it to be appreciated first of all in other countries.

It is not surprising that no official biography of Mackenzie has yet seen the light. Great respect is paid to his name; but a study of his principles would lead to the reappraisal of much that has passed for progress in the last thirty-five years.

SUMMARY

James Mackenzie devoted himself to a quest for the prognostic value of symptoms. With this end in view he saw clearly the permanent importance of the

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cellular doctrine. He regretted that a great number of investigators had virtually abandoned the theory while they pursued biochemical and electrical minutiae.

Mackenzie was first and foremost a thinker and never a technician. His thoughts were always on the unsolved problems of medicine. His life was dedicated to a principle and consistent from start to finish. He was never prepared to rest on his own achievements but used them only as springboards for the next advance.

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