THE IMPORTANCE OF THE INFINITELY LITTLE.

BEING THE MACKENZIE DAVIDSON MEMORIAL LECTURE.*

BY

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In 1798 there died in Bologna one who was born and lived there. His name, which has reverberated down the ages, was Aloysius Galvani. Destined for the Church of Rome, but later expelled from that body, he happily turned to science, and became Professor of Anatomy and Physiology at the University of his native city in 1762. The story of his well-known discovery of what was later called galvanism is well known, and does not need recapitulation here. Helmholtz, writing nearly a hundred years later in an appreciation of Galvani's pioneer work, said:

"When Galvani touched the muscles of a frog with different metals and observed their contraction, who could have dreamt that all Europe would be traversed with wires flashing intelligence from Madrid to St. Petersburg with the speed of lightning? In the hand of Galvani, and first even in Volta's, electrical currents were phenomena capable of exciting only the feeblest force, and could not be detected except by the most delicate apparatus. Had they been neglected on the ground that the investigation of them promised no immediate results, we should now be ignorant of the most important and most interesting of the forces of nature."

Had Helmholtz been alive to-day, how greatly might he have expanded this theme; for even he did not foresee the possibilities of electricity and its ramification into every branch of our daily life, including its applications for the detection and alleviation of many of our ills. Animal electricity in its medical aspect is, it is true, as old as galvanism itself. In its early days thinkers imagined the secret of life had been found, and attempts were made to convert dead into living bodies by its means. It soon lent itself to the worst forms of charlatanism and quackery. But as knowledge progressed and ignorance was dispelled, it found its proper sphere, and the importance of the sphere is evidenced by the existence in our Royal Society of Medicine of a Section devoted to electro-therapeutics.

To trace even in outline the various steps which have led to the present proud position in which this branch of science stands to-day would be a task beyond my powers and beyond your powers of endurance, but I may take as my text to illustrate one feature in the advance (if not its mainspring) a reminiscence of my own.

In 1888 I attended at Bath a meeting of the British Association, and as it was almost the first I had been to I listened to the Presidential and other addresses with great attention and with becoming reverence. The President that year was the great engineer, the late Sir Frederick Bramwell, and well do I remember how he started his address. He began by alluding to a speech he had heard from the late Lord Iddesleigh, who charmed an audience for a whole evening by speaking on the very important subject, "Nothing." Sir Frederick said he would not try to copy this feat, but would do his best to speak on "Next to Nothing." By this neat phrase he meant those little things which are of supreme importance. He gave numerous examples from his own subject to show how it was that attention to details had converted crude machinery into effective and useful instruments, whether they were guns or bridges, engines or ships. Among other subjects he took to illustrate his theme I remember he singled out the telephone as a triumph of science which the "next to nothings" had done so much to perfect. At that time he was naturally not aware of how in later years red-tapeism (and the like) would have taken upon itself to neutralize some of the excellent qualities that science had bestowed upon it. At the conclusion he ventured to prophesy that it would not be long before men were able to fly.

But gifted as Sir Frederick Bramwell was with the prophetic instinct, he did not at that time, now thirty-three years ago, foretell the discovery of those vibrations

which it is now customary to term x rays, nor of those other kinds of radiant energy which the name of radium calls up. Still less could he have predicted the value of these discoveries to medicine and to surgery, and least of all would he have pictured even in imagination the coming of a man who so fully illustrated the importance of attention to details, to the "next to nothings," a personality whose name we are met together to commemorate this evening. Sir James Mackenzie Davidson, whose sterling and genial character we all remember with affection, was first and foremost one who never spared trouble; he was one whose numerous inventions, the result of his painstaking attention to apparently small and trivial things, succeeded in making the bare bones of his subject live, just as his skiagrams represented them in life-like perspective.

I wish that your Section could have selected someone more capable than myself of dealing with this subject from the technical point of view. But you could not have chosen one who has a greater admiration for the genius and ability of our lamented friend. Your choice has fallen on a physiologist whose labours have been more directed into chemical than physical channels, and I regard it not so much as a compliment to myself, as an honour to our band of quiet workers who are seeking out the ways of Nature by the way of experiment, and are doing their best to give to the art of medicine the sound basis of scientific knowledge. For too long the workers in the laboratory, and those by the bedside, have been groping out their own salvation in separate ways. Your request that a physiologist should address you to-night is evidence that the *entente* between us which is now happily growing needs still further strengthening.

I feel, also, that it does us all good to get at times out of our own special ruts. I feel this evening renewed vigour as I come into the fresh air of electro-therapeutics; I can only trust the members of your Section may be able to return the compliment, and find something useful or even instructive in what I have still to say, even although it deals in the main with another corner of medical science than that they are accustomed to live in.

I am not here only to utter sentiments however heartfelt, or platitudes however true, still, before coming to what after all is my main subject, there is one general consideration which I should like to place before you.

The crowded condition of the medical curriculum, in which the poor unfortunate student is presented with an ever-growing number of subjects for study while the length of the day still remains at the usual standard of twenty-four hours, is producing just now one of those attempts which recur periodically to revise his scheme of study. We are told that there is no need for him to learn his anatomy so thoroughly, that his organic chemistry must be reduced to a minimum; and, last and worst, his physiology course must be drastically shortened, and this in spite of the fact that all these subjects are growing fast, and that medical men are seeing more and more the truth that physiology is the corner stone around which the superstructure of medical science is built. Although physiology still figures on paper as quantitatively large, the restriction suggested is in the kind of physiology to be taught, and the term applied physiology designates that what is wanted for the student is physiology in its direct bearing on medical practice. The frog, which has served for so long as the object lesson of so many physiological lessons, is to be deposed from its high position, and, so far as is possible, experiments on man himself are to be substituted.

In speaking of Galvani's work, I have already given one example of how a subject of purely scientific interest, studied with no ulterior or utilitarian motive, was found to be of inestimable value to mankind. Such instances could be multiplied indefinitely. How would Lister's work have been possible without the preliminary academic labours of the chemist Pasteur? When Miescher set out to investigate the chemistry of the roe of the salmon, did he think that it would be on that investigation that our knowledge of the pathology of gout would be founded? When Bayliss applied himself to study colloids, he could not have dreamed that a powerful weapon against wound shock would be discovered in that by-path. But I need not weary you with other instances. When a scientific man studies Nature for the sake of pure knowledge, who can say to what practical use his followers may adapt it?

* Delivered before the Section of Electro-Therapeutics of the Royal Society of Medicine.

In deciding in my own mind whether I approve or disapprove of these attempts to reform or revolutionize medical training, I am torn by conflicting emotions. On the one hand, I sympathize deeply with the student, and realize the impossibility of getting a quart into a pint jug; on the other hand, there is my love of pure science, and the conviction that any and every truth must ultimately bear practical fruit. I am not conservative by nature, and welcome every true reform, and I have little sympathy with the legendary professor at one of our ancient seats of learning who, at the end of a life devoted to laborious research, thanked God he had never done anything that would be of the slightest use to anyone. One has in such an impasse to face facts and exercise one's common sense. A thorough grounding in general physiological knowledge must remain a *sine qua non*, but in the details of its many ramifications one must make a judicious selection, and the choice must naturally first fall on those parts of the subject in which the practical outcome is already realized rather than on those the application of which is still to seek. From the point of view of those in this Section, and of those who aspire to join its ranks later, one trusts that the electrical phenomena which are so easily demonstrated in all essentials on the muscles and nerves of frogs will not fall under the ban of those who are trying to limit the excursions of the student into the scientific aspects of the subject.

In speaking further, I thought the occasion might not be inopportune to say a few words on some of the modern problems of physiology, and tell you briefly of some of the progress we have made and are making at the present time. To attack all these questions in the space of a single address would be impossible. Again, one has to make a selection, and I intend to limit myself to three. I think it will be found that in these three cases the importance of the "next to nothing" principle will be abundantly illustrated. This is the day of great things, because we are realizing the importance of the infinitely little.

The invention of the word hormone dates from the discovery made by Bayliss and Starling of the chemical messenger which is elaborated in the intestine under the influence of the gastric acid, and which, after absorption, stimulates the pancreas to pour out its juice at the time when it is wanted to carry on to completion the digestive work begun in the mouth and stomach. Previous to this time we were imbued with the teaching that the harmonizing or, to use Sherrington's phrase, the integration of the bodily functions is due to the activity of that ruling system of the body known as the "nervous system." The nervous system is not displaced from its high estate, but for the first time in the history of our science we realized to the full the valuable help rendered to the telegraphic service of the body by humbler but none the less useful ministers to our comfort which Starling aptly compared to the postmen. Although the actual word hormone was not coined until secretin was discovered by Bayliss and Starling, the importance of chemical agents had been really recognized somewhat earlier, and more especially in relation to that group of formerly mysterious organs known then as the ductless glands, but now generally dubbed the endocrine organs; they are so called because they form an internal secretion, that is a secretion which leaves by no specific duct, but by the blood or lymph that streams from the organ in question. It was no wonder that ignorance prevailed for so long as to their function, seeing that the new chemical principle each forms is masked by the protein-rich fluid which it enters. But now, thanks to the overcoming of this and other difficulties, we know a good deal about the thyroid, the adrenal body, the pituitary gland, the islets of Langerhans, the corpus luteum, and others.

Many details have still to be worked out, and some of our ductless glands are territories almost as unknown as Central Africa was in our youthful days. The chemical messengers are all grouped together under the general name hormone, a term which immediately "caught on." Attempts have been made to distinguish classes among the chemical messengers to indicate that some stimulate, some depress, and so forth. But the terms introduced with this object by Sharpey Schafer, and more recently by Gley, have not yet at any rate passed into general usage. Speaking of our French colleague, Professor E. Gley, reminds me that the term "internal secretion" was

first employed by another great Frenchman, Claude Bernard, in relation to the liver's important work in pouring sugar into the blood stream at a steady pace. In most cases the index pointing the way to discovery has been the result of removing the organ and of injecting extracts of it into the blood and noting the results. Professor Gley has recently in one of his published discourses laid down the conditions which must be fulfilled in order that a gland may be admitted to the class of endocrine organs. He very properly decries trust being placed merely upon the results of ablation or the effects of injecting extracts. In addition there are three main conditions which must be conformed to in order that a gland may be enrolled within this category: first, the anatomical, that is, the absence of a duct; secondly, the chemical, the recognition in the venous blood of such organs of a specific chemical product; and thirdly, the physiological, the possession by the venous blood of specific physiological properties, and this last is of course the superlative test. He takes the work of Bayliss and Starling on secretin as an example; it was not until Fleig, and Enriquez, and Hallion actually worked with the venous blood coming from the duodenum that the probability of the truth of Bayliss and Starling's views founded upon the results of injection of duodenal extracts was rendered a certainty.

Professor Gley has done good service not only by his own experimental work, but in pointing out the way in which work on this subject must be continued. For we must confess that up till now our conclusions in reference to many of the endocrine glands do not rest on experiments which fulfil all of Gley's conditions. We must further recognize that it does not follow that because most of these ductless organs form internal secretions, all of them do so. Nature seldom works in one pattern, but her *modus operandi* varies. The parathyroids, for example, probably form no substance useful to the rest of the body's machinery, but probably act by removing or neutralizing harmful products formed elsewhere. Noël Paton and his colleagues have shown that the poison they detoxicate is a guanidine compound derived from muscular metabolism, and if this is not removed tetany is the result.

Restricting ourselves, however, to the truly endocrine glands, let us dwell for a moment, not on what we know, but on the gaps in our knowledge. The chemical constitution of that iodine complex which is secreted by the thyroid has been unravelled by Kendall in America. The constitution of adrenaline secreted by the suprarenal medulla is so well recognized that it has even been synthesized by laboratory processes. The composition of pituitrin secreted by the posterior lobe of the pituitary body looks as though it will be the next to yield to the chemist's manipulations. But what do we know of the internal secretion of the part of the pituitary which is probably most essential to life, or of that of the suprarenal cortex, which is certainly the most important portion of that gland, or the nature of the internal secretion of the pancreatic islets, or of the corpus luteum in the ovary, and even of secretin itself? I mention these few hiatuses in our knowledge to illustrate how much our wisdom is in its infancy, what fields are still to be tilled, and lest we swell with undue pride at our present accomplishments. But, whatever gland we think about, we may be sure that quite minute quantities of their various secretions are sufficient to do the necessary work, and that these infinitesimally small amounts are indispensable, not only for our well-being, but for life itself. This, at any rate, has been proven for those secretions which can be quantitatively examined. Even although our knowledge of pituitrin is still over the border, we know that extreme dilutions of pituitary extract can exert marked power in causing plain muscle to contract vigorously, and, in the case of adrenaline, one can demonstrate that the injection of a few cubic centimetres of a solution containing only one part in a million or more of neutral saline diluent will provoke marked physiological effects on heart and blood vessels.

Other examples of organic substances which call forth physiological effects in equally minute or even more attenuated concentrations might be given; there is, for instance, an acetyl derivative of choline, one of the constituents of our body, and the powerful amine known as histamine, which may be mentioned. In anaphylaxis, also, similar infinitesimal amounts of organic substances produce gigantic effects. Such minute doses make the doses of that product of a past generation known as

homoeopaths seem enormous in proportion; a reflection which will awake an echo in the hearts of those who deal with radium emanations.

From the days when we learnt physics, we doubtless remember that important natural law which states that action and reaction are equal and opposite. The law holds in the opposing activities of our hormones, and an important branch of study has been to ascertain how such opposing actions are balanced so that they work together for good. The way in which the different organs, endocrine and otherwise, act and react upon each other has been one of the most instructive and interesting outcomes of the discovery of the internal secretions themselves. I do not think one could find any other subject which has in the present day so deeply influenced medicine as the hormone conception. Instead of remaining, as many physiological discoveries have remained, dormant as praiseworthy laboratory curiosities, the application to the practical study of disease has here been immediate, and medicine, surgery, gynaecology, and the numerous specialities of practice have all been profoundly influenced by the new doctrines. Among the specialities one must here particularly allude to the one represented here this evening. Those who, on the one hand, are employing in diagnosis and treatment various electrical forms of energy, and those who are similarly engaged in radiology, have recognized that they have the power of controlling and influencing the endocrine organs to form more or less of these internal secretions for the benefit of their patients. I wish I had the special knowledge to dwell for a moment on this aspect of the problem, but those who are listening to me will be able to fill in the details of this part of the picture. The discovery of radium has been one of the greatest feats of modern science, but I need not tell my hearers that this new power for good may, like the α rays, be also in unwise hands an equally powerful agent for evil. When the activity of its emanations on living cells were first demonstrated there was perhaps naturally too great confidence displayed in its ability to cure every ill, including those which, like cancer, had defied every previous effort to conquer them. That phase is now passed, and the proper place of radium in our armoury is being adjusted to the facts. History is always repeating itself, and the story of radium is a repetition of what has occurred before when startling new discoveries had been revealed to the world. In the old days of the alchemists, who sought by magic and by the help of astral and similar agencies to discover the philosopher's stone and the elixir of life, the disappointments and failures were as numerous as the attempts to discover the secret of vitality. When alchemy was replaced by more exact science, new revelations were wistfully and hopefully regarded as likely to yield the long-hidden secret; two of these epochs I have already alluded to to-night—one was the discovery of galvanism in the eighteenth century, the other of radium in the twentieth.

May I digress and linger a moment to mention one more which marked a similar epoch in the seventeenth century? I allude to the discovery of phosphorus. In the early years of that century a substance was prepared by heating heavy spar with combustible organic matter (egg white and charcoal) and this substance glowed in the dark, and for many years the name phosphorus, or light-bearer, was given to any substance which had the same property. The actual element we now call phosphorus was prepared by Brand about 1670, and was at first made in small quantities only from animal products—namely, urine and bones. Can it be wondered at, that in those days of superstition and mysticism the discovery in animal products of a substance which burnt and emitted light without ignition was hailed as a discovery which at last had hit upon the vital principle? Phosphorus played an important part in the development of the theory of phlogiston which soon afterwards dominated philosophic thought, but in time died like so many other theories before and since. The *furor* created by the discovery of phosphorus had been paralleled by the discovery of radium in recent years. Only let us congratulate ourselves that the 250 years which intervened between the two events have taught us more wisdom and we are not so likely to repeat the hysterical enthusiasm of our ancestors.

This, however, is a parenthesis which originated from my mention of the fact that hormones and all that they connote are not simply of chemical interest, but that their importance is recognized as a factor in electro-therapeutics as in other branches of medical science. I do not think I can say the same thing about the second subject I have selected to bring before you. My only excuse for so doing is that it is one on which I can venture to speak at first hand. It may not interest you as electro-therapists, though it is not devoid of importance to you as human beings, for to all living creatures the question of food is of superlative value. The particular portion of this wide problem I intend to say a few words about is one in which also the quantitatively little is qualitatively great. I allude to those substances in our diet which we term the vitamins. The word "vitamin" is not as old as the present century, and although it is not an ideal term it has come to stay, and is certainly less cumbersome than the phrase "accessory food factor" which is its synonym.

The lecturer then gave a brief summary of our knowledge of the vitamins, and alluded to the importance of the "next to nothing" principle there. Though accurate quantitative methods are still to be devised for their estimation, one thing is perfectly certain; and that is that the requisite amount is extremely minute, and this small amount is capable of converting a useless into a useful diet. He then continued:

Before I leave the subject of food may I unburden myself of a suggestion? Empiricism is not always to be condemned. What we call empiricism is frequently the result of past experience. As an example, take a prescription of cod-liver oil, or of butter and cream. A few years ago it would have been impossible to explain why these forms of fat are superior, we will say, to olive oil and vegetable margarine. The mere fact that they are better was empirical, and now the practitioner has been fully justified, and research at last has told us the explanation—namely, the existence in the fats, which are the more valuable for remedying malnutrition, of a health-giving vitamin.

May not this in the future be repeated? If you have high blood pressure why does your medical man tell you you may take fish and poultry and eggs, but that you must abstain from beef and mutton? I can picture a sceptical and argumentative physiologist saying, "Why? The materials you mention and I am advised to take or refrain from taking are all in the main composed of protein, and surely it is not physiological to give me such futile advice." My answer to this would be, "True, it is not explicable yet on physiological grounds. It is the mere result of empirical experience. But wait a few years, and it is quite on the cards that by that time science may have stepped in and explained the puzzle, just as a few years ago it was able to explain why cod-liver oil is better than olive oil." There is probably in the harmful meats some hitherto unrecognized principle, unrecognized because it is present in minute quantities; or it may be the absence of an indispensable material. It is one of the "next to nothings," but it makes all the difference. "There is one kind of flesh of men, another flesh of beasts, another of fishes, and another of birds." I wonder if St. Paul ever imagined these pregnant words contained more than what he intended to convey by them.

The third topic the lecturer selected to illustrate the importance of attention to apparently insignificant minutiae was that of the capillary circulation, a subject which rose into importance during the war in relation to "shock." Here, again, especially in some forms of secondary shock where actual haemorrhage may have been insignificant, but where crushed tissues were the usual accompaniment, it seems inevitable to accept the views urged by Dale and others, that it is a toxæmic condition. The poison is produced from tissue breakdown, and operates by reducing capillary tone, so that the blood is stagnant and side-tracked in the capillary lake. Whether histamine, which certainly produces a shock-like state in this way, is the actual poison in secondary traumatic shock, or the only poison, is a question still to be answered. But, whatever the poison is, it is one of which a very small quantity produces a very large result.

The lecturer concluded as follows: In conclusion, I must thank you for the patience you have exhibited in listening to me for so long. I wish I could have chosen a subject, or subjects, more akin to your own speciality. But if anything I have said in my disjointed remarks will help you to realize how widespread is the importance of the infinitely little my task will not have been in vain.