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ON THE URGENCY OF RESEARCH ON THE GREAT PORTAL TO DISEASE IN THE BODY[1]

IN selecting as the subject of my address on this occasion the urgency of research in a line along which little progress has been made, I am led to do so by considerations which I think will appeal to many of my hearers. It is, first of all, one which is of transcendant importance as an antecedent to any great advance in scientific medicine in the near future. On looking over the road on which so much progress has been made in the last forty years, one cannot but be impressed with the idea that all the old lines of research have been developed as far as they are capable of yielding results commensurate with the expenditure of time and energy given to them and that we are now in the stage of diminishing returns. The record since 1880 is crowded with discoveries in scientific medicine which will preserve from oblivion those who have made them, but unless some new lines of attack on great problems are to be thrown open the record for the next thirty or forty years will not have to its credit similar achievements. A recognition that our present methods of research in scientific medicine are not to give solutions of some of the great problems in disease which still confront us is already beginning to prevail. The distinguished clinician, Sir James MacKenzie, who has been during the last thirty years one of the keenest students, on the scientific side, of clinical medicine, is so convinced that scientific medicine as now developed is not going to yield any further conquests of importance that he has been compelled to seek a new line of research which may give results which will initiate a new and great advance in medical science. The new line which he has taken is the study of the beginnings of disease in the individual, that is, a close and very careful observation of

[1] Address of the vice-president and chairman of Section K—Physiology and Experimental Medicine, American Association for the Advancement of Science, Boston, December, 1922.

the changes in the normal condition long before the individual is impelled to consult his physician or is aware that anything is wrong with him. Sir James hopes that in this way a great amount of knowledge may be accumulated which will throw a flood of light on the origin of many of the diseases and thus inaugurate what may be justly called a great advance in medicine, comparable with any great advance made in the past.

It is hardly possible to doubt that a careful study of the organs of the body as they function in the supposedly normal individual, will, if systematically pursued, ultimately give a lore that will be of inestimable value in determining a fundamentally rational treatment of disease. The application of our present clinical methods is confined almost wholly to the manifestations of disease in its more or less pronounced stages and the features of the initial stages attract the attention of only a very few clinicians. Here, therefore, is an almost fallow field, where any one who enters to work steadily and systematically may reap a worthy reward for the toil of all his years. This combined with a closer, a more thoroughly scrutinizing study of the manifestations of disease in its later stages of development would result in a very great addition to our lore of medicine, and bring us back to the ancient Hippocratic rôle of closely observing and recording which, pursued for periods during the last twenty-four centuries, has made the Art of Medicine of the Western World an ornament of our civilization.

It is, however, doubtful if there is in our generation enough of those of the class of which Sir James MacKenzie is representative to make such an immediate advance in medicine as he believes possible. Progress is due to the activities of the almost inconceivably few. All the ideas, all the knowledge which determines our outlook on the physical world and the world of life of to-day are based on the results of the discoveries and inventions of less than one ten-thousandth of one per cent. of the population of the Western World during the last three thousand years. Even in the medical profession it is the inconceivably few to whom all progress in the past has been due. The rest have accepted and applied the results of the great discoveries of the few. Of the 400,000, more or less, who in Europe and America during the last century and a half have been members of the medical profession, how many have made, as a result of their researches and observations, great additions to our knowledge of the causation and treatment of disease? I would venture to estimate not more than thirty, that is, one out of every 13,000 in the ranks. These were the pioneers in the regions of the unknown to whom we owe the great generalizations which constitute the foundations of what we call medical science. Without their achievements there would have been no advance in it during the last three centuries and medicine would still be but a lore of impossible hypotheses and theories like that which darkened understanding amongst the physicians of the sixteenth and seventeenth centuries. There were indeed others who by their observations in their own limited field of activity added fact upon fact in verification of the great generalization and who by their support of these made their general acceptance possible, but they would not have been of service in any other way to medical science had it not been for the great discoveries of the pioneers.

To extend this science to-day, to make here and there great additions to it, pioneers of the same type are still required. Are such now in training, or beginning their career, or ready to launch some new line of extension?

Sir James MacKenzie does not apparently think there are or will be such, for his Newer Medicine is to owe its achievements to organizations the members of which will devote themselves to the observation and correlation of the facts which may be gained from a continuous, systematic study of the very earliest manifestations of alteration of function which mark the commencement of disease in the supposedly healthy individual. He is apparently extremely sceptical of the value of the laboratory by itself as a factor henceforth in the advancement of our knowledge on the treatment of disease. Research on the laboratory side is carried on by workers who, he holds, are out of touch with the problems in medicine and in consequence their contributions offer little in the way of a solution of these, which must be undertaken by the physicians themselves who are in immediate contact with the problems on the purely clinical side.

It must I think be admitted by all who are

in touch with the present laboratory methods associated with the diagnosis and treatment of disease that the effort spent in the development of them by a multitude of workers in laboratories and the narrow range of the results obtained make it appear as if the vast majority of investigators concerned believe the great problems that can be attacked successfully are all solved and that there remains only to be developed an ever more and more refined technique which will be concerned only with circumscribed problems such as the hydrogen ion concentration, basic metabolism, new reactions of the class of Widal, Schick and Wassermann, more exact methods for the determination of sugar, urea, uric acid, ammonia and other constituents of and metabolic products in the blood, and so on. These and like matters of limited interest and range of application constitute the vast majority of the problems which are now being investigated if the contents of the original papers published in the journals devoted to physiology, biochemistry and pathology give a trustworthy indication of the character of the research that is being carried on in these sciences to-day.

If even a new subject of more than ordinary importance is advanced there soon results a multitude of contributions on it, the great majority of which deal only with details while the central part of the problem is not attacked or only incidentally. An instance may be cited. On the vitamins, which are all important constituents of a normal diet and which were first made known sixteen years ago by Gowland Hopkins, there has been a vast amount of effort expended but chiefly or almost wholly on determining their distribution in different foodstuffs and the effects of diets, from which they are absent, on animals, all in a statistical or empiric fashion, while but little has been attempted or accomplished as to their constitution although a basic explanation of their action in the body can only be obtained when their chemical composition is accurately known.

Then there is the labor that is directed to the determination of hydrogen ion concentration in physiological media. From a survey of the multitude of contributions on this subject which have been made in the last five or six years one cannot but believe that an excess of emphasis has been placed on it which is not justified by the results obtained or any generalizations drawn from them. As much also may be said of the work that is done on a number of problems in immunology.

It must not be inferred from what has been said that I underrate the real value of the results of much of the work that has been done in these lines. I recognize that they have a value, but a value that is not commensurate with all the effort expended in obtaining them for it involves an emphasis on details which should be placed on important problems the solution of which would open new and fundamental lines of development in our knowledge of living matter in its normal condition and in disease. The emphasis placed on details is diverting the energies of a large number of young workers of promise away from the more important problems in the investigation of which they might develop a capacity for adding very greatly to our knowledge and thus achieve a career of distinction in research for themselves. This attention to details on such a large scale at the present time can be justified only on the plea that all the great or more important problems are solved. Even if they did appear to be, it is difficult to believe that a young potential Pasteur, Virchow, Lister, Koch, or Ehrlich would content himself with the investigation of such details and yet I believe there are such potentialities amongst the younger generation of researches who may easily be induced to devote all their energies to problems of outstanding importance.

It may be asked: Are there such important lines of investigation yet to be undertaken? My answer is that there are, and not a few, and that, further, more may eventually be found than are now conceived possible. The chemical constitution and the fundamental action of the vitamins are two of these. There are the questions concerning the nature and action of the bacteriophagic lysins, our knowledge regarding the existence of which is the product of the activities of several keen young workers during the last seven years. The interpretation of the character, origin and action of these lysins in dissolving bacteria will ultimately depend on the results of research to be carried on in the next few years. Meanwhile, it would appear that the bacteriophage is a factor in immunity, especially in the intestinal

tract, which may not be classed with the antibodies which hitherto have been regarded as the only or chief immunizing substances produced in the body to resist bacterial invasion. The bacteriophage question has, therefore, thrust on our attention problems of a high order of importance.

Behind all these problems there are at least several which concern the causation of a considerable number of pathological changes and alterations in function in the organs of the body. These problems are all related to the functions of the intestinal mucosa. Such functions are only very imperfectly known. One involves the absorption of the products of the digestion of the foodstuffs. In this absorption the mucosa has been, and is still too often, regarded as if it were only a physical membrane separating the blood from the intestinal contents, through which the peptones, amino-acids, glycerine and sugars diffuse to reach the vascular channels. What we have to set over against this physical concept are a few facts the significance, however, of which is not clear. Soaps and fats which are colloids enter and go through the epithelial cells of the mucosa and a number of proteins, those of egg yolk particularly, pass unchanged readily into them, but how the former and the latter are so taken up is still unknown or only dimly comprehended. The salts of iron and potash can be traced microchemically in their passage through the epithelium and the phenomena involved appear at first view to be caused by the simple forces of diffusion but on further consideration one must postulate that other and more important factors are concerned. We know, further, that the mucosa, especially of the upper half of the small intestine, secretes a number of ferments, such as erepsin, invertase, maltase, lactase, and the activator of trypsinogen, enterokinase, and that secretin, the hormone of the pancreas, is a product of the duodenal mucosa, but, except in the case of secretin, we do not know definitely what elements of the mucosa form them.

This, in brief, comprehends our knowledge of the activities of the intestinal mucosa and yet how exiguous it is in comparison with what may yet be obtained through careful and well-directed research. The mucosa is, in its properties and functions, something very much more than a physical membrane. Because its superficial layer is composed of living cells it is not, it cannot be, a passive element, for the cells have, as living units always have, the capacity to accept or reject whatever constituents of the chyle there may be and this capacity is exercised by them through the long life of the individual. They even maintain themselves against the invasion of bacteria of the ordinary type.

This epithelial membrane then has functions which make it unique, functions which are not performed by any other organ. It is the absorbent of practically all that goes to nourish the body, a rôle that involves a variety of activities assigned to no other class of cells in the body. It prevents also the passage through it of the ordinary bacteria of the intestinal cavity and of their products, toxic and otherwise, and therefore it must be regarded as the first line of defense of the body, at its most vulnerable point, against disease. As no other structure in the body is so much exposed, and constantly to bacteria and to invasion by them it is difficult to exaggerate its importance in this respect.

That the cells constituting this membrane, battling against hosts of bacteria and subject to the action of the products, many and varied, of putrefactive fermentation, may finally fail to "play up" must naturally be expected. Then pass into the circulation some or all of those elements which the cells in their fully normal condition do not absorb, or if they do absorb, do not transfer to the underlying tissues.

It is not too much to say that in this failure on the part of the epithelial cells an explanation may be found of the origin of a large number of diseases of the body. It is my firm conviction that arteriosclerosis, hepatic cirrhosis, acute yellow atrophy of the liver, nephritis in some of its forms, angina pectoris, senile dementia and dementia precox are all due to failure, more or less pronounced, on the part of the intestinal epithelial cell to play its normal part. In some cases this failure may develop suddenly as in acute yellow atrophy, in other cases it may involve a gradually lessened capacity of the epithelial cell to reject or neutralize the products of putrefactive action. That dementia precox has this origin is indicated by the facts that it is frequently associated with intestinal stasis more or less pronounced and that not unfrequently in this

disease there may be atrophy of the testes or ovaries, facts that can only be explained by supposing that not only this atrophy but the degeneration of the cortex are due to the action of toxins of intestinal origin. Senile dementia, when not of arteriosclerotic origin primarily, is probably due to a gradually lessened capacity of the intestinal cells to reject the toxic products of putrefactive fermentation.

The intestinal mucosa must then be regarded as the great portal to disease of the body. This portal may be completely closed as it is in the normal healthy condition of the mucosa or it may be gradually or suddenly pushed open and disease, chronic or acute, may result. If this portal could be kept closed always old age might be indefinitely postponed and bodily vigor maintained for a much longer period than it is now. There is no reason to suppose that the heart, the skeletal muscles, the liver, the kidneys, the nervous system and the endocrinous organs cannot function indefinitely if they are not subject to toxic action and in their normal condition they must be much less subject, through any other portal, to bacterial infections than they are when their condition is altered by the access of toxic material absorbed from the intestinal cavity. The complete closure of the great portal permanently maintained would greatly lessen the incidence of disease and increase the average length of life.

It is probable that excess in diet, especially in its protein constituents, may task the capacities of the epithelial cells and diminish their power to react normally, with the result that they allow to pass through them, and to the underlying tissues and the circulation, the products of intestinal putrefaction which in their healthy vigorous condition they do not permit to enter them. This would explain some of the pathological results of a high protein diet. It is also very probable that the primary and most important action of vitamins in diet is on the epithelial cells which, with the glandular structures below them, as McCarrison has found in his observations on animals fed on autoclaved food, undergo marked atrophic and necrotic changes, followed by an extensive invasion of the mucosa by bacteria. The changes which other organs show in avitaminosis have yet to be shown due directly and not indirectly to their deprivation of the vitamins. Once the Great Portal is thrown wide open, neuritis, degenerative changes in the pancreas, thyroid and spleen, atrophy of the testes and ovary, and hypertrophy of the pituitary and adrenals may be of toxæmic origin. Constipation also seems to be one of the earliest results of avitaminosis and its causation may be similarly explained.

The importance then of a thorough knowledge of the functions of the intestinal mucosa and especially of the epithelium covering it cannot be overestimated. To obtain that knowledge is to place us in a position from which we can make a great advance in the treatment of disease or in the prevention of it, comparable with any one of the great advances of the past in scientific medicine. That knowledge can only be obtained by a profound study of the epithelial cells themselves, of all the forces that are concerned in their normal activities, of the character of the proteins and other organic elements of which they are constituted, of the action of bacterial toxins on them and of their defence against them.

The attainment of all this knowledge is not to be an achievement of the very immediate future. That would require a number of specially trained investigators who would devote themselves to intensive research in this line for some years. Investigators of the kind necessary are rare. They would have to be trained as few are being trained to-day in physiology, biochemistry, or pathology and this could not be accomplished immediately. They should acquire an excellent knowledge of chemistry, organic, physical and colloidal, more especially of biochemistry, microchemistry, cytology and the physical forces that obtain and operate in, and on the surface of, fluid and colloidal systems. They must have also a good working knowledge of bacteriology and of the technique employed in immunological research. Only thus qualified would they be able to undertake research on the intestinal mucosa with any prospect of obtaining noteworthy results.

It may be held that the training of such researchers is an impossibility because it appears to postulate that each of them shall be as highly qualified in several sciences as a specialist may be in one of them. It may be

admitted that the training necessary to conduct successfully research in this line must be of a more thorough kind than is undergone by those of to-day who are preparing for a career in research in any one of the medical sciences, but it is not more than can be exacted of a capable student free, but under special direction, to give attention for a few years to special branches of the several sciences, the knowledge of which is required. That there are few so trained now is no indication that none can be. The training of physiologists, biochemists and pathologists has hitherto been largely determined by chance conditions. There has been no guidance in it and too often it has been of an elementary or very limited kind. Many of those so prepared have in their own specialties done considerable service in the way of research, but the problems that remain demand of those who attack them more thorough and wider knowledge along different lines and in consequence the preliminary training must henceforth be extended to cover all the different sciences or branches of them, a knowledge of which is concerned in such research.

Such a training would qualify as well for important lines of research in pathology, bacteriology, immunology, physiology, and pharmacology, for the highly trained worker is to be henceforth as necessary in research in these fields as he is in biochemistry, otherwise the yield in results of more than a narrow significance will be very scanty. Only thus can the blight of spelunculism in the medical sciences, which is now in prospect, be prevented.

To produce these researchers is the duty which must be undertaken by those in command of the various departments of these sciences in our leading universities. They must exact of the young students under their charge a higher standard of attainment if research in the causation and treatment of disease is to achieve greatly in the coming generation. The demand for investigators of this type will be urgent and insistent in the next two or three decades and the failure to train them will reflect on those controlling the advanced teaching in these sciences.

With even half a score of such highly trained researchers working in this new field in the next few years results would be obtained some at least of which would compare in importance with those which marked the history of medicine in the last seven decades. We would then have a greatly increased, perhaps a profound knowledge of the functions of the organ which serves as the Great Portal of disease in the body. This knowledge would make possible new and highly rational lines of treatment of a large number of diseases, it would enable us to lessen very greatly their incidence and with its aid a regimen might be devised which would delay in the individual senescence, and even death, it may be, indefinitely.

The call for research in this line is urgent, for only through it is another great advance in medicine possible.

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BAIRD, THE MAN[1]

THE policy of the Smithsonian Institution under Professor Henry was to disperse as widely and freely as possible the worked-up material, and to enlist in the process of elaboration the aid and enthusiasm of every American naturalist, each in his special field.

To make this policy a success, such as it eventually became, required qualifications of no ordinary kind. Not only must the work of mediation be guided by the most advanced biological science of the time, but the individual intrusted with it must possess a spirit of impartial liberality, tempered by a sound discretion in business methods; a thorough knowledge and just estimate of men; an untiring patience to meet the peculiarities and caprices of the independent and often one-sided specialists whose cooperation was essential; a geniality to enlist the willing but unscientific collaborator; and an instant detection of humbug in every guise. Providentially for the future of natural science in this country, the need and the man met in the selection of Professor Baird. In qualifications for the work he stood preeminent—head and shoulders above any man of his time, and perhaps above all other scientific men of any time. He joined

[1] One of the addresses given at the meeting in commemoration of the one hundredth anniversary of the birth of Spencer Fullerton Baird, held in the U. S. National Museum on February 3, 1923.