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The Harveian Oration ON SOME EPOCHS IN MEDICAL RESEARCH

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BY

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Among his many and generous benefactions to the College, which long held a central place in his interest and his devotion, William Harvey, as you know, provided for the delivery of an annual Oration, to commemorate all the benefactors of the College, and "to Exhort the Fellows and Members of the College to search and study out the secrets of Nature by way of Experiment." Harvey thus formally bequeathed to us a great tradition, and took care that we should annually be reminded of its meaning and its claim. A Fellow of this College could receive no higher honour than to be called upon thus to commemorate William Harvey himself, as the greatest of our benefactors, and to obey his injunction; and I thank the President for having, in this year, accorded this honour and this duty to me.

We remember with pride that Harvey was lecturing on anatomy to this College during the twelve years which preceded and led up to the publication of his immortal book. It is on record that the transforming conception of the function of the heart, as a pump driving the blood "as it were in a circle," had already taken shape in his mind when his first course of these lectures began. Of the earlier course of development which had led him to the great discovery we know little beyond what he tells us in his book, and there in logical rather than historical order. We may feel certain, however, that the initial incentive to his inquiry was received during his studies in Padua. He tells us, indeed, that the discovery and description of the valves in the veins, by his teacher, Fabricius, acted as a direct stimulus; and there was other knowledge already then available, and waiting only for the central conception with which Harvey was to give it unity and simple meaning. The passage of blood through the lungs, from the right to the left side of the heart, had been clearly put forward in the book of Realduus Columbus, who may have seen it in the earlier tract of Servetus; Caesalpinus had apprehended the meaning of the heart valves, had argued that expansion of an artery with the pulse must be synchronous with the systole of the ventricle, and had even recognized that blood flows from the heart in the systemic arteries and to it in the veins. We might receive the impression that a simple step only was needed for the discovery that the blood has a continuous and double circulation. My predecessor of two years ago, Sir Thomas Lewis, suggested to us, indeed, that the discovery could not long have been delayed even had Harvey not made it, and that with the introduction of the microscope it could not have

remained concealed. I suspect that, in that opinion, too little influence may have been allowed to the blinding effect of age-long tradition and doctrine, to question which was still an impiety, and which still befogged the minds even of those among Harvey's predecessors who had most nearly arrived at the truth.

I feel no strong conviction that even Malpighi, when the microscope showed him the movement of blood in the capillary vessels, would have known the meaning of what he saw, if Harvey's experiments, presented in a masterly array of argument, had not swept away the doctrine of Galen before the capillaries could be seen. It is clear that Harvey's own teacher, Fabricius, though he saw the valves in the veins and even observed their obstructive effect when the blood was pressed towards the periphery, thought of them only as preventing a too rapid passage in what still seemed to him a natural direction of the flow. We know, too, that when, after years of experiment, demonstration, and argument before this College, Harvey gave his discovery to the world, it found a world unready to accept it, even in those circles which had the same access to knowledge of all that had been done before Harvey. The rare combination was needed of the scientific insight of genius with a character and a courage of the highest order, to enable Harvey to break through the mists of hallowed error and to walk boldly into the light of a new epoch.

I am in the fullest agreement, however, with Sir Thomas Lewis, and with others amongst my distinguished predecessors, in regarding as Harvey's greatest achievement, not that he made a discovery of such profound and permanent significance, but that he created and displayed for all time the method by which such discovery may be attained and made secure. In the dedication of his book *De Motu Cordis* he lays down the principle of his method—"not from books, but from dissections; not from the positions of philosophers, but from the fabric of nature"; and then, in the book itself, he gives us the supreme example of its application. Again and again in his writings he recurs to this new principle of research, and proclaims his creed with an apostolic fervour. Thus, in his less familiar book on the *Generation of Animals*: "It were disgraceful, therefore," he writes, "with this most spacious and admirable realm of nature before us, and where the reward ever exceeds the promise, did we take the reports of others upon trust, and go on coining crude problems out of these, and on them hanging knotty and captious and petty disputations."

To the men of his day Harvey was preaching a new doctrine, and proclaiming a new method of increasing and securing knowledge. In this, indeed, he moved with the advancing thought of his time, and of the great men with whom he had had contact; for Galileo was a professor in Padua when Harvey studied there, and Francis Bacon was Harvey's patient. To us it may seem now to be a platitude that science advances by experiment and by direct appeal to nature rather than by disputation about what others have observed or we ourselves have thought and believed. Yet, as Harvey seems to have foreseen, all of us, whether our effort to advance knowledge is made by the bedside or in the laboratory, need still to be reminded of this now familiar truth. The winning of real knowledge by experiment is slow and laborious, and exacts a stern discipline, while speculation offers an easy invitation to the ingenious mind. Theories we must have, to give system to our facts and direction to our experiments; and the temptation is ever present—to the eager experimenter even more, perhaps, than to the quiet observer—to press new facts into the framework of a plausible theory, and to distrust or to disparage those which refuse to fit easily into a fancied picture. We stand all in daily need of Harvey's exhortation, to approach Nature with clear vision and alert attention, so that we may receive her teaching with free and humble minds.

Harvey and Clinical Research

Sir Thomas Lewis has rightly claimed that Harvey, the physician, was the father not only of physiology, but of clinical science. In Harvey's work we may find, indeed, the true beginning of the whole fabric of experimental medicine, of which our own times have witnessed so prodigious a development. No man with Harvey's passion for inquiry and with his faculty for patient and precise observation could have failed to accumulate material of great interest and significance in his practice as a physician. It is sad to think how little of this remains on record for us. In *De Motu Cordis* he foresees that "every part of medicine, physiology, pathology, semeiotics, and therapeutics" can be illuminated by the new truth of the circulation which he has declared, and that a field for study has been opened so vast that his "whole life, perchance, would not suffice for its completion."

In his first argumentative pamphlet addressed to Riolan in defence of the circulation, published in 1649, he still speaks of his intention of publishing his "Medical Anatomy," which from his description of its contents might have made him the first of morbid anatomists. Elsewhere, in the essay on parturition, which is richer than most of his writings in clinical records, he refers to one case as introduced from his "Medical Observations." We shall never know how much of Harvey's records of clinical research may have been lost to us by the political robbery and destruction of his papers during the civil war. Scattered through his published work we find but a sample here and there, as in the clinical experiment introduced, with but little relevance indeed, into a chapter of *De Generatione*. There Harvey describes a young nobleman who, as a result of fractured ribs followed by suppuration, was left with a permanent open cavity in his side. At the bottom of this Harvey's exploring fingers encountered the rhythmically protruded apex of the heart, covered only by a layer of "fungous flesh"; so that he can now verify on man, and demonstrate to the King, the correspondence of the apex beat and of the pulse at the wrist with the systole of the ventricle, in conformity with what experiments on animals had shown him long before; but he can also add the new observation, which no animal experiment could have enabled him to make, that the normal heart is without any sense of touch.

The Genesis of the Royal Society

Harvey was a physician and approached his problems as such; but he was a man of his own period, or in advance of it, ranging in eager inquiry over the whole animal kingdom and using everywhere the simple methods of investigation which came within the scope of his training and his equipment. In *De Motu Cordis*, and again, more definitely, in *De Generatione*, we find reference to another of his intended publications, which should have dealt with the "Causes, Uses and Organs of Respiration." In the earlier and justly more famous book we find him still accepting the old doctrine that the function of air in the lungs is to mitigate the heat engendered in the heart; but by the later date he has had a glimpse of a truth which could not have been clearly seen with the knowledge of his time, and was not to be truly revealed till eleven years after his death. Discussing the need of the newly born infant for air, when once it has breathed, "it is," writes Harvey, "as if the heat were rather enkindled within the foetus than repressed by the influence of air." He makes the suggestion with doubt and hesitation, admitting that it deals with a question of the greatest difficulty. It is no more, indeed, than an inspired guess; but it brings Harvey into another association, to which he belongs as of right, and to which we may feel certain that he would have belonged in fact, had he lived but a few years later. As early as 1645, when Harvey was still attached as physician to Charles the First, a group of men had begun to meet for discussion of the new experimental philosophy, stimulated by the writings of Bacon and by the news of physical discovery coming from Italy. Harvey's *De Motu Cordis* must also have been known to them. Later they met in two groups, in London and Oxford; and the group meeting in London included Harvey's close friend, Dr. George Ent, while among those meeting in Oxford was another of his friends, Dr. George Bathurst of Trinity College. Bathurst had even shared in Harvey's embryological observations; for Aubrey tells us that Bathurst "had a hen to hatch eggs in his chamber, which they [Harvey and Bathurst] opened daily to see the progress and way of generation."

Harvey, as we know, retired in 1646 to his brother's house; and when, after the Restoration, the groups of experimental philosophers became, in 1662, incorporated as the Royal Society of London by a Charter from the new King, who desired "with a particular grace" to "encourage philosophical studies, especially those which by actual experiments attempt either to shape out a new philosophy or to perfect the old," Harvey had been dead for five years. But the spirit of the men who formed the new society was that of Harvey, and their activities were explicitly determined by the principle which he had so insistently advocated and of which his own work had given a shining example. His intimate friend, George Ent, who was his junior by twenty-six years, was a member of the Royal Society's first Council.

The Meaning of Respiration

The Royal Society, in its early years, may even be regarded as having, in a more particular sense, continued the work which Harvey had begun. Malpighi had seen the blood capillaries before the society was incorporated, but Leeuwenhoek's much fuller observations on them were made public in a letter to the Royal Society, as were so many of the discoveries which he so amazingly made with his simple microscopes. It was a group of the early Fellows in the society, including the great Robert Boyle, Robert Hooke the society's first curator of experiments, Richard Lower, and John Mayow, who made the first new stride forward in the science of physiology which Harvey had founded.

Harvey, as we have seen, had begun already in 1651 to doubt the doctrine that the function of respiration was to cool the blood, and to suspect that the air in the lungs might even "enkindle" the heat in the body. He himself could have carried the idea no further, but we may imagine how he would have rejoiced, if he could have been with Boyle and his associates, to watch its development in the light of their new discoveries. For, while Harvey's discovery of the circulation was based on the application of simple mechanical principles to precise anatomy, and on the experimental examination of the working of the heart and the blood vessels in living animals, the meaning of respiration could only be revealed by a knowledge of the chemistry which Boyle and his followers were newly creating for themselves. It had to be recognized that the function of the respiration involved a process of the same nature as combustion; and neither process could be understood until the discovery of oxygen had essentially been made. And this, in effect, was what Boyle, Hooke, and Mayow appear to have achieved, though the full significance of their discovery was long lost to sight. Lower, the only physician of the group, who also made important extensions of Harvey's work on the heart, added to the study of respiration the important discovery, which Harvey himself might have made, that it is exposure to the air in the lungs which changes the dark venous into the bright arterial blood; and Hooke gave a demonstration to the Royal Society which Harvey might well have made to the College of Physicians, when he showed that life was maintained with an open chest when air blown steadily into the trachea was allowed to escape from holes made in the surface of the lungs. But the essential function of the air, and in particular of what they called its "nitro-aerial spirit," in supporting a kind of slow combustion in the body could only be apprehended by these men who were studying air and its relation to combustion in general in the light of the new sciences of physics and chemistry, of which they were themselves among the founders.

Separation of Physiology from Clinical Medicine

It seems to me to have been inevitable that under these conditions the study of respiration, and with it the centre of progress in physiology, should for the time have passed out of the hands of the physicians and into those of investigators ranging the whole field of natural philosophy. The divorce from medicine, of physiology, especially in this country where Harvey had brought it to birth, not only became nearly complete—more nearly complete, I believe, than it can ever become again—but it persisted for more than a century. And this may have been partly due to the fact that progressive minds in medicine became preoccupied with the systematic task of describing and classifying diseases; but the long persistence, I believe, was due in greater measure to the failure of chemistry to adhere to the principle which Harvey had proclaimed. It seemed to turn its back on the truth which had so nearly emerged from the early experiments of the Royal Society, and followed Stahl, a learned chemist but a dangerous and speculative theorist, who led it, and much of physiology with it, into the fog of the phlogistic theory. For more than a century progress was retarded and truth was obscured as the results of experiments were fitted or distorted into this frame of error. It began to be shaken with Black's discovery of carbonic acid; but even Priestley, when he rediscovered oxygen, could only regard it as "dephlogisticated air," and respiration, with putrefaction and combustion, as a "phlogistic process." The experimental genius of Lavoisier was needed to sweep the cloud away, and to let the light shine, which had already been dawning more

than a century earlier, so that physiology and medicine could once more go forward with clear vision; and Lavoisier thus became the greatest physiologist as well as the greatest chemist of his day.

Of the leading actors in this rather sad interlude Stahl was a physician, as Harvey had been; but Stahl had forsaken Harvey's methods and relapsed into those which he condemned. I think it can properly be argued, however, that from Boyle to Lavoisier the basal discoveries required for the understanding of respiration had to be made by those who were laying the foundations of physics and chemistry, without any insistent preoccupation with the structure and functions of the human body, in health or in disease.

Conditions of Renewed Collaboration

Already, then, at the very beginning of experimental science, when, as we are apt to think with envy, the whole of the new experimental knowledge could still be assimilated by a single trained intelligence, some division of function began to show itself among the promoters of physiology, according to their way of approach, from the side of medical training or from that of the fundamental sciences. The division has inevitably grown deeper and the lines of cleavage ever more numerous. Such reproduction by fission is common to all the sciences, and is almost a condition of their growth; but, as with all but the lowest organisms, rejuvenescence and renewed vigour of development is dependent on fertilizing intercourse between units which have acquired a relative independence. There are those who see with fear and with regret the extent to which large and actively progressive sections of physiology, and even of pathology, have now loosened, or almost broken for a time, their connexion with the parent medicine, and formed closer alliance with physics, with chemistry, or with other branches of science. I believe the fears to be groundless, and I am sure that the regrets are vain. It would be deplorable, indeed, if there should be any failure in the succession of those who, coming to physiology from the side of medicine, devote themselves to increasing knowledge of the functions of the normal animal or human body as a whole, and make their contribution to the growth of medical knowledge in close co-operation, and even in functional interchange, with those whose centre of activity is in the wards. I see no reason to fear such failure: on the contrary, I think there are many signs of a growing recognition that both physiology and clinical medicine have still this duty and this need of a more immediate co-operation. But, as at the new birth of experimental science in the seventeenth century, so to-day, there are still domains opening to physiology which can only be explored by men, some of them trained in other disciplines than that of medicine, who must find their fruitful alliances in other fields of progressive scientific knowledge.

I have no qualm of doubt that the result, in the future as in the past, will be ultimately to infuse new life into medicine itself, and to promote its renewed advance, provided only that one condition be fulfilled. And I speak now in warm endorsement of the plea which Sir Thomas Lewis urged here with such conviction two years ago. The condition is that clinical medicine itself, in the hands of those who devote themselves to the increase of knowledge rather than its application, should remain, and should increasingly become, an experimental science, as Harvey saw it. As science grows, each of its followers must of necessity limit his expert knowledge and special technique to an ever-narrowing field; but the condition for stimulating and fertilizing contacts is not community of expert equipment, but a common priority of interest in the advancement of scientific knowledge and a common direct experience of the method by which that advance can be promoted. Harvey gave the first great example

of that method, and wished that we should be exhorted still to follow it. By obedience to that exhortation clinical medicine can remain in full communion with the other departments of experimental science, giving them its full co-operation and taking its full share in the general advance.

De Generatione Animalium

Harvey's *De Motu Cordis*, though its contents changed the face of medicine and opened a new epoch in science, is little more than a pamphlet in length. It may be supposed that, during the years in which he tested and confirmed his facts and interpretations, in lectures to his colleagues, Harvey was sifting his materials and clearing his mind, and was thus able to achieve this masterpiece of compact and orderly presentation by which the reader is carried with him to a triumphant and irresistible conclusion. Very different in this respect is the other book which he left us, *De Generatione Animalium*. This contains a wealth of careful and accurate observations in the two series dealing with the development of the chicken on the successive days of incubation, and with the appearance and development of the foetal deer on successive days after impregnation of the doe or the hind. Harvey's description of the earlier stages of embryogeny, and especially of placentation in the Cervidae, for the observation of which his royal master and patient allowed him to have unrivalled opportunity, might, one feels, gain a new interest, if edited and interpreted in the light of the comparative knowledge of these processes, which has been so greatly extended in recent years. Harvey, however, though he could, as always, observe faithfully and give a precise and vivid description of the things and the changes which he saw, lacked for their interpretation all that the microscope began to reveal so soon after his day. And though his description of the origin and development of the chick deals faithfully with the sometimes fantastic errors of his teacher Fabricius and others of his predecessors, it cannot stand with that which Malpighi was to send to the Royal Society some twenty-two years later, and which remained with remarkably little need of change for another two centuries.

This book, we may feel sure, is not in the form in which Harvey would himself have prepared it for publication. It is long and diffuse, and full of digressions which interrupt the progress of the argument. We know, indeed, from George Ent, that it would not have come to publication at all had his persuasion not prevailed over Harvey's reluctance. Thus we have here presented to us not the concise account of new observations and of conclusions directly to be drawn from them, which Harvey in the days of his mind's full vigour might have given us. We have, instead, together with records of brilliant observation, mostly set down long before, the long-drawn and wordy cogitations which had probably accumulated over many years; in particular we have, at each stage, long discussions as to the points on which Aristotle was already right, or as to those on which Fabricius can be shown to have gone astray.

Harvey was an ageing man, tired with the controversies in which he had been involved by *De Motu Cordis*, unwilling to publish more, and depressed by the thought that his work on reproduction was left permanently incomplete by the loss of his observations on insects. We may be very glad, however, that Ent overcame his scruples; for this book not only gives us further insight into Harvey's method, when he "addressed Nature herself," and "consulted his proper senses," but allows us also to see into what vague and fruitless speculations even he could wander, far beyond the facts available to his observation, when he forsook his own precepts. Harvey, with no microscope, could have no knowledge of spermatozoa, though it is curious that he should have

missed the follicles and corpora lutea of the mammalian ovary. Like his predecessors, he seems still to regard the ovary as a kind of female testis, but he rejects the view that the male and the female seed mingled in the uterus and there gave rise to the ovum. He knows, of course, that the hen can produce ova without fertilization by the male. Not finding the semen in the uterus after coitus, he denies that it penetrates so far. For him the semen exerts a mysterious fertilizing influence on the whole female organism, under the stimulus of which the uterus conceives a fertile ovum as the brain conceives an idea. He seems almost to allow himself to be misled by a metaphor; for, having seen waves of contraction passing over the uterus of a recently impregnated deer, he even wonders whether the brain would show such movement if we could watch it in the act of conception.

Some discussion has arisen with regard to Harvey's views, as indicated in various passages of this remarkable book, as to the possibility of spontaneous generation. It is, indeed, not easy to be certain as to his belief. On the title-page and early in the text he clearly states that "all animals are produced from ova." Later, in the same chapter, we find him stating: "Even the creatures that arise spontaneously are called automatic, not because they spring from putrefaction, but because they have their origin from accident, the spontaneous act of nature, and are equivocally engendered, as it is said, proceeding from parents unlike themselves." Here he seems to believe that, though the egg must always be the first stage, it may in some cases arise spontaneously or from parents of a different species. Later in the book, however, we find another passage, written perhaps at a later date, which, if taken by itself, would suggest that Harvey had reached a conclusion much further in advance of the knowledge of his day. "But on these points," he writes, "we shall say more when we show that many animals, especially insects, arise and are propagated from elements or seeds so small as to be invisible (like atoms flying in the air), scattered and dispersed here and there by the winds; and yet these animals are supposed to have arisen spontaneously, or from decomposition, because their ova are nowhere to be found." We are left wondering what we may have lost by the destruction of Harvey's records of his observations on the generation of insects; how they might have related his experiments to those of his contemporary, Francesco Redi; and what basis of observation they might have shown us for this remarkable passage. Harvey, we must remember, had no knowledge of any animals, or living things, too small for detection by his unaided vision. But this conception, even in relation to the living things which he knew, is much in advance of his age, and seems to link him in thought, across the coming centuries, with Spallanzani, and even with Pasteur and Tyndall.

Research of To-day

It is customary on this occasion to review some recent phases of active experimental development in the field of the medical sciences. We could pay no more fitting tribute to the memory of the founder of experimental medicine. The task of selecting items for such mention, and especially of associating them with the activities of particular men, will probably become year by year less easy. It becomes, indeed, ever more difficult for any investigator to scrutinize and to appraise even those published observations and experimental records which are related to his own special field of work. It begins to be the rule rather than the exception for some new and definite advance to be announced almost simultaneously from more than one laboratory, and often from more than one country. The position

may well look different in historical retrospect ; but to us who live amid this urgency of accumulation it must seem unlikely that a new epoch will ever again be opened by a Harvey or a Darwin, sifting and testing his evidence for patient decades, before he gives his theory to the world. Meanwhile we can try to distinguish tendencies and lines of more rapid development, promoted by the activities of many, which the future may recognize, perhaps, as epochs dating from our own time.

Ultramicroscopic Viruses

We date the beginning of the great epoch of bacteriology, dealing with organisms which the ordinary microscope revealed, from the work of Louis Pasteur and Robert Koch. Harvey had no knowledge of living beings below the limits of unaided visibility ; but he had only been dead twenty years when Leeuwenhoek, in one of his letters to the Royal Society, first described and even recognizably figured bacteria, as seen with his simple lenses. Two further centuries passed, however, before Koch was able to give the first completed identification of a bacillus as the specific cause of a disease. When, after a period of progressive triumph, bacteriology still failed to reveal the causes of some of the most familiar and deadly among the infectious diseases, there came in our own time the intensive study of a further order of living, infective agents, below the range of ordinary microscopical vision. It is unlikely that the future will identify any outstanding names with what may be the beginning of another epoch as important to medicine as that of bacteriology, concerned with the viruses still called "ultramicroscopic" or "filterable" ; though special microscopical methods have already rendered many of them visible, and all can be stopped, and even differentially separated, by filters of an adequate and accurately graded fineness. We associate the names of Ivanovski and of Beijerinck with early discoveries of such a virus as the cause of a plant disease, and those of Loeffler and Frosch in a similar sense with the virus causing the foot-and-mouth disease of cattle. But the general advance in this field, which did not begin until a quarter of a century later, has been on a wide front, and investigators in many laboratories of many lands are engaged in it. In rapid succession the agents responsible for infectious diseases which bacteriology had left as unsolved problems are being identified as belonging to this group, which but a few years ago seemed so inaccessible to further research.

My colleague C. H. Andrewes, in his Oliver-Sharpey Lectures of 1934, discussed before this College the many respects in which conformity to this type is shown by the infective agents which transmit certain tumours in experimental inoculation. One of the recent additions to the general list of diseases transmitted by viruses, and one which has excited interest in circles beyond that of medicine, is epidemic influenza, for the study of which by my colleagues Laidlaw, Andrewes, and Smith, the earlier work of Laidlaw and Dunkin on dog distemper had provided some ground of experience, and had brought to notice a suitable subject of experiment in the ferret. Further advance in the study of this, and of many other virus infections, is dependent not only on the provision of opportunity by Nature and by clinical medicine, but also on the development of new methods, which is in active progress in many laboratories. New principles of immunity, for which bacterial immunology has given at best imperfect analogies, are coming into view. The greatest difficulties of conception, however, are those connected with the dimensions of the infective units of the different members of a series showing so many points of uniformity in their general behaviour ; for these units are, at the upper end of the

scale, just visible by ordinary microscopy, with the appearance of very small cocci ; while, at the lower end, the units of such viruses as those of foot-and-mouth disease and poliomyelitis appear to be of comparable dimensions to the molecules of certain complex proteins. Here, if the data of measurement have been rightly interpreted, we seem, through a continuous series, to pass from definite though very minute organisms to a borderland between organization and colloidal dispersion where biology and physical chemistry must, perhaps, join hands in interpretation of a new order of vital phenomena. It may be noted that, quite recently, confirmation has been given of a previous claim to have obtained the virus of a plant disease in the form of protein crystals.

An Epoch of Chemistry in Medicine and Biology

If I were asked to name a prevailing tendency of the present time in medical, and indeed in a wider range of biological research, I should refer to the rapidly increasing dominance of chemical methods and chemical ideas. Within the memory of many of us organic chemistry had still but a small and precarious footing in this domain. To-day not only has biochemistry firmly established its claim to separate recognition and enrolled a growing army of investigators, but physiology, pathology, immunology, even embryology, are increasingly permeated by chemical ideas and chemical methods, which are yielding a surprising harvest of discovery in fields which till recently seemed beyond hope of such cultivation. I can permit myself to choose but a few examples.

Hormones

Research on the hormones is one of the directions in which, at the moment, chemistry can show a record of the most rapid advance and of unforeseen achievement. Twenty years ago, of the hormones then recognized adrenaline alone had been chemically identified and made by synthesis. Of the others, only thyroxine, on account of its great stability, seemed possibly accessible to structural chemistry ; though few could have expected that its structure would so soon be determined and its synthesis achieved. Secretin and the active constituents of the pituitary posterior lobe had been obtained in stable, though highly impure, solutions ; but for the other ductless glands, even the formation and secretion of hormones by them was a matter of inference rather than of direct demonstration. There seemed little likelihood that such hormones would ever be extracted, and the possibility of their isolation for chemical study seemed too remote for consideration. I believe that the successful preparation of insulin by Banting and Best had an influence far beyond that due to its immediate importance for medicine and for the understanding of carbohydrate metabolism, in that it aroused a new spirit of enterprise and optimism with regard to the possibility of obtaining other hormones which had seemed equally intangible. Insulin itself, being of protein nature, still presents a difficult problem to the structural chemist ; but it has been crystallized, and the interesting discovery has now been made (Scott) that the crystals are insulin in combination with metallic ions, normally those of zinc. Since insulin was first prepared methods have been found for extracting the hormone of the parathyroid glands and that of the suprarenal cortex, and it seems probable that the latter has now been obtained in a pure crystalline form in more than one centre.

A series of hormones from the gonads have, in the space of a few years, been isolated, identified, and in more than one case even made artificially by partial synthesis. These hormones determine secondary sexual characters and cycles of sexual activity ; they provide for implantation of the fertilized ovum and for the

development of the placenta and the active mammary gland. The generation which immediately followed Harvey saw the recognition of the ovarian follicles by De Graaf and the description of the spermatozoa by Leeuwenhoek; but even by the end of the nineteenth century such problems as the causes determining the development of accessory reproductive organs, and the nature and causation of the sexual cycles in different animals, had only been touched by the investigations of such lone pioneers as the late Walter Heape. And even till the second decade of the present century the work of Heape and of F. H. A. Marshall, whom the College to-day honours with its Baly medal, stood almost isolated in this country in its bold attack on what seemed the almost impenetrable tangle of sexual physiology. To-day we are already in clear sight of the ascription of each phase of the female sexual cycle to the action of a separate, chemically identified ovarian hormone; a hormone from a ripened ovarian follicle being responsible for the oestrus in which the uterus is prepared and sensitized for its function, while another, from the corpus luteum, in due course brings about the endometrial hypertrophy which provides for implantation of a fertilized ovum, or, failing it, terminates in the menstrual breakdown. There are yet many complexities to be unravelled; but these two ovarian hormones, as also a testicular hormone, are already substances of known chemical structure; and the luteal and male hormones have been artificially prepared from different inert sterols. In the case of the oestrogenic and of the male hormone, chemistry can now indicate, in each case, precise structure of a less active form excreted in the urine, and of a more active form obtained directly from the respective gonad, and presumably representing the true, effective hormone.

Behind this immediate control, moreover, and determining the development and successive phases of activity of the gonads themselves, is the anterior lobe of the pituitary body, with its complex of hormones still beyond the reach of structural chemistry but ever growing in apparent number with the progressive recognition of the multiple functions of this little gland. The breath-taking rapidity of experimental progress in this particular field may be inducing a too facile postulation of a new hormone to account for each new set of phenomena observed; but if observation is accurate and uncoloured by preconception, the true meaning will emerge in due course. In any case it is clear that the anterior pituitary lobe exerts some kind of hormonal control over the development and activities of practically every other endocrine organ, and therewith over almost every phase of growth and of metabolism. Even more mysterious in their meaning are the recent observations of Collip and his co-workers, showing that some of these hormones, on continued artificial injection, provoke in the recipient a resistance to their own actions, which its blood serum can then transmit to another animal.

We have noted that such of the sex hormones as have been isolated have points of common structure with the sterols, and can, in some cases, be prepared by chemical modifications from members of this group. This brings them into a curious relation with other substances, also structurally related to the sterols and possessing intense biological activities of widely different kinds—the anti-rachitic vitamin D, the cancer-producing constituents of tar, and the heart-stimulating glucosides of the digitalis group. There is evidence, again, that the organization of the cells of the early embryo into the characteristic foetal structures is effected by a chemical stimulus, and that the substance concerned also partakes of the molecular pattern common to the sterols, and to so many substances of intense but apparently unrelated activities.

Vitamins

In the group of the vitamins, which so recently might have been regarded as intangible traces of unstable and probably highly complicated substances, chemistry has found in recent years so successful an application that three vitamins have already been chemically isolated, including the vitamin D already mentioned, together with the natural precursor of another; and one has already been made by artificial synthesis. In some ways comparable to the action of the vitamins is that newly discovered for choline. The recent work of Best and his co-workers seems to show that the presence of choline, or of the allied betaine, in very small quantities in the diet, is in some way essential for the maintenance of a normal adjustment between the deposition of fat in the liver and its mobilization from that organ.

Other Applications of Chemical Methods and Ideas

Many other examples could be quoted of this increasingly prevalent and successful application of chemical methods to problems in all departments of medical science which even recently seemed to be beyond the reach of such attack. Thus, structural chemistry already has its place in immunology, and begins to reveal the nature of antigenic specificity. The late Dr. James Collier made reference here, last year, to the evidence which is being obtained by my colleagues and myself of the intervention of known chemical stimulants, and in particular acetylcholine, in the transmission of the effects of nervous impulses across the gap between the ending of a nerve fibre and an effector cell or another neurone, apparently throughout the peripheral nervous system. The chemical changes in a muscle accompanying its contraction seemed but a few years ago to be adequately comprised in a cycle of cleavage and resynthesis between carbohydrate and lactic acid. They are now revealed as a highly complicated chain of linked reactions, involving creatine, adenylic acid, and phosphoric acid, in addition to carbohydrates; and the complexity still grows. Sir Thomas Lewis and his co-workers, whose earlier experiments on the skin vessels of man brought evidence of the release of a chemical substance as the cause of their reactions to injury or irritation of the epidermis, thus making contact with our laboratory investigations on the occurrence and actions of histamine, now trace the pain caused by ischaemia of a muscle similarly to a chemical source.

Conclusion

If we allow ourselves to pause a little and to ponder, standing aloof for a moment from the insistent quest for new experimental data, with its growing multitude of eager followers, we may begin to ask whither it is leading us. We have only to look back to the beginning of this century to realize how all aspects of medicine—diagnosis, treatment, and prevention—have been involved in, and in some directions transformed by, the change which has been taking place. But are we really at the beginning of a new, great epoch, or merely involved in one of which the end can already be seen from afar? We can now speak familiarly of the chemical structure, and even the artificial synthesis, of hormones and vitamins of which the very existence was but recently a mere presumption from observed effects; but we have no basis even for speculation as to why a precise structure endows a substance with an effect so potent, and often so complex. We can identify in the body the types of cell which are specifically sensitive to acetylcholine, and we can find evidence that impulses, passing down nerve fibres which end in contact with these cells, excite or inhibit their activity by releasing that sub-

stance; we can even make an estimate of the number of molecules of acetylcholine released by a single impulse at a single ganglionic synapse; but we are no nearer to a conception of the meaning of a specific sensitiveness to a substance having that structure, or as to why its presence should augment the activity of one type of cell and inhibit that of another. The complex changes accompanying a muscular contraction are known in much greater detail than those of any other kind of functional metabolism; but there is yet no knowledge clearly relating these changes, or any part of them, to the mechanical event of the contraction.

Are we witnessing the early stages of a major advance in which a finer physical conception of the structure of living matter will ultimately give order and meaning

to the knowledge, now so rapidly accumulating, of the chemical changes which accompany vital activities, and of the chemical substances which so mysteriously condition or control their occurrence? Or will physiology find itself brought early to a halt in the line of its present advance, baffled by a complexity which its methods have revealed, but which they cannot yet begin to resolve? None of us, I think, can answer such questions. We must be content to follow patiently what clues we find, and to go forward in the faith of Harvey, that

"Nature herself is to be addressed; the paths she shows us are to be boldly trodden; for thus, and whilst we consult our proper senses, from lower advancing to higher levels, shall we penetrate at length into the heart of her mystery."

OESOPHAGEAL OBSTRUCTION*

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Obstruction of the oesophagus is one of the most distressing conditions by which any individual can be afflicted. It is true that it is only a symptom, but it is a symptom of such gravity that the problem of its relief entirely overshadows that of the removal of its underlying cause, and it is well that one should recognize that this is the case, since if relief is difficult cure is only too often impossible.

Of the many causes of obstruction we shall only deal with two—carcinoma and cardiospasm—since in frequency and in surgical interest they far exceed all other sources of dysphagia. Moreover, these two conditions may present a nice problem in diagnosis, their treatment is altogether different, and the results are in equal contrast.

Carcinoma of the Oesophagus

Carcinoma of the oesophagus is essentially a disease of elderly men, 90 per cent. of the male cases occurring after 50, and the maximum incidence lying between 65 and 70. In women it is much less common, one woman being affected for every three men, and in women it occurs more or less uniformly at any age after 40. Moreover, in men it is commonly a disease of the lower oesophagus, 80 per cent. of the cases occurring below the tracheal bifurcation, while in women it occurs in any situation, and a large proportion arise from post-cricoid growths.

The first symptom is almost invariably a steadily increasing dysphagia, although occasionally the onset is so abrupt as to give the impression that a foreign body has become impacted. At first there is difficulty in swallowing solid food, then liquids only pass down slowly, and, finally, food may be regurgitated in unaltered form. Inability to swallow saliva is a very serious inconvenience, and this is increased by the secretion of a stringy mucus, so that the oesophagus becomes filled by a tenacious froth, which further impedes swallowing. We regard this froth as a diagnostic sign of the first importance. At first it is white and odourless, but in the later stages it becomes blood-stained and foul, indicating a fungating and ulcerated growth, and producing a marked fetor.

At a still later stage involvement of the respiratory passages gives rise to an important group of secondary symptoms. The secretion of mucus is increased and is accompanied by a constant irritable cough. Finally, the growth perforates the trachea, or bronchus, or the lung itself, a fistula is formed, and a septic pneumonia develops. Yet the tolerance of the lung is remarkable, and we have

seen a stream of barium emulsion cascading through a fistula into the whole of the lower lobe with no apparent inconvenience to the patient, who ultimately coughed it up. Occasionally a large vessel is opened up, and haemorrhage quickly closes the scene.

The pathological features correspond to the advanced clinical picture, and indicate one of the most malignant and remorseless growths with which surgery ever has to deal. Operative exposures and post-mortem examinations agree in revealing growths which have invaded surrounding structures at an early stage, and it is rarely that a

Fig. 1.—The oesophagus in carcinoma and in cardiospasm.

growth will be found which even the most optimistic surgeon could regard as operable. One soon realizes that dysphagia is a later development, and that in the great majority of cases the growth is far advanced before it gives rise to this, the earliest indication of its presence.

In our opinion, then, the practical problem of carcinoma of the oesophagus is to enable the patient to swallow, and, fortunately, it is usually possible to achieve this by comparatively simple means. It is only rarely that the question of radical removal can even be raised, and, in spite of a few brilliant results, it seems to us most unlikely, from pathological considerations alone, that it can ever become a practical method. The depth at which

* A special clinical lecture given by request at the Melbourne Meeting of the British Medical Association, September, 1935.