ASPECTS AND PROBLEMS OF COMPARATIVE MEDICINE.*

NEED FOR CO-OPERATION BETWEEN SPECIALISTS IN HUMAN AND ANIMAL DISEASES.

BY

J. BASIL BUXTON, M.A., M.R.C.V.S.,
Professor of Animal Pathology, University of Cambridge.

IN presenting this small and, I fear, quite inadequate contribution for discussion by the Section of Comparative Medicine I feel that I cannot do better than quote the words of the late Sir Clifford Allbutt in another place and upon a similar occasion:

"If for years slowly and almost silently our work makes its way we must be content; our experience of the world teaches us to be content; but happily, now and then, after long hewing in the dark forest we break into light, we find ourselves almost suddenly upon a peak, our way open and bright before us, and our cause justified before men. The barriers of convention, which ought to be so slender and occasional, are of all the most inveterate and impregnable. Of such have been the barriers devised by mediaeval perversities which, to its grievous injury, have split up medicine into fractions. As physic was divorced from surgery and mind from body, so the diseases of animals and plants were separated from those of mankind."

In that last sentence Sir Clifford put the case of what is called comparative medicine in a few words. It has become separated from the mother science, medicine. For some reason or other, but probably through ignorance of what has gone before, comparative medicine has come to be regarded by many as something in the nature of an innovation—a breaking of new ground, an inculcation of new ideas, and perhaps even the initiation of a new branch of the science of medicine. But this is not so. During the past century there has been a steady, sure progress in the study of comparative medicine in all parts of the world, but especially in tropical and subtropical countries. The reason for this is that animal diseases, particularly those caused by protozoal parasites and invisible viruses, have been recognized as a serious economic menace, and therefore more or less adequate facilities have been provided for their investigation. The general progress which has been made in comparative medicine appears to have received but little notice; indeed, it is not an uncommon experience to find the comparative aspect of the many phases of the mother science, medicine, regarded as something quite new—in fact, almost unique, or at best a more or less comprehensive recital of some of the diseases of the lower animals which may affect man also.

This misconception of the real state of affairs is probably easily explained. The encyclopaedic tradition which had persisted from Aristotle through the Arab and mediaeval schools down to Herbert Spencer has ceased to exist. It is forced upon us in our own day that in a pursuit so many-sided as medicine, whether in its scientific or in its practical aspect, we have to submit more and more to that division of labour which has been a condition of advance in all other walks of life. It is now fully recognized that that division of labour which may appear to disintegrate the mother science of medicine really unites it. While pathology, for example, which is especially the science of medicine, was winning territory on one side from physiology, of which, in a sense, it is but an aspect, and on another was making progress of its own in the *post-mortem* room and museum of morbid anatomy, and was fusing these gains in the laboratory so as to claim for itself as a special branch of science, by virtue of peculiar concepts, its due place and provision—provision in the establishment of chairs and of special laboratories for its chemical and biological subdivisions—clinical medicine was illustrating the truth of the experience that teaching and research must go hand-in-hand, the one reinforcing the other.

* Report of a discussion at a joint meeting of the Sections of Comparative Medicine and Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Edinburgh, 1927. Principal O. C. Bradley presided.

Unfortunately, the necessary development of specialism has led to the almost inevitable sequel—watertighting. The many children, grandchildren, and great-grandchildren of the mother science seem in their self-centred interest to forget that they are but the offspring of the parent. That branch which deals with the comparative aspect of disease has been accused of drifting farther and farther away from the parent sciences during the past century, but the fault, if fault there is, is not peculiar to that one branch of medicine. Fortunately, the current of thought is now changing, and the attitude of splendid isolation is less evident. Any attempt to prescribe a dividing line between the scientific study of the diseases of the lower animals and those of man is inevitably doomed to failure, and this fact is, fortunately, becoming better realized. Pasteur shed light upon all aspects of medicine, but above all upon comparative medicine. The stimulus provided by the master has been directly responsible for the world-wide progress which has been made during the past century. But an attitude of complacency must find no response in the hearts or minds of those who are engaged in contributing to the study of comparative medicine.

A most cursory survey of some of its many problems which have been or are in the process of being investigated cannot fail to create in the minds of those who are responsible for the prosecution of those and similar problems an overwhelming sense of responsibility in relation to the general well-being of men and animals.

The field of comparative pathology perhaps affords one of the best examples of the essential nature of the demand for close co-operation between specialists in the study of human and animal diseases. This does not for one moment suggest that the importance of such co-operation rests with a discussion of those diseases which affect both men and animals, for, however important they may be, they are relatively few in number in comparison with the diseases which are peculiar to the individual species, but which, nevertheless, have a general importance in the study of disease processes as a whole. It is true that the fact that a causal organism is common to both man and the lower animals greatly facilitates the work of the histologist, bacteriologist, immunologist, and epidemiologist. Tuberculosis probably affords one of the best examples of this, for it is only by the study of the artificially produced disease in experimental animals, and in those which acquire the disease under natural conditions, that much of our knowledge has been gained, and it is certain that any advance in the prevention or cure of tuberculosis in man will depend upon observations made in animals. Again, recent advance in the investigation of tumours has resulted from work carried out in animals in which experimental tumours can be produced, and others in which a peculiar form of tumour occurs naturally. One cannot fail to be impressed by the possibilities which might result from a systematic study and comparison of the apparently closely related neoplasms which occur in man and in various of the lower animals.

Whatever may be the outcome of the controversy concerning the etiological identity of the variolas of man and the lower animals, the fact remains that the observations of Jenner were of fundamental importance in establishing at least a cross specificity in the case of cow-pox and small-pox, and it is equally certain that any progress which may be made in the study of cultural and immune processes will depend upon investigations into the variolas of the lower animals.

Unfortunately, from the experimental point of view, it not infrequently happens that the causal organism of a disease in man is either non-pathogenic for the lower animals or produces in them lesions which do not resemble the human form of the disease. In such instances it is impossible or at least difficult to study etiological and preventive measures which might be applied to the human subject. But it is sometimes possible to find that a disease peculiar to one animal species has a very definite resemblance to a disease which is peculiar to another species—as, for example, distemper in the dog and influenza in man. A comparative study of the two diseases may reveal many common features, and knowledge gained from the study of the one may prove to be of value in the study of the other.

As a result of investigations into a number of the diseases which are peculiar to certain of the lower animals and which are caused by invisible viruses—for example, rinderpest, foot-and-mouth disease, dog distemper, and others—several methods of inducing immunity to the disease have been devised, and it is reasonable to hope that, apart from the benefit which is likely to be conferred upon the natural host, further research may reveal the possibility of applying similar methods to diseases of a like nature which are peculiar to man.

The impetus which was given to the study of the anaerobic infection of wounds during the war has left its mark upon the bacteriology of several diseases of the lower animals, for while it was previously well known that many of the spore-bearing anaerobes which were found to play an important part in the pathological complex "gas gangrene" were commonly associated with certain well known and similar diseases in the lower animals, great progress was made in the etiological, cultural, and toxicogenic properties of these organisms as soon as their significance in the military economics of the time was realized. Under normal conditions, however, they are of little importance in pathological conditions in man as compared with the lower animals, and it is certain that, while the further study of these organisms may receive but little attention at the hands of the human pathologist under peace conditions, much further light will be shed upon their relationship to pathological changes in the lower animals, and upon specific toxigenic variations in members of the same family—as, for example, has been observed in the case of *B. botulinus*.

Quite recently nutritional diseases have occupied a prominent position in comparative medicine. Contributions to the study of various aspects of organic and inorganic deficiencies under experimental conditions have done much to increase our knowledge concerning the probability of certain diseases of animals which are kept under apparently normal conditions being due, in part at least, to a deficiency of one or more of the accessory factors. One of the most important questions which have arisen as a result of purely laboratory experiments is whether, and to what extent, the results obtained with one animal are applicable to the case of other animals and to man. We know from carefully conducted experiments that deprivation of vitamin B will cause paralysis in rats as well as in fowls and in pigeons, that the elimination of vitamin C from the diet of monkeys and guinea-pigs will result in the production of the characteristic haemorrhages and bone lesions of scurvy. Similarly, in rabbits fed with such limitations, while there is an absence of haemorrhages, the characteristic pathological changes can be observed in the bony tissues. White rats, on the other hand, are little affected by the absence of vitamin C in their diet, but fail to breed satisfactorily under such conditions.

The absence of vitamin A has been shown to result in ophthalmia (first described by McCollum in rats) in poultry and in infants, in defective calcification of bone in puppies, rats, poultry, and young children. And further, the action of light in correcting a deficiency has also been demonstrated. Thus there is a schedule involving several vitamins and a series of corresponding "deficiency diseases." But there is an even more important issue represented by the widespread disturbances of a non-specific nature which are perhaps produced by vitamin deficiencies—disturbances which have a direct effect upon the severity of other diseases, especially bacterial infections. It is not an uncommon experience, when investigating widespread outbreaks of disease, especially in pigs, to find that the organism which appears to be responsible is one which, under ordinary conditions, is regarded as of little pathogenic significance, yet it appears, for some inexplicable reason, to have developed an exalted virulence. The ration usually appears to be well balanced and all that could be required, yet slight alterations in the constituents—especially in the direction of increasing the amount of vitamin C—frequently lead to a marked improvement in the general condition of the animals.

Another and equally important aspect of deficiency diseases has been investigated at the Rowatt Research Institute, Aberdeen.

Research into some problems of mineral metabolism has already been productive of information of considerable economic and scientific value. Investigations have shown that natural pastures with a low content of minerals have a low nutritive value for sheep, and that not only is the percentage of progeny from these animals low, but the mortality is often high. These and similar observations are proving of considerable importance, not only in the case of animals in this country, but particularly in some of the colonies. Of no less importance are the experiments which have been carried out to show that artificial ultra-violet irradiation is capable of increasing the absorption and retention of calcium and phosphorus in young pigs. Again, the importance of colostrum in the early life of young animals, apart from its purely medicinal effect, is well known, especially in regard to the temporary protection which it is believed to afford against bacterial invasions. It has hitherto been generally assumed that this protective power is to a large extent due to the high antibody content of the material, but it has been found that the iodine content is also very high, and in view of the claim which has been made that the feeding of potassium iodide to mares is a preventive of joint-ill in their progeny, the possibility that iodine may play an important part in the protection of the newborn animal against disease is worthy of serious attention.

Investigations into the physiology of reproduction which have been carried out at the Animal Nutrition Institute at Cambridge have added considerably to our knowledge of these normal processes, and open up a large field for investigation into the abnormal conditions which are so commonly met with in the lower animals and in the human subject.

Marshall's contribution to the study of the conditions governing parturition cannot fail to stimulate further research in this direction, especially since, as he points out, although certain factors are common, the conditions, though generally constant within a particular species, vary widely in different species, and even among closely related forms as well as in individuals.

There are, of course, many other aspects of deficiency diseases which are of great interest from the comparative point of view; these no doubt will be dealt with by others who are to take part in the discussion.

Experimental comparative physiology has not received the attention which it deserves, especially in the case of the lower animals. It has not infrequently happened that an attempt has been made to study the abnormal rather than the normal, often with results which, if capable of any sort of interpretation, have been entirely misleading. There is an enormous scope for research which will lead to a better understanding of many of the normal functions of and processes in the animal body. Such a study should progress with, and not independently of, that of the abnormal.

Another aspect of comparative medicine is that which has been termed tropical veterinary medicine. Here, again, the relationship between the diseases of man and of the lower animals is of the most intimate character. We may take as a fair example of this those which have been grouped under the heading of trypanosomiasis. The classification of the causal parasites is now recognized to be far more difficult than was originally supposed. The morphological and biological characters are in themselves insufficient for this purpose, whereas the mode of development in the fly is of fundamental significance. As a result of more recent work, it has been found to be necessary to recognize different strains of the same species of organism, but the process of evolution of such strains yet remains to be determined, as also do the changes in virulence and in morphology which result from passage. There is also a call for improvement in the methods of diagnosis of infection with the various species of trypanosome. Watson showed the value of the complement fixation test in the diagnosis of dourine, while E. M. Robinson in South Africa has confirmed this, and in addition has shown that animals infected with *T. brucei* react to the test when *T. equiperdum* antigen is employed; while the serum of those affected with *T. congolense* or *T. vivax* does not usually react in the presence of that antigen, but the former may do so with the specific antigen. The many

chemotherapeutic problems relating to these diseases which yet remain to be solved can only be satisfactorily carried out in animals, and preferably in those which are naturally the subjects of the disease.

It would not be possible to close even such a sketchy and incomplete contribution as this undoubtedly is without some reference to the vast field of experimental comparative medicine represented by artificially acquired immunity. Since the time of Pasteur it has been recognized that experimentation with animals offers the only satisfactory method of determining the relative merits and demerits of the various methods of inducing a state of specific resistance to disease, not only on account of the relatively small value of the subject, but because large numbers of animals can be employed for the purpose, and, moreover, they can be maintained under natural conditions. Observations upon active immunization of horses against tetanus by means of toxin-antitoxin mixtures rendered a similar procedure possible in soldiers during the great war. Parallel experiments which have since been carried out with the modified toxins of other spore-bearing anaerobes have enabled us to confer an active immunity against a variety of diseases of sheep. The use of bacterial suspensions, consisting of living virulent or avirulent organisms, or of those which have been killed by a variety of means, has enabled us to control a number of serious epizootic and enzootic diseases of the lower animals. Experimentation along these lines is constantly progressing, and cannot fail to be of economic importance from the agricultural point of view as well as from that of mankind.

For an opening address on the subject of some aspects and problems of comparative medicine I realize that my remarks may be considered too narrow in their scope. But the aspects and the problems are so many, while the range of each is so extensive, that it is impossible in the present circumstances to do more than mention a few, and that in a very cursory manner. Those who are to follow me will no doubt make good the deficiencies which are so very obvious in my remarks.

DISCUSSION.

Dr. ANDREW BALFOUR (London) thought that one aspect of comparative medicine which would appeal to all was the essential unity of human and veterinary medicine; one problem well worthy of discussion was how this unity might, at least in some degree, be realized. This was probably better exemplified in the field of tropical medicine than elsewhere. As comparatively recent examples he cited Pfeiffer's work on rabbit coccidiosis and its relation to human malaria, and Theobald Smith's work on the tick in Texas fever; since those days human and veterinary medicine had advanced hand-in-hand in the tropics. He recalled Sir Patrick Manson's announcement about Ross's work twenty-nine years previously: his talk was largely about sparrows, crows, and mosquitos. After referring to trypanosomiasis, leishmaniasis, myiasis, ankylostomiasis, rabies, and bubonic plague, he passed to the consideration of the experimental method, and the necessity of enlisting the aid of the veterinarian when employing animals in medical research. He maintained that no laboratory engaged in work on tropical medicine was properly and fully equipped unless veterinary medicine was represented, and he mentioned in this connexion the system in operation at the London School of Hygiene and Tropical Medicine, with special reference to the value of its association with the Zoological Gardens. He regretted the tendency to cleavage in tropical medicine, and pleaded for combination under a research roof, while routine and clinical work could be carried out in laboratories attached to the respective hospitals. He hoped that the new Research Committee of the Colonial Office would accomplish something in this direction.

Dr. W. H. ANDREWS (Ministry of Agriculture) remarked that the problem of the filterable viruses furnished an excellent example of the essential unity of pathology and of medicine on the scientific side, although in the practical applications there were fundamental differences. The filterable viruses and the diseases they caused were now

attracting much attention in medical and veterinary circles in both temperate and tropical regions. They constituted the most urgent problem of the present day, and the slow progress in their study suggested that new conceptions and a new technique were needed. Veterinary pathology had already furnished much that was valuable for the human pathologist, but more could be expected from research work organized on less restricted lines than in the past. The veterinary pathologist should have the great advantage of working with experimental animals of the species naturally affected by a disease, but this advantage had usually been sacrificed to financial considerations. It was known how narrowly specific might be the relations between host and parasite, and it should be recognized that guinea-pig and rabbit studies, however convenient and valuable (as long as their limitations were realized), could be entirely misleading when applied to animals of other species. Moreover, the reaction to a poisonous substance could also be narrowly specific; for example, *Matricaria nigellaefolia*, apparently harmless to all other domestic animals, induced a fatal intoxication in bovines. Recent work on chronic plant intoxications in animals had great interest for the human pathologist, but much of it was not at all widely known. In connexion with mineral deficiencies, the outstanding work of Theiler and Green at Pretoria deserved special mention. They had succeeded in establishing the etiology of the bovine disease lamsiekte, but their work had had results far exceeding that of controlling lamsiekte, although that disease had formerly caused very heavy losses indeed (see JOURNAL, September 24th, p. 559). With respect to vitamin deficiency, it seemed very doubtful whether any of the domestic herbivora, under ordinary conditions, ever suffered severely from this cause, but specific avitaminoses occurred naturally in pigs and dogs, and probably in fowls also. Dr. Andrews felt confident that, however important such work might prove later to the human pathologist, the study of the diseases of the domestic animals would be best and most successfully pursued for its own sake, although human and veterinary pathologists should naturally co-operate and exchange information as freely as possible.

Mr. G. W. DUNKIN, M.R.C.V.S. (Mill Hill), stated that the vast fields awaiting investigation and the numerous diseases common to man and the lower animals lent ample support to the suggestion of closer and more intimate co-operation between human and veterinary medicine. The Section of Comparative Medicine of the Royal Society of Medicine was flourishing, its membership was still increasing, and its meetings continued to be of the greatest interest to both branches of medicine. Nevertheless, the facilities already existing for co-operation between the two branches were inadequate for the necessary development of this team work. He stated that, with Dr. Laidlaw, he had been engaged for the past four years in the investigation of dog distemper. Although this disease was specific for the dog and ferret and did not affect human beings, there were, nevertheless, many phases which closely resembled other conditions in man, and it was hoped that the results of this research would tend to the better understanding of certain human ailments. Another disease (John's disease of cattle) which was receiving his attention did not, so far as he knew, possess any analogy in human medicine, but it was evident that the results would not be without interest to human bacteriologists and pathologists. It was good to know that diseases of lower animals and their investigation could be of assistance in this way, but he submitted that they were matters for team work, in order that a better understanding of the baffling pathological conditions could be obtained.

Mr. JAMES McALLAN, M.R.C.V.S. (Aberdeen), suggested that the public health aspect of comparative medicine was by no means the least important, and he emphasized the necessity for a very close co-operation between the two professions. In the field of meat inspection, while the medical officer of health would always have the last word on the fitness or unfitness of meat for human food, it seemed necessary that the veterinary surgeon should co-operate, since he had the better knowledge of animals in health and disease. In Scotland this co-operation had

been fully established. In the production of milk from the hygienic standpoint the veterinary surgeon had a big field, which was further extended by the control of milk-spread tuberculosis. From personal experience the speaker could emphasize the value of co-operation between the two professions in the investigation of food poisoning outbreaks spread by milk. On two occasions he had been able to trace milk-borne outbreaks of food poisoning to the infection of cows with Gaertner's bacillus. It was on such occasions that he appreciated clearly the value which would accrue to medical practitioners from making full use of the veterinary surgeons on the public health staff.

Professor D. C. MATHESON, F.R.C.V.S. (Edinburgh), said that for the past fourteen years he had acted as veterinary pathologist to the Scottish Zoological Society. As a matter of routine every herbivorous animal was examined microscopically for anthrax before the necropsy, while in the case of carnivores the possibility of glanders had always to be considered. These animals frequently suffered from "menagerie pneumonia," and cultures from the lesions on potato often yielded an early growth of *B. coli* with a superficial resemblance to the glanders bacillus. A recent survey of the records showed that among the animals, excluding birds, tuberculosis occurred in 4.7 per cent.; in birds the incidence was 7.1 per cent. Among domestic fowls examined in the laboratory for the same period the incidence was 10.3 per cent. Impaction of the intestine by vegetable fibre, twisted by the peristaltic movements into a veritable rope, was not uncommon among the larger cursorial birds such as the rhea. Impaction of some portion of the intestine, usually with vegetable fibre, was responsible for death in 10.1 per cent. of the fowls examined during a period of thirteen years. Neoplasms were rare among the animals in the gardens.

Dr. J. G. NASMYTH (Edinburgh) emphasized the necessity for investigations into the origin of epidemic and epizootic diseases, and into the periodicity of epidemic diseases that were now controlled and no longer seriously menaced the health of the community. It was also desirable to know why, in the case of "carriers," the causal organism was able to lie dormant for long, and yet, when a suitable host offered, assert its pathogenic power. He also emphasized the importance of co-operative and co-ordinated investigations by the biologist and the biochemist in association with the pathologist and the clinician. He believed that it would be to the benefit of comparative medicine if the Veterinary College were affiliated to the University, and the Animal Diseases Research Association were similarly linked to the Veterinary College in Edinburgh. Such affiliations he was convinced would lead to co-ordination in research, and the consequent benefit of mankind by the discovery of the fundamentally common conditions which caused human and animal diseases.

Dr. F. A. E. CREW (Edinburgh) remarked that so much stress had been laid upon the need for greater co-operation between the medical and the veterinary professions that he could not refrain from asking whether they knew of what and to whom they spoke. Co-operation in research must always be between individuals. He who sought help eagerly found it, if such help was available, in the communion of minds. Those engaged in research were conscious of shortcomings, and the true searcher after knowledge recognized no monopolies: the knowledge of one was available for all. Co-operation was not based on professional organization but on common humility, for no professional organization could override personal antagonism. Far too much was made of the distinction between the medical practitioner and the veterinarian; it was the problem and technique of investigation, and not the material, that really united men. Medicine was too disposed to content itself with study of the causes and the effects of disharmony. They ought to recognize clearly that the control of the future evolution of man and of animals lay in the hands of man himself, and that they must help to decide what man should become and how animals might evolve, setting themselves the task of guiding man and beasts in the lines of their destinies. It was for them to think of the eradication of those hindrances,

and the securing of that degree of material and physical comfort which was a prerequisite of spiritual development. Their great contribution would concern the breeding of man and animals naturally highly resistant and immune to diseases which threatened their existence.

Professor E. E. GLYNN (Liverpool University) believed in the advantage to human medicine of the study of comparative pathology. His own pathological museum contained many specimens of animal disease which he used in teaching medical students.

Mr. W. A. POOL, M.R.C.V.S. (Edinburgh), stated that there was obviously agreement as to the necessity of greater co-ordination between the two branches of medicine. Investigation of factors concerning animals, both in health and in disease, had in the past been almost limited to consideration of those which were of immediate economic importance or of use in throwing light on problems affecting mankind. As a result they lacked essential knowledge of many things which should at the present day be well understood. Outstanding examples could be quoted in the field of physiology, such as digestion in ruminants and ungulates, and also in connexion with pharmacology, as, for example, the action of certain alkaloids on the autonomic nervous system of equines. This was due to research into animal problems being limited to those of urgency and by methods of applied science; there had not been enough investigation for the sheer desire for knowledge. Prominent examples of problems in which greater co-ordination of the two branches of medicine was necessary were the study of the streptococci of the bovine udder and the effect of nutrition on resistance to disease. The policy adopted in distributing public funds to finance investigations into problems of animal disease tended to foster this policy of attending only to questions of immediate practical importance. Subsidized laboratories were expected to justify their existence in the eyes of the public as they proceeded. This entailed the early and frequent issue of reports, and, to ensure the certainty of having something to report, investigators felt bound to limit their sphere of actions largely to problems which, while being of immediate practical importance, were also likely to produce definite results.

Lieut.-Colonel E. D. W. GREIG (Edinburgh) strongly favoured close co-operation between medical and veterinary pathologists. From his experiences in the East, he gave several instances of the importance of this combination, including the investigation and treatment of rabies and the study of tuberculosis in India. He was convinced that the recent appointment by the Colonial Office of a Medical Research Committee would help materially in co-ordinating research in the two branches overseas.

Dr. T. W. M. CAMERON (London) drew attention to the fact that no one had yet attempted to formulate a definition of "comparative medicine." There was a tendency to regard it as veterinary medicine, or, more frequently, as veterinary diseases in relation to man. He thought that it was neither of these. Defining medicine as the arts and sciences of preventing or removing disease, then comparative medicine was the comparison of the arts and sciences of medicine as relating to man, the domestic animals, the non-domestic animals, and even plants. Of these, probably the most important was comparative pathology. If physiology were regarded as a study of the normal reactions of an organism to normal stimuli, then pathology was, for the most part, the study of the normal reactions to abnormal stimuli; neoplasms and similar conditions of unknown etiology might well prove to be abnormal reactions to either normal or abnormal stimuli. Comparative pathology, then, would be the comparison of the host reactions of various hosts to the same abnormal stimulus. Its aim would be to elucidate the fundamental laws underlying the methods by which the body became diseased and by which it fought against disease. Thus, while including both human and veterinary pathology, it was coextensive with neither. It was, moreover, different from bacteriology or parasitology, sciences concerned with causes only, while pathology was concerned with effects.

The speaker then illustrated this concept of comparative pathology by describing the reactions of a variety of hosts to the tubercle bacillus and to the hydatid cyst. Comparative pathology was a natural sequel to comparative physiology, and was a subject as capable of standing by itself in the university curriculum as any of the other divisions of science. If comparative pathology and the other ancillary medical sciences were regarded in this way, then obviously "comparative medicine" should really be called "medicine," and what was generally regarded as "medicine" should be rechristened "human medicine." Man was only the most domesticated of the mammals, and in these neo-Darwinian days there was no reason why an unqualified name should be given to the purely human sciences, while grouping those concerned with the other domestic animals under the cumbersome title of "veterinary medicine." He could not accept the statement that human medicine was the mother of veterinary medicine; she was merely the elder sister who for so many years had acted as foster mother. The true parent was only now being recognized as comparative medicine, and it was to her that both the sisters, the elder as well as the younger, must look for the fundamental principles which were necessary before any real understanding of disease was possible.

TREATMENT OF TOXIC GOITRE.

I.—THE PLACE OF SURGERY IN THE TREATMENT OF TOXIC GOITRE.*

BY

T. P. DUNHILL, C.M.G., M.D.,
Assistant Director of Surgery, St. Bartholomew's Hospital.

I HAVE chosen the term "toxic goitre" because I believed it would be the wish of this meeting to discuss the treatment of the types of goitre which cause ill-health through disordered secretion.

Clinical Terms.—There will not be universal agreement on terms. That is because, although most goitres fall into well recognized clinical types, many minor differences occur. Any two types are linked up by intermediate cases.

Pathologically also many cases fall into definite groups, but practically every type of histopathological condition may be found somewhere in a diseased thyroid gland. There is a tendency to multiply types and subdivisions, but I have come to feel that the different types are related; I believe pathological evidence is tending to bear this out, and that it will ultimately be found that the differences are only in degree. Take exophthalmic goitre, with which, in its orthodox manifestations, we are familiar. Clinically we recognize a primary and a secondary type of this, but we may not be able to define where the primary type ends and the secondary type begins. Histopathologically also we recognize a primary and a secondary type, but some cases which histopathologically are undoubtedly secondary would clinically have been considered primary. There may be great differences between examples of the secondary type, and some of them approach very closely to what we are in the habit of calling toxic adenoma.

As we examine the symptoms we see progressive differences which conform to the differing appearances in the gland. A case of primary Graves's disease has well defined features; an early secondary case is scarcely distinguishable from it. In the late secondary case exophthalmos has become less and may scarcely exist, the nervous phenomena are less obvious, but the cardiac changes are more manifest, auricular fibrillation occurring frequently. Working backwards from the other end of the chain, a toxic adenoma is well recognized, but sometimes there is more than one adenoma, and, farther still, a gland may be bilaterally symmetrical, the nodules in it scarcely recognizable as adenomata, capable of being shelled out (as is a single

adenoma), the whole gland approaching the type of late secondary exophthalmic goitre.

Etiological Factors.—What are the etiological factors which cause these differing appearances? Why does the gland of a primary type appear to be a solid cellular organ? and why does the gland of an early secondary type often look like a simple colloid goitre, and a late secondary look like an old fibrotic goitre with some adenomatous masses in it? We presume that a thyroid gland is normal until puberty approaches. We can agree that there is at that time of life a tremendous but quite normal call on the gland, for we believe that the thyroid secretion determines the energy output of every cell in the body. This extra demand is successfully met in the majority of people, but in order to meet it there is some temporary hypertrophy—possibly not enough to be noticed, possibly just noticeable, and, if so, rightly called a physiological hypertrophy. Involution should occur after the demand is successfully met, but if the demand is not successfully met involution does not occur, and a colloid goitre remains. These processes occur in meeting a physiological stimulus.

Now let us take notice of a pathological stimulus. We need to keep in mind two hypotheses: first, that the stimulus which causes exophthalmic goitre is situated without the gland, and secondly, that this stimulus induces changes in the gland, which in turn cause the manifestations which we recognize as the signs and symptoms of the disease. Some may not agree with this statement; if so, the argument must come later. The stimuli which induce these changes may be active from beginning to end of the disease. There is a time early in the disease when these stimuli urge the gland intensely, and there comes a time when they lessen in their intensity, but when the results induced by them in the thyroid gland dominate the clinical picture. This has to be borne in mind in deciding the treatment to be followed at the different stages of the disease. Possibly the stimulus is a sub-conscious sex disturbance; possibly some psychic trauma; possibly focal sepsis is added; and possibly there is deficiency of available iodine. If that pathological stimulus is directed on to a normal gland the whole gland is able to respond; it changes into a solid cellular organ—the gland of a primary exophthalmic goitre—and we have the signs and symptoms of a primary exophthalmic goitre. If that pathological stimulus is directed on to a gland in which post-puberty involution has not occurred—in other words, on to an early colloid goitre—the whole gland cannot respond, cannot change into a solid cellular organ, for most of it already consists of enlarged colloid vesicles, and the only parts of it which can respond to the abnormal stimulation are the cellular areas between the vesicles. These scattered areas become solid, opaque, whitish, and similar to the whole gland in the primary exophthalmic case. Both these types are quite definitely exophthalmic goitre. Both have prominent eyes, a hot skin, tremor, a rapid pulse, and both follow a similar course. Why separate them? Only because the appearance of the gland, macroscopically as well as microscopically, is so different, and because the second type links up with the late secondary type, and may help to explain the late toxic nodular goitre.

Now take late secondary Graves's disease. In this we have a woman who has had a goitre for many years. We know from our own experiences that the colloid goitre of puberty about the third decade loses its smooth surface and becomes nodular. It is still symmetrical, but fibrous strands develop, constricting and isolating areas throughout the gland. In the woman who "has had a goitre all her life" this change has been progressing until the fifth decade. How does this condition become toxic? The same factors which affect a younger woman with a normal gland, giving her frank exophthalmic goitre, or another woman with an early colloid goitre, giving her early secondary Graves's disease, can be brought into action at any time during a woman's life, but if these factors are directed on to an old fibrotic goitre the areas in it which are able to respond are small and scattered. We cannot at this stage expect the whole gland to respond as the normal gland did which produced exophthalmic goitre, or even as the early colloid goitre responded; and so we get a

* Read in opening a discussion in the Section of Surgery at the Annual Meeting of the British Medical Association, Edinburgh, 1927.