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The Third

John Stewart Memorial Lecture*

W. E. GALLIE, M.D.

Toronto, Ontario

THE establishing of memorial lectureships in honour of our distinguished colleagues of the past is a very beautiful Anglo-Saxon custom. It is one of many evidences that even in these materialistic days we still love to think that we are members of universities, that we belong to a learned profession, and that tradition is something that we hold most dear. It was with the greatest pride, therefore, that I learned that you have thought me worthy to represent you in doing honour to the great man whose name this lecture bears.

I am, indeed, delighted to deliver a John Stewart Memorial Lecture because I knew him so well and admired him so much. I venture to think, too, that I am one of the last of your John Stewart lecturers who will have known him in his prime and who will really know what sort of man he was. The years have slipped around since 1917 when he was Colonel Stewart, Chief Consulting Surgeon of the Canadian Army and I was a major, in charge of a division of surgery in one of our Canadian hospitals. I recall the pleasure his inspections gave us and the thrilling stories he told us of the days when modern surgery was on the make in Edinburgh and in King's College in London. I remember one night as we sat around the messroom fire with Fred Tees, Fred MacKay, John Fraser and Murray MacLaren, all of whom many of you must have known, he told the story of his coming to London with Lister. It seems he had been reading Sir Walter Scott's novel, "The Heart of Midlothian" and was so impressed by the exploit of Jeannie Deans in walking from Edinburgh to London that he decided to do likewise; and he actually did it, in faster time than Jeannie and at considerably less cost. I have often pictured those long legs stepping off the miles on the Great North Road coming up to London Town to help in the greatest mission that surgery has ever known. That was just 73 years ago, before most of us were born.

Stewart, as you know, came up to London with Lister when he became Professor of Surgery at King's College Hospital. In that way he became one of that band of devoted disciples of whom I have known Hector Cameron, Rickman Godlee, Watson Cheyne, and Frederick Grasett, who in the teeth of indifference, disbelief and actual violent opposition carried to every corner of the earth the gospel that is the very basis of modern surgery. You will find the story in Stewart's Lister Oration.

I am inclined to think that nothing is more important in the life of the young surgeon than close contact with great inspiring personalities. Each of us, as we look back, can recall the influence of some such personality, particularly during that impressionable period between twenty-five and thirty years of age. In my own case, amidst the crowds of distinguished men I have

*Read before the Dalhousie University Faculty of Medicine Annual Refresher Course, November 7th, 1951.

known, there stand out the faces of George Peters and Clarence Starr in Toronto and Royal Whitman and William Coley in New York. Time and again, when I have been in doubt or difficulty, I have heard their voices speaking to me across the years, just as they used to do when I was their house surgeon, helping me to a good decision. It has always seemed to me, therefore, that it should be the aim of all who aspire to be surgeons, and particularly to be teachers of surgery, to seek out those inspiring personalities as did Lister when he sought out Syme and as Stewart did when he sought out Lister. Much can be learned from study and from books but it is nothing compared with what can be learned from close association with those who wrote the books.

This brings me to a review of the place that surgery should occupy in the undergraduate curriculum and later to a discussion of the education of the modern surgeon and of the modern surgical specialist.

When Stewart was a young man the whole undergraduate course in Medicine occupied three years. The course in Surgery consisted of systematic lectures, clinical lectures and bedside clinics. Each student served for a number of weeks on the wards as a dresser. At graduation he either took his university degree or a diploma from one of the Royal Colleges. If he wished to go further and establish himself as a surgeon he joined coaching classes and prepared himself for the stiff primary examination in Anatomy and Physiology and later the final examination in Surgery and Pathology for the Fellowship in one of the Royal Colleges. I can remember with what awe we viewed the occasional academic adventurer who returned to Canada, triumphant after years of sweating over those Fellowship examinations in London.

As the years have gone by, however, great changes have occurred in Surgery. As a result of the studies of Lister and the group about him enormous expansion has taken place so that now the surgeon approaches with confidence such formerly prohibited fields as the articulations, the thoracic cavity, the brain and, more recently, the heart. Not only pathological processes such as tumours of the lung and diseases of the stomach and intestines have yielded to surgical treatment but disturbed physiological processes such as hyperinsulinism and the vagaries of the internal secretions of the suprarenal and pituitary glands have attracted the attention of the experimental surgeon. With this great expansion has come an enormous increase in our knowledge of the biochemical changes involved in operations, and of the proper pre-operative and postoperative treatment of our patients.

This expansion of the field has become so great that it is no longer possible for an undergraduate student to acquire more than a hazy outline of the principles involved. Indeed, during the past fifteen years, there has been a general abandonment of the effort to teach the Practice of Surgery to undergraduates. Instead the teaching has concentrated on history taking, physical examination and diagnosis. Indeed, it is simply the teaching of general medicine on the patients found in the surgical wards, with actual practice limited to general principles and to minor pathological conditions and traumas of family practice. Gradually the teaching of the practice of surgery has become a postgraduate responsibility, with students selected from graduates who have had a year or two rotating internship or a term as a doctor's assistant. The degree of Doctor of Medicine or Master of Surgery which we so proudly received on graduation day has ceased to have significance in surgery.

This brings me to the subject which I wish particularly to discuss with you today. I would not have you think that I have come down to your university by the sea to tell you how you should run your own affairs. It is rather that I may discuss with you, who stand so high in all matters of education, those thoughts that exceptional opportunities over fifty years have gradually developed in me. I am hoping that in presenting these thoughts to you I may ever have the spirit of John Stewart beside me, as he so often was in the past, to help me crystalize those that are good and to discard those that are bad.

All of us who practise surgery and who are over forty years of age know that a tremendous change has taken place in surgical education. When we were young most of us went into general practice and then, by dint of hard work, constant reading, occasional trips abroad, but mostly by trial and error, gradually acquired the skill and confidence that led to our recognition as surgeons. Most of the distinguished surgeons of our land learned their craft in just that way. But those days are gone forever. It just isn't possible for the modern graduate student to acquire proficiency in general surgery in less than three or four years of intensive training, and if he inclines towards one of the surgical specialties, a longer time still. I remember that on my paper in surgery for the M.B. degree at Toronto, the last of four questions was "discuss the pathology involved and the treatment indicated in a penetrating wound of the eyeball" and on my surgery paper at the Royal College of Surgeons of England one quarter of the paper read as follows:—Discuss the signs, symptoms, pathology and treatment of acute and chronic glaucoma! Imagine letting a recent graduate deal with a punctured eyeball, or a fellow of the Royal College of Surgeons of England touch a case of glaucoma!

Well, since those days the ophthalmologists and the otolaryngologists have cut adrift. Then came gynaecology and soon after it urology. And now a whole swarm of surgical specialties have been recognized and are occupying special sub-departments in our hospitals and schools. I remember that twenty-five years ago when I was surgeon-in-chief of the Hospital for Sick Children in Toronto I was general surgeon, neurosurgeon, orthopaedic surgeon and plastic surgeon. That was before the days of the thoracic surgeon, the vascular surgeon and that odd combination of surgeon and radiologist known as the cancer surgeon. That, of course, sounds ridiculous except that in those days the so-called general surgeon did not venture far afield in the specialties. Now, however, he who would be a surgical specialist, such, for instance as the neurosurgeon, must not only be prepared to master general surgery but he must spend long years of training in the specialty. About six years intensive study and training must be faced before a candidate can try his examinations for certification or fellowship and he is 31 or 32 years of age before he can enter practice. But, on the other hand, it is well worth while. When I compare the quality of the work I did in neurosurgery at the Hospital for Sick Children with that done nowadays, let us say by Dr. Stevenson in your own school, I must simply hang my head. And the same is true of all the other specialties.

There has, of course, been a good deal of resistance to the dividing up of general surgery into specialties and I must confess that I was one of those who resisted. It was not that I didn't think that specialization led to better sur-

gery for there simply isn't any sense in maintaining that the skills and techniques of the neurosurgeon, the orthopaedic surgeon, the thoracic surgeon and so on can be mastered by surgeons whose principal anatomical field is the abdomen. My objection arose rather from the difficulty I found, as Professor of Surgery, in fitting these surgical specialties and specialists into the programme of undergraduate teaching. I found that the minute a group of patients such as the urological patients were separated from the general surgical group and placed under the care of a staff of specialists, there at once arose a demand for segregation of the patients in special wards in order that the special type of nursing and the special equipment required might be provided. Indeed, from the patient's standpoint and from that of the surgeons it was much better so. But the minute this segregation occurred, both patients and staff seemed to be lost to the undergraduate student. Not only are the patients moved away to some remote part of the building but the staff cease to be interested in teaching anything except their specialty. It is difficult to get anything out of them except a few didactic or clinical lectures.

This is a problem for which I have not yet found a complete solution. I think, however, that it will be found in an increase in the principle of the full time teaching staff. If the professor is at the same time surgeon-in-chief of the hospital and, in principle, responsible for the surgical care of all the public ward patients and for the activities of all the surgical staff and house staff on the public wards, he can plan the programme of teaching and see that it is carried out. In the specialties he can get help from the juniors and he can leave to the *prima donnas* the responsibility for the graduate teaching. I keep wondering, however, if we are not on the verge of developing a new specialty, viz., that of the teacher of surgical principles. He would be a young man who devotes the greater part of his time to teaching and hospital work, who is learned in applied anatomy, applied physiology and applied pathology and who has the priceless gift of the teacher in that he can make his students interested in the problem before them. He can show his students that the premedical sciences which they have studied so long have some relationship to the sick and injured. I don't think that undergraduate students should be taught their physical examination and diagnosis through the specialist's speculum, cystoscope or sigmoidoscope. What they need is guidance in associating symptoms with normal and abnormal anatomy, disturbed physiology and broad pathological principles, in order that they may be able to make a provisional diagnosis and to understand the significance of disease. This is the kind of young man that every professor is looking for and to whom preference should be given when the hospital and departmental appointments are being made. Such men, of course, will have to be paid a reasonable stipend as they are much too valuable to be allowed to drift too early into competitive practice.

One word on the full time professorships. In my opinion these have come to stay. A glance at what is happening in the United States, in Great Britain, and, indeed, right here in Canada, will show that the idea is spreading and that many of the best known schools have adopted the principle in some form. It simply isn't possible for the Head of the Department of Surgery to direct a first class teaching programme for undergraduates, to keep control and to

give leadership in the management of the surgical services of the hospital and to run a graduate school for surgeons, and at the same time compete seriously in private practice. Nowadays his time is taken up almost completely with planning and directing the under-graduate curriculum, with conducting ward rounds, with directing the training of the surgical residents, with giving leadership and assistance in clinical and experimental research and with the countless duties associated with a modern hospital service. By the time he does all these things well and goes through the daily list of consultations on the medical and other wards there is no time left for much private practice. The truth is that when he accepts the post of Professor and Surgeon-in-Chief he has said farewell to the old type of life and has dedicated himself, usually with considerable financial sacrifice, to a life of service to his hospital and school. Whether he is successful or not will be indicated by the place his students achieve in the community, by the quality of his hospital staff and by the amount of competition for intern and resident appointments under his direction.

The teaching of surgery has, in brief, become a graduate affair. Only a few years ago when a young man graduated with his M.D. degree he ceased to be a responsibility of his school and with or without a rotating internship he went into general practice. Now, however, the signs of the times are indicated in the setting up of the Specialty Boards and the College of Surgeons in the United States and of the Royal College in Canada. These not only conduct searching examination of the candidates but they outline the programme of apprenticeship each candidate shall undertake and they determine in what institutions this training shall be carried out.

In order that a hospital may receive approval of its graduate training programme it must demonstrate that the appointments it is offering are not primarily for the benefit of the hospital or of its staff (what the Americans call an exploitation programme) but that they are part and parcel of a post-graduate training programme, sponsored by the medical school and leading to a graduate degree or to certification by one of the National Boards. The course, therefore, provides advanced training in anatomy, physiology, and pathology in addition to residencies in the various branches of general surgery. The ideal course is one in which the resident, during the three or four years he spends in hospital is gradually stepped up from responsibility to responsibility until in his final year he is doing a large part of the operative work of the public wards. This, of course, is a great change from what obtained when we were young. To carry the plan out successfully there must be a complete rebirth in the ideas of the staff. They must no longer hold the view that their chief function, when they receive their appointment, is to do the surgery of the hospital well, but rather that it is to teach others to do it well. This means that the good teacher must be prepared to spend hours assisting his intern or superintending his work so that step by step he is guided to a place where he is qualified to stand alone. The schools and hospitals where such programmes are being carried out are the ones where the best graduates are clamoring for admission to the course.

It has been suggested that with programmes of graduate teaching such as this established in all our medical schools we may soon provide more surgeons than our country can absorb. There are two strong arguments that, in my

opinion, refute this completely. First, all our Canadian people, whether they live in Halifax or in Northern Cape Breton or in Toronto or Moosonee deserve first class medical care. With the development of the ambulance aeroplane and the establishment of outpost hospitals there is no reason in the world why our people should not have adequate care, if we in the medical schools see to it that properly trained physicians and surgeons are provided. Second, those of us who are doing the surgery of the country now must sooner or later retire and our places must be taken by others. These, if I read the signs of the times rightly, will all require certification by the Royal College before they will be acceptable for appointment to the surgical staffs of our hospitals. This is certainly what is happening in Great Britain and in the United States and there are definite signs of it here. Then where is this great band of surgeons to be trained? The answer is that each Canadian medical school must take its share in postgraduate teaching. Each must be prepared to pilot its graduates through the apprenticeship demanded by the Boards and to prepare them for the certificating examinations. This is made doubly necessary by the steadily increasing difficulty that Canadians are meeting in getting satisfactory apprenticeships abroad. Great Britain, France and the United States have graduate training programmes of their own which do not provide for Canadians. Indeed, right here in Canada, now that fellowship in the Royal College and certification have become so important, it is becoming increasingly difficult for graduates of one school to get intern appointments in another.

These arguments seem to be conclusive that if we are to provide our country with properly qualified surgeons, or indeed, specialists of any kind, each school must share in the programme of graduate education.

If the programme I have outlined is carried out it should not be necessary for the ordinary candidate to spend much time abroad. Occasional visits to well-known clinics are probably all that are required. For those, however, who are destined for teaching appointments something more is necessary if we are to compete successfully with the American and British schools. To keep the staffs of our teaching hospitals abreast of the constantly changing and expanding field of surgery we must keep sending out scouts who will bring back to us who stay at home the new knowledge that is being acquired in the various medical centres all over the world. Thus we should send a young man to Stockholm to get first hand news of the advances in radiotherapy and of the use of the new isotopes. We must have one of our best young men trained in the new surgery of the blood vessels and the heart. Again we must be kept in touch with all the changes that are occurring in neuro and thoracic surgery. In brief we must be kept aware, in a practical way, of all that is new in the world if we are to do our share in maintaining the high quality of Canadian institutions.

As Dean and Professor of Surgery the problem of financing this most necessary postgraduate education of the young members of our staff was a constant nightmare to me. There never seemed to be any difficulty in obtaining funds for fundamental research in the medical sciences or for the investigation of specific pathological problems such as cancer or rheumatism. But how to get funds to improve the education of the clinical teachers seemed to be an insoluble problem. On several occasions we lost most promising

young graduates simply because we couldn't finance them adequately and we have had the humiliating experience of watching them rise to glory in the service of some other university.

This unhappy situation, however, has been met by the generosity of Mr. R. S. McLaughlin of Oshawa, formerly President of General Motors of Canada, who has established a foundation, the income from which will ultimately be available to provide "travelling fellowships" for graduates of Canadian Medical Schools who have completed their graduate training and have been selected for clinical appointments in their own or some other Canadian Medical School. These funds will also provide for a number of clinical research fellowships which will be available for the support of these travelling fellows for the first year after they return.

The significance of this princely gift will be appreciated when it is realized that it will ultimately be available to the clinical departments of all our Canadian schools and that it should make it possible for us to attract to the service of our schools and teaching hospitals the best young people we have, quite irrespective of their private financial position. I venture to predict that twenty-five years hence a large percentage of the clinical chairs across Canada will be occupied by former McLaughlin Fellows.

Reference to research fellowships suggests to me that you might like to discuss the place of research in a clinical teaching programme. Is it possible for a clinical department, nowadays, to engage in such epoch making studies as those in which John Stewart aided Lister? And is it desirable that such studies should form part of the activities of a clinical department. My answer, as you might suspect, is a forcible "yes". I am fully aware that effective research in the medical sciences, such as physiology and biochemistry requires long preparation and probably full time devotion to it. Is it worth while, therefore, to encourage research in clinical departments, where the chief interest is not in the technique of effective scientific research, but is in the treatment of the sick?

This is one of the chief problems that are being worked out in most medical schools to-day. Gradually there have developed in these schools departments of physiology, biochemistry and pathology, all with separate full time staffs, almost all of whom are aiming at careers in their own particular medical science. Their chief interests are in problems of their own which have arisen in their laboratory work, often of first-rate fundamental importance but often with little obvious relation to the sick in the hospital wards. This segregation of the medical sciences has gone on so far that in some centres it has seemed that they were becoming walled off completely, to the practical exclusion of the clinicians.

As cooperation between the scientists and the clinicians lessened, some of the wealthier clinical departments began to build up physiological and pathological subdepartments of their own in the hope that in that way they could carry out effective research. Examples of this can be seen at Billings Hospital in Chicago, at Columbia in New York and at the University of Minnesota. This plan, however, is expensive and, indeed, wasteful, and, in our opinion should be avoided if at all possible. If the clinicians would recognize that the

medical sciences have really become great sciences which henceforth will be independent, and if the scientists would remember that their reason for existence in a medical school is to help in the treatment of the sick, some scheme of cooperation could be evolved which would be of advantage to all.

A study of this division of the interests of the scientific and clinical departments has led me to the conclusion that there are two chief troubles at the root of it. First, the rapid growth of the sciences has forced the workers to spend more and more time in their laboratories and has led to less and less contact with the wards and the clinicians. Indeed, in recent years many of the scientific workers have been doctors of philosophy without any knowledge whatever of the problems of medicine. The result has been a rise of individualism and a decline in team play. A second cause for lack of cooperation has been a financial one. When the annual budget of a scientific department is presented it naturally is designed to cover the essential expenses of that department and does not include funds for the maintenance of members of other departments or for the financing of researches other than their own. The result is that when clinical departments come asking for help in solving problems on the wards they are not received with enthusiasm. I recall that on several occasions the Department of Surgery was told that while the scientific department would be glad to give a research worker space in the laboratory and would aid with advice if he wished it, it could not assume responsibility for the research or for the expenses it involved.

The answer to all this is that some scheme must be discovered which will keep the scientific and the clinical departments in closer touch with one another and which will relieve the scientific departments of the financial burden of studies that are not of primary interest to them.

Such a scheme has been initiated in Toronto and there is reason to hope that it will be satisfactory. It is based on the almost self evident conclusion that effective research on clinical problems should be conducted by clinicians, and that the cost will be borne by the clinical department involved. Of these requisites the financial is the more easily solved. It simply means increasing the budget of the clinical departments by a sufficient amount to cover the expense. The problem of training the clinician to conduct research, however, is not so easy. But steps in that direction can be made by making it a *sine qua non* that candidates for clinical appointments shall have had a year or more of training in one of the scientific laboratories. During this period he will have become familiar with its routine and have learned a great deal of its technique. Even if he never pursues scientific research further, this year will have given him a scientific attitude of mind, a respect for accuracy and an understanding of statistical evidence that is so necessary in a good clinician. More important, however, is the fact that in his earlier years as a clinician he is reasonably well qualified to take his clinical problems to a laboratory with which he is familiar and where he will probably receive a welcome. Thus the clinician is conducting scientific research and the scientific department is being kept in contact, in a most practical way, with the greatest collection of unsolved scientific problems that can be found anywhere.

Having in mind that modern research in the medical sciences requires considerable technical skill and that the busy surgeon often hasn't the time or

the training to acquire it, the question is sometimes asked as to how much emphasis should be placed on research in clinical departments. It is suggested that we attend to our business of treating the sick and leave the exploration of new fields to those specially trained for it. This, however, is a short sighted view which leads to complete stagnation. It has been my observation that young surgeons who devote themselves solely to learning what other people have said or done, seldom get very far. Whereas those who in their earlier years have applied themselves to solving some problem of their own may not only make an actual contribution to knowledge but, even if they do not, they are quite likely to become authorities on the subject which they have studied. It is common knowledge that investigative work done between the ages of 20 and 30 often colors a surgeon's whole career and raises him from the ordinary to the extraordinary.

So it seems clear that in addition to the routine treatment of the sick it is the duty of clinical departments to carry out investigation. This need not be complicated or difficult at first but if any clues are uncovered it may lead on to all sorts of thrilling results.

Young men sometimes say to their seniors "I can't think of anything I can do". The answer is "Look around you for there are unsolved problems in every bed." Take a simple fracture, for instance, such as a Pott's fracture-dislocation of the ankle. How many surgeons really know what are the results of treatment? Perhaps this could be learned by an intelligent study of fifty or a hundred old cases. I venture to suggest that if this were carried out vigorously by one of these young men he would find himself a recognized authority on fractures of every kind. Then he might go further and investigate why some of these fractures unite quickly and others do not, and why some fail to unite at all. This may lead him to the animal laboratory where ideas suggested in the ward might be investigated further. And finally he may be led on to consideration of the fundamental chemical principles that govern healing, and of the possibility of influencing those principles by artificial means. What a wonderful thing it would be if we could definitely hurry the healing of a fracture!

But under any circumstances and by whatever means seem best suited to local conditions we must keep the fires of clinical research burning, for a department in which interest in research has died is dead indeed. It is not necessary to have great laboratories or complicated machines although these are often useful. What is really needed is the enquiring mind, an interest in what is new and strange and an enthusiasm for pursuing investigation further. Even the lowly "follow up" if conducted thoughtfully is often productive of better ideas and is well worth while.

The years have rolled around since John Stewart and Alexander Primrose and I first discussed the possibilities of a course of graduate training in surgery. I can recall how interested they were and how full of helpful suggestions. I know they would have been delighted if they could have attended last month the annual meeting of the graduates of this course when fifty of them with their wives came from all over Canada and the United States to spend two days in their Alma Mater.

Briefly, the course they have followed is this:—After a year of rotating internship and, in some cases, a spell of general practice, they were enrolled in a four year graduate course designed for the training of a surgeon. The minimum curriculum for men who will be going out to do general surgery includes six months medicine, six months pathology, one year as Assistant Resident in general surgery in the Toronto General, the Western, St. Michaels or Sunnybrook Hospitals, and six months in three of the surgical specialties, neurosurgery, orthopaedic surgery, urology, paediatric surgery, and a combination of three months gynaecology and three months urology. During this period he is given instruction for one evening a week during the school session in anatomy and once a week he attends a lecture in applied physiology or biochemistry. He is prepared therefore for the examination for the diploma of the Royal College.

Of the ten or twelve who graduate from this minimal course five are selected each year for appointment as Resident Surgeons in one of the associated hospitals. This, of course, is the prize that every man in the course strives for, for under this system the Resident does more public ward surgery than any other member of the staff. As Resident he is not only the senior of the house staff but he is also a member of the Attending Staff and so is free to operate without the presence of one of the staff surgeons. It is from this group that permanent staff appointments in general surgery are made.

If the student decides during his course that he would prefer a surgical specialty he replaces the residency in general surgery with a residency or fellowship in the specialty. Thus if a student during his four years of general training has been attracted by neurosurgery or urology he can return to the specialty of his choice (if he is welcome there) for a year or more of intensive training. After that I am hoping that for those who have been chosen for academic appointments the McLaughlin Travelling Fellowship will provide the finishing touch.

A unique feature of the plan I have outlined is that it provides a broad training which in its final stages leads either to a career in general surgery or to a career in one of the recognized surgical specialties. It makes sure that the general surgeon has a fair working knowledge of specialties and, just as important, it makes sure that the specialist has had a practical training in the broad underlying principles of surgery. In these two regards the plan is infinitely better than those in vogue in many postgraduate schools where there is no cooperation between the general surgeons and the specialists and none of the reciprocity in training that is so essential to each. To make such a plan work, however, it is essential that the Professor of Surgery shall be Surgeon-in-Chief of the hospital and director of the activities of both general surgery and the specialties. The creation of separate autonomous departments such as Urology and Neurosurgery would ruin the programme.

A discussion of the training of the surgeon would not be complete without some reference to the years that follow the completion of the graduate training course. To assume that such a course as I have outlined will carry a surgeon through his lifetime would be the greatest mistake for the changes taking place, year by year, are enormous. Constant reading is, of course, essential, but if

you resemble me you will find that reading is not enough. It has been my experience that no matter how carefully you read books and papers on new work you always find it different when you visit the laboratory or clinic of the writer. The up-to-date surgeon is one who takes the trouble to get a close-up view of the new work and to talk it over with its author. And if you take my advice you will do this before you are forty for after that it is pretty difficult to learn anything. In my own case the most valuable postgraduate education has come from membership in small interurban travel clubs which have met once or twice a year at the hospital and school of one of the members. These clubs should not have more than thirty members and the cities should not be more than twelve hours apart. In my case the cities were Toronto, Buffalo, Montreal, New York, Philadelphia, Pittsburg and Baltimore. A yearly visit to one of these cities did more for the members of the Club than all the reading and all the memberships in the large societies put together for it let us see the new work in the making and gave us ample opportunity for intimate discussion.

I never think of Nova Scotia without feelings of the profoundest gratitude for the spontaneous and generous way in which its citizens contributed to the rescue of my close friend, Dr. D. E. Robertson, at the time of the Moose River disaster. During those hectic ten days I met the Premier, Mr. Angus MacDonald, the Minister of Mines, Mr. Michael Dwyer, the Minister of Health, Dr. Davis, Mr. Messervey, the Provincial Engineer, Professor H. K. MacDonald and the underground engineers and draegermen. The impression I got was that like John Stewart the Bluenoses were a race of men.

The University of Toronto, which owes so much to Dalhousie and to the Provinces by the sea sends you her hearty greetings.

Streptomycin and Pas in the Treatment of Tuberculosis*

S. J. SHANE, M.D.,

Medical Superintendent, Point Edward Hospital, Sydney, N. S.

INTRODUCTION

IT would, of course, be impossible to deal adequately with a subject so broad and so widely explored as this, in the short period of time allotted to me. An attempt to even touch on all aspects of this huge field would result in merely scratching the surface of each facet. May I, therefore, request your permission to confine my remarks almost entirely to a discussion of recent advances in this field, with an occasional look into the future, to foresee what changes may be expected in the chemotherapeutic and antibiotic management of tuberculosis within the next year or so. May I, in addition, request your permission to confine my remarks to those aspects of treatment with streptomycin and PAS, with which I have had personal experience, and of which I can therefore speak with at least a small degree of authority.

I am sure that we all recollect that, when streptomycin was found to have tuberculostatic activity, *in vitro* and *in vivo*, it was generally felt that this antibiotic would become a complete cure-all for tuberculosis. This, as we know, has not been the case, and the best anyone can now say for streptomycin is that it plays an adjunctive, rather than a definitive role in the treatment of most forms of tuberculosis. This change in the status of streptomycin in the treatment of tuberculosis has been brought about by the existence of two limiting factors, which are inherent in the drug itself and in its relationship to the human body, and these two limiting factors must, of necessity, obtrude themselves into any detailed discussion of the effects of streptomycin in chronic diseases such as tuberculosis. These factors are (a) toxicity, (b) resistance.

The subject of streptomycin toxicity can be dismissed in a few words. With the exception of a few minor irritative phenomena, mostly depending on hypersensitivity, the toxicity of streptomycin is confined to the 8th cranial nerve, primarily the vestibular division, but also, with moderate frequency, the cochlear division. Involvement of the vestibular division is so common that, using streptomycin, 65% of patients receiving two gms. daily for 120 days will show evidence of marked impairment of vestibular function.¹ Involvement of the cochlear division, with resulting deafness, is less common, but occurs with a sufficient degree of frequency to be considered with a great deal of respect.

The result of numerous discussions and published articles by various authorities on the subject of toxicity has led to the establishment of a more or less standard dosage of streptomycin in tuberculosis, namely 1gm. daily. There is a certain amount of rather poorly documented evidence that 0.5

*Read before the Nova Scotia Sanatorium Refresher Course for Health Officers, Kentville, N. S., January 11-13-1951.

gm. daily will produce a clinical result equivalent to that produced by 1 gm. This smaller dosage, however, has not obtained wide currency, and, in most institutions, a daily dosage of 1 gm. is considered standard practice.

With the advent of dihydrostreptomycin it was, for a time, considered that larger doses, up to 2.0 gms. daily could be given with impunity, since it was believed that this modification is less toxic to the 8th nerve than is streptomycin. With this in mind, we carried out a study at Point Edward Hospital, in which twenty-one patients were treated with dihydrostreptomycin, 2.0 gms. daily, for ninety days.² Frequent caloric tests on these subjects revealed no impairment of vestibular function throughout the course of treatment, indicating that dihydrostreptomycin is apparently less toxic to the vestibular division of the 8th nerve than is streptomycin. However, two of our patients became deaf, at or near the end of the course, without any warning in the form of impaired vestibular activity, and we, with others, were forced to conclude that dihydrostreptomycin in 2.0 gm. daily doses for long periods is equally as toxic as streptomycin, albiet in a different manner. There is also a certain amount of rather indefinite evidence that dihydrostreptomycin gram for gram, has slightly less tuberculostatic potency than streptomycin. The opinion is therefore becoming rather general, that dihydrostreptomycin has little to recommend it over streptomycin in the antibiotic therapy of tuberculosis.

The fact that tubercle bacilli, exposed to streptomycin for long periods of time, develop the property of resistance to this antibiotic, has been known since the earliest work on these agents, and has led to some rather interesting theories as to the mechanism of this phenomenon. At least two theories are at present current, which purport to explain the development of such resistance. One concept deals with the occurrence of mutations in a population of tubercle bacilli, all members of which are originally sensitive to the action of streptomycin and the propagation of these mutants by a process of "survival of the fittest." The other theory which competes for acceptance, postulates the presence, in any population of tubercle bacilli, of a certain number of organisms which are initially resistant to the antibiotic, and are propagated in the same fashion. At present the second concept probably has more adherents than the first, but this academic problem is by no means as yet settled. It is, however, known that the development of resistance to streptomycin depends on the length of treatment rather than the individual daily dosage of the drug, and out of this knowledge have grown two schedules of treatment with streptomycin alone, which are believed to be instrumental in delaying the emergence of resistant strains of tubercle bacilli. It is now generally agreed that the optimum schedule of dosage consists of 1.0 gm. daily for forty-two days, and it has been shown that, on this schedule, the occurrence of resistance is negligible. Another dosage-schedule which seems likely to become extremely popular, however, consists in what is known as "intermittent therapy," in which 1.0 gm. is given every other day or three times weekly; and the theoretical concept on which this dosage-schedule is based has recently been ingeniously explained by Garrod.³ He found that, in a growth of the H37rV strain, exposed to a high concentration of streptomycin, there resulted the death of a large proportion of organisms within two or three hours, resulting in a marked lowering of the viable count at the end of that period.

Applying these findings to a comparable situation within the human body, he reasoned that a sufficiently high serum and tissue level of streptomycin in the body would bring about the death of most of the accessible tubercle bacilli within a few hours. It would then require two or three days before the inaccessible organisms, incarcerated in foci of caseation and necrosis, could multiply sufficiently to invade the tissues again. By that time, of course, a further dose of streptomycin would have been given, resulting in the death of an overwhelming proportion of these invading organisms. If we add to this theoretical concept the statement, made above, that it is the length of unbroken treatment which determines the emergence of resistance, the theoretical value of intermittent treatment is readily understood. Although treatment schedules of this type have not as yet become highly popular, it is quite probable that they will find their rightful place in the future.

One of the most important advances made within recent years in the antimicrobial therapy of tuberculosis has been the discovery that combined therapy, that is the addition of a chemotherapeutic agent such as PAS, to streptomycin regimens, will prevent or delay the emergence of strains resistant to streptomycin. Although this is generally conceded to be the case, it must be noted that very little work offering definitive proof on this point has actually appeared in the literature. For this reason we, at Point Edward Hospital, have been engaged in a study of this nature for almost two years, using combined therapy with streptomycin and PAS, and determining the presence or absence of streptomycin-resistance *in vitro* by repeated tests. The studies are not as yet complete, and the figures will probably be too small for statistical analysis, but we are satisfied that the addition of PAS in 5.0 gm. daily doses to streptomycin regimens will, in most cases, delay almost indefinitely the emergence of resistant strains.

With these limitations, namely toxicity and resistance, which are now known to be inherent in streptomycin therapy, we are now in a position to discuss the results which may be expected in pulmonary tuberculosis from this antibiotic.

In the first place, it should be obvious that, since streptomycin produces its effect by direct bacteriostatic and possibly bactericidal action on the tubercle bacillus, it cannot be expected that this antibiotic will have any effect on lesions in which tubercle bacilli are inaccessible by virtue of being incarcerated in avascular, necrotic or caseous tissue. Conversely, lesions which are very acute and consequently highly vascular, with accessible tubercle bacilli, are likely to show satisfactory results with streptomycin therapy. It is for this reason that streptomycin is rightly considered to be specific for miliary tuberculosis. As a corollary of this reasoning, it is quite possible to predict the result which is likely to be obtained in the usual type of tuberculous pulmonary lesion, which is, in most cases, a combination of the exudative (vascular) and the productive or caseous form. In such a lesion, which is by far the most common, we can usually expect a high degree of resolution of the exudative component, with very little effect on the avascular or caseous component.

Since these limitations are the rule rather than the exception in pulmonary tuberculosis, it follows that, except in miliary tuberculosis, streptomycin should be used almost exclusively, as an adjunct to more definitive forms of treatment, such as collapse therapy, either medical or surgical.

In recent months, however, there has been, among competent authorities, a swing toward a less conservative view of streptomycin therapy, particularly in the case of minimal tuberculosis. In the past the reasoning has been that streptomycin should not be used in minimal tuberculosis, on the basis that "the rabbit should not be attacked with our major weapon, for fear that it may later become a lion and be impervious to that major weapon." We are gradually becoming more amenable to the reasoning that "the rabbit *should* be attacked with our major weapon and killed, while it is still a rabbit, in the hope that it may never become a lion." It is my opinion, therefore, that in the foreseeable future, we shall be treating more cases of minimal tuberculosis with streptomycin with earlier recoveries, and lesser hospitalization costs to Public Health Departments. Furthermore, in view of the general acceptance of the power of combined therapy to prevent or delay the emergence of resistant strains of tubercle bacilli, the danger of "shooting one's bolt" with streptomycin therapy has distinctly lessened.

As indicated above, one of the most potent weapons in our therapeutic armamentarium, close to streptomycin in importance, is the chemotherapeutic agent, para-aminosalicylic acid (PAS). You are all familiar with the claims which have been made for this agent, most of which have been at least partially substantiated. It may be said that the effects of PAS on pulmonary tuberculosis are similar to those of streptomycin but in lesser degree. The limitations with regard to vacularity of disease and accessibility of organisms are similar to those obtaining in the case of streptomycin. The administration of PAS in pulmonary tuberculosis can therefore likewise be expected to produce a degree of resolution in the exudative component, with little effect on the caseous or necrotic component. We have already discussed in sufficient detail the place which PAS holds in combined therapy. A few words regarding dosage of PAS appear to be in order. Most publications advocating the use of PAS, recommend dosages in the 10 to 20 gm. range, and there is even some doubt as to whether doses of this order constitute the minimal effective range. Unfortunately, it has been our experience, corroborated by others,⁴ that 50% of patients cannot tolerate doses larger than 5.0 gms. daily, because of the gastrointestinal irritation which such larger doses produce. Our results, previously quoted, indicate that in combined therapy, for the purpose of delaying resistance, a daily dose of 5.0 gms. is sufficient. But when PAS is used as a single therapeutic agent, doses of 10 gms. or more are most certainly indicated. We have found, at our hospital, that we can give 10 gms. per day of the sodium salt (sodium para-aminosalicylate) with impunity, and we are at present investigating the possibility of giving even larger doses of this modification. It has also been noted by certain observers⁵ that a benzoic acid derivative, *when given concurrently with PAS, can be expected to raise plasma levels of PAS, by competitive inhibition of renal tubular excretion of PAS. If this can be corroborated, and we are at present engaged in a confirmatory study, it may be possible to produce the same plasma level of PAS with 5gms. daily, as might be expected with 10 or 20 gms. daily, a dosage is almost certain to be prohibitive because of gastroin-

*Benemid (Sharp & Dohme).

testinal irritation. The results of our studies on this preparation will be presented in a later communication.

To this point we have been concerned entirely with the use of streptomycin and PAS in pulmonary tuberculosis. At Point Edward Hospital, we have had a moderate amount of experience with the use of these agents in non-pulmonary tuberculosis, and it might be of interest to outline to you the results of our limited experience in these cases.

It is well known that tuberculous tracheo-bronchial disease is specifically affected in a beneficial manner by both of these agents. Our own experience has corroborated this finding to the degree that, if a clinical diagnosis of tracheo-bronchial disease has not been confirmed bronchoscopically we are frequently willing to use streptomycin in the form of a therapeutic test.

The situation as regards tuberculosis of the larynx is quite similar, lesions of this organ responding with almost dramatic rapidity to moderate doses of streptomycin, either with or without PAS.

As regards tuberculosis enterocolitis, I would add a word of warning. Present-day opinion is that intestinal tuberculosis results from the ingestion of large amounts of sputum, containing tubercle bacilli, from active pulmonary lesions. It should be quite obvious, therefore, that unless the pulmonary lesion is controlled, no permanent result can be expected from either of these therapeutic agents in the treatment of tuberculous enterocolitis.

It is the opinion of most responsible investigators that the statements made above regarding caution in the treatment of pulmonary tuberculosis with streptomycin, particularly the admonition concerning the combination of antibiotic therapy with more definitive surgical measures is equally applicable in the case of genito-urinary tuberculosis. Although streptomycin is highly valuable in relieving symptoms in tuberculosis of the kidneys and bladder, it should be considered reprehensible to treat genito-urinary tuberculosis with streptomycin alone, without regard to the irreversible mechanical changes in the urinary tract which can be eradicated only by surgery. It is also my impression, confirmed by others, that tubercle bacilli in lesions of the genito-urinary tract tend to become resistant to streptomycin with greater rapidity than is the case in lesions of other organs. I think that it is safe to say that the treatment of genito-urinary tuberculosis with streptomycin should never be undertaken without careful surgical evaluation, and that, particularly in this system, surgical treatment and streptomycin therapy should be carried out concurrently.

In the case of tuberculosis of the peritoneum, it may be said that, at least in a large percentage of cases, particularly those without major mechanical factors, streptomycin has to a great extent replaced surgery. There is evidence also, that tubercle bacilli which have invaded the peritoneal membrane develop streptomycin-resistance more slowly than they do within the respiratory tract. The cause of this late development of resistance is not clearly understood, but it can be said that, in the absence of absolute indications for surgery, prolonged treatment with streptomycin either with or without PAS, can be expected to produce satisfactory results in the large majority of cases.

At Point Edward Hospital we have had very little experience with bone and joint tuberculosis. However, from that experience, together with a rather

wide perusal of the literature, it would appear that, in osseous tuberculosis, streptomycin therapy should in all cases be combined with the more orthodox practices of immobilization and surgery.

A word of warning is required here with regard to the treatment of tuberculous sinuses and fistulae with these antibiotic and chemotherapeutic agents. It is well known that streptomycin is specific for the treatment of tuberculous sinuses and fistulae. It should be remembered, however, that a fistula is usually the external tract of a deep-seated abscess or caseous focus. It is obvious, therefore, that regardless of antibiotic therapy, deep-seated abscesses should be sought for and eradicated either prior to or concurrently with streptomycin therapy.

I have purposely separated the discussion of streptomycin therapy in tuberculous meningitis from the main body of this paper, because I wish to stress the point that the limiting factors which circumscribe streptomycin therapy in other organs, namely toxicity and resistance, do not apply in the case of tuberculous meningitis. The question of toxicity of streptomycin has little or no bearing on the treatment of tuberculous meningitis, since it is obvious that it is preferable to suffer from deafness or dysequilibrium from streptomycin therapy than it is to be dead of tuberculous meningitis. The factor of resistance seems to have little bearing in the case of tuberculous meningitis, since there is well-documented work which indicates that tubercle bacilli in the spinal theca have less tendency to develop streptomycin-resistance than have organisms in other sites.

At Point Edward Hospital we treat our cases of tuberculous meningitis intensively, with high dosage of streptomycin intramuscularly and PAS to the limit of tolerance, with frequent intrathecal instillations of streptomycin. This treatment is carried out over long periods of time, with short breaks in therapy. We have had excellent results using such a regimen; and it is my opinion that the high percentage of treatment-failures reported from other centres is due to a schedule of treatment which is not sufficiently intensive for the severity of the disease and the otherwise ultimately fatal outcome. Another cause of failure which I cannot stress too strongly is the lack of early diagnosis before patients are admitted to hospital, and the consequent admission to hospital of hopeless and moribund patients, for whom nothing could be done even by the most intensive schedule of treatment ever devised.

There are also certain mechanical factors within the spinal canal, which have been, to a degree, responsible for a certain proportion of treatment-failures. I mention these merely to indicate that much investigative work is at present in progress in an attempt to resolve these mechanical difficulties. I refer firstly to the tenacious gelatinous character of the exudate, which adheres to the meninges at the base of the brain, and mechanically prevents access of the antibiotic to the causative organisms.

Recent work with streptococcal desoxyribonuclease (streptokinase-streptodornase) has shown promise of resolving this mechanical factor, as indicated by Cathie's work in England.⁽⁶⁾ We have, as yet, had no experience with this form of treatment, although we are tentatively planning a study along these lines in the near future. Intrathecal tuberculin in infinitesimal dosage has also been advocated by British workers for the same purpose. We have had experience in only one case, but were unable to detect any beneficial effect.

The occurrence of intrathecal blocks has also constituted an important mechanical factor in treatment-failures in tuberculous meningitis. In cases in which lumbar blocks occur, due either to the trauma of repeated spinal punctures or to the local irritative effect of intrathecal streptomycin or to both, I would make a plea for wider usage of cisternal puncture, which has saved numerous lives in cases of spinal block.

Another method which has been advocated by British workers for the circumvention of spinal blocks in tuberculous meningitis has been the intraventricular administration of streptomycin through bifrontal burr-holes. This is, of course, a neuro-surgical procedure, and requires technical aid beyond the scope of most tuberculosis sanatoria. Moreover, it is still doubtful whether future work by other competent investigators will fulfill the enthusiastic claims for this procedure by its originators. At present the hope for most cases of tuberculous meningitis, I believe, still lies in early diagnosis and prompt and intensive treatment by the present traditional methods.

I have attempted, in the short period of time at my disposal to summarize broadly the present day concepts as to the treatment of tuberculosis by streptomycin and chemotherapeutic agents. Admittedly, in many instances, I have merely scratched the surface. It is my sincere hope, however, that I have been able to paint a broad picture for you, which will outline the remarkable advances which have been made in the treatment of all forms of tuberculosis during the past five years. As extensive as this review has been, however, I can assure you that we are merely standing at the threshold of a new era in the treatment of a disease which has devastated the populations of the world for many centuries.

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ACCOMMODATION AT BANFF

The Eighty-third Annual Meeting of the Canadian Medical Association will be held at Banff, June 9th to 13th, 1952. The total accommodation of the Banff Springs Hotel and Chateau Lake Louise has been reserved for the members of the Canadian Medical Association, but the demand is so heavy that early reservation is desirable.

Members planning to attend should make application to Dr. A. E. Wilson, Chairman, Housing Committee, 904 Greyhound Bldg., Calgary, using the Application for Accommodation printed in the November and subsequent issues of the Canadian Medical Association Journal.

Railway identification vouchers which permit members to take advantage of reduced railway fares may be obtained from the General Secreatry, Canadian Medical Association, 130 St. Clair Ave. West, Toronto 5. Early reservation of sleeping car accommodation with local passenger agents is desirable to insure that the necessary rolling stock will be available.

Your assistance in this matter will be much appreciated.

Yours faithfully,

A. D. KELLY,

Deputy General Secretary

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Abbreviations used:—Ab. for abstract; anon for anonymous; biog. for biographical note; C. for correspondence; C.R. for case reports; diagr. for diagrams; Ed. for editorial; illus. for illustration; Pers. for personal item; port. for portrait; rev. for review.

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