When the subject of forming a new Society of Chemotherapy was first discussed, it was necessary to justify its existence. It was not only to be a component of an International Society with attendance at meetings presenting advances in the field of antibiotics, but more important, it was conceived as fulfilling certain needs in the complex areas of clinical evaluation and administration of drugs. It had been obvious to us for some time that despite the activities of other societies in the field of research and clinical investigation, there was required closer communication and co-operation between government, industry and the medical profession. In organizing the Canadian Society of Chemotherapy we formulated three broad aims.

The first is ‘The promotion of contacts and collaboration between persons and institutions concerned with progress in the field of Chemotherapy’. This aim recognizes the need that particularly here in Canada, because we are in the main a country that imports drugs and has been dependent on outside sources for our information, there should be encouragement of interest in chemotherapy on a national as well as on an international basis.

In searching for the best ways to use what we learn and to try to learn more, another need is to create personal contacts between members of this Society and others with similar aims and to stimulate exchange of ideas so that pharmacologists, investigators, and clinicians could share problems, information and ideas.

The second broad aim is ‘The advancement of research in Chemotherapy’. The report of the Special Committee on New Drugs’ appointed by the Royal College of Physicians and Surgeons of Canada made the following comments. ‘Already, there is a considerable amount of clinical investigation being carried out in this country. There is a need for much more work in the general field of the investigation of disease processes and this investigative work should be extended to studies of their specific therapy.’ This excellent report further states that ‘there is an urgent need for collaboration on the part of all bodies concerned with, or interested in, the clinical testing of new drugs (which, in its simplest form means those concerned with the production, distribution, control, investigation, and use of these therapeutic agents) to assess the magnitude of the problem, the facilities presently available, the expansion necessary to enable adequate clinical trials to be carried out in Canada and the roles which each could, or would, be willing to assume in this matter’.

Research requires financial support and since it is in the public interest that such research and clinical trials be carried on, government should more actively support such projects.
The third broad aim is ‘The development of better techniques and standards for the evaluation and presentation of chemotherapeutic agents’.

Schecter President’s Address

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There has been much criticism about the manner in which clinical trials are conducted. For example, in a recent article entitled ‘The Evaluation of Antihypertensive Therapy, Co-operative Clinical Trial Method in Annals of Internal Medicine, November 1964, the authors state: ‘The need for adequate clinical trial of therapeutic agents is particularly evident in the field of antihypertensive drugs. It is not possible for individual physicians to evaluate properly the plethora of agents available and recommended for use. The mounting evidence that early and effective therapy is beneficial lends urgency to the need to know which of, or in what combination, these agents are most efficacious and least toxic. Guidelines based on valid clinical trial must be established. ‘Many efforts have lacked validity due to insufficient numbers of cases, lack of appropriate controls, and failure to eliminate bias.’

They present what they call the co-operative study method which appears to be a very effective approach to the problem with very interesting results as to the efficacy or non-efficacy of antihypertensive drugs. This study points up the need for evaluation not only of new drugs, but old ones as well.

Thus, one of our fundamental aims is to examine ways and means of improving the quality of clinical evaluation of drugs and since the field of medicine is so large we must have knowledgeable people from the various areas. It is not a matter of discussing the relative merits of one drug versus another, but to determine the guidelines necessary for arriving at an ideal study for evaluating drug therapy.

Opportunity will be provided at the business meeting at noon today for members to voice their opinions and give us of their wisdom in furthering the aims of this Society.

Progress in science and medicine during the last two decades has produced more new and effective drugs than during the past two thousand years. The pharmaceutical industry has made outstanding contributions to the health and welfare of people all over the world. The discovery of antibiotics, corticosteroids, poliomyelitis vaccine, and more recently, the psychopharmacotherapeutic agents, has transformed medical practice with incalculable benefits to our patients.

However, with the advent of these powerful agents have come problems which make the study of pharmacotherapy both fascinating and at the same time full of complexities that, in many cases, baffle the scientific mind.

It is apparent that problems occur at the levels of drug discovery, drug testing and drug administration. I would like to touch briefly on some of the difficulties that confront the laboratory pharmacologist, the clinical investigator and the physician.

The great dream of Paul Ehrlich to find a chemical agent with the power to destroy all pathogenic microorganisms without injuring the human body, is a myth because there is no absolutely safe and effective medicine.

Biostatisticians tell us, and we know this from clinical experience, that no medicinal chemical will have 100% specificity and also that no individual will be precisely like another in reaction to any given chemical agent. In the practical world of medicine, this reduces itself to the conclusion that all chemotherapeutic agents will have an incidence of side effects of some percentage, and that the therapeutic effect will never exceed about eighty percent of theoretical expectations.
We were aware of the toxic effects of morphine, digitalis, quinidine and the bromides, but in
general we looked upon the average patient as being uniform, that his responses would be
standard and static and that he would parallel his brother in all things. The growing awareness of
the inherent variability of patients in their response to medicinal agents, the idiosyncrasies never
even thought of that modify the pharmacodynamic response, and the increasing development of
hypersensitivity reactions, are phenomena that are making us more alert and should make all of
us more cautious in the clinical testing and evaluation of drugs.

Schecter
President’s Address
The Laboratory Pharmacologist
Modern drug planning is far removed from the empiricism and folk-lore that led, for example, to
the use of belladonna in Parkinsonism or to the pseudo-scientific rationale that produced bromide
therapy in epilepsy. Nowadays the development of pharmaceutical agents is usually according to
a definite plan. It begins with the chemical properties of a projected agent and proceeds as
thoroughly as possible through animal and human studies. This sounds simple and yet the
enormity of the problems which confront the laboratory pharmacologist when he sets out to find
a new drug for clinical use in the treatment of a particular disorder is perhaps best exemplified in
the remarks of Dr. J.E. Toman, Associate Professor of Physiology and Pharmacology, Chicago
Medical School. Speaking at a Symposium on Evaluation of Drug Therapy in Neurologic and
Sensory Diseases he said: ‘Today there are only an even dozen useful antiepileptics, but behind
that dozen there stand more than a hundred which have received some kind of clinical trial, more
than 6000 for which there is some laboratory data in the published literature, possibly at least
10,000 which have received some laboratory test whether reported in the literature or not, and
again, at a rough estimate, perhaps 100,000 substances of some known biological action which
were thought about before deciding on anticonvulsant testing. Thus, in very round numbers,
some pharmacologists somewhere have contributed to the laboratory study of 10,000 substances
which stand behind each single useful marketed antiepileptic.

The important point is that even with modern drug planning, the problems have to be solved by
man-power, by empirical methods, and by sheer weight of numbers rather than by theoretical
guidelines leading straight to clinical prediction.

As knowledge of body chemistry grows greater, it is conceivable that empirical animal testing
may grow less, but at present, it appears that the pharmacologist will have to continue testing
large numbers of drugs on animals. Thus, we have not progressed much beyond Paul Ehrlich.

The Clinical Investigator
The carrying out of clinical trials on patients as it is now done falls far short of the ideal. It has
been reported that some clinical trials are totally spurious, that is to say manufactured out of
whole cloth. Others, in which drug samples are distributed to practitioners for trial on their
patients and who then submit testimonials on their findings, are hardly better. There is no doubt
that standards of clinical trials must be improved and several questions must be answered, for
example,

How should the placebo effect be assessed?
What factors are necessary to make a study of clinical testing of drugs statistically sound?
Are different clinical investigators dealing with the same illness, for example headache, vertigo?
There are many drugs that are similar in chemical structure. How can one compare these for
clinical effectiveness?
Then there are the chronic disorders that require continuous suppressive therapy. Here, it is said that animal toxicity studies are not of too great a help because despite negative animal findings, drugs long administered may produce clinical toxic effects on skin, kidney, liver, and bone marrow.

The clinical investigator must not be overoptimistic and overlook minor side effects or minimize more serious drug reactions or fail to recognize spurious placebo reactions. He must not substitute enthusiasm for objectivity. Conversely, the qualified clinical investigator should not be pessimistic and reject a drug easily without giving a sufficient account for his reasons for rejection.

It is apparent that what is needed is more detailed investigation on each new clinical investigational drug. Perhaps then we will not have situations such as the disastrous results encountered with tranylcypromine administration and the thalidomide tragedy. Some research workers have stated that they were not surprised that monoamine oxidase inhibitor reactions would develop in reference to food. They knew about amino acid toxicities, yet it was only after a number of cases of toxic reactions had been reported that Blackwell, writing in the August 24, 1963, issue of the Lancet, was the first to correlate side effects with the consumption of cheese. The clue came to Blackwell from a pharmacist who related that his wife had developed a reaction after eating cheese. The prime reason for the disastrous interactions with severe headaches, intracranial bleeding and deaths, was found to be the presence in cheese of preformed tyramine and tryptamine.

This is an example in which the total impact of a chemical was modified by the presence of a positive factor in the diet. Should not the clinical investigator have been aware or made aware of such a possibility?

In the case of thalidomide, it appears that defective nicotinamide nutrition may have contributed to the teratogenic effects. Landauer had reported in 1957 that nicotinic acid antagonists caused fetal abnormalities and that these abnormalities were prevented by nicotinamide. Here the adverse reaction seems to have been due to the absence of a dietary component essential for normal fetal development. In this case a very good sedative and hypnotic agent was rendered dangerous and useless because of the lack of knowledge that a dietary deficiency would produce such serious drug complications.

Another area that is causing concern are the effects on the growth of infant and child by drugs. We are aware of the growth effects of some commonly used hormonal agents for example the adrenocortical steroids and androgenic hormones. Less well known and more unexpected are the growth effects of nonhormonal therapeutic agents such as tetracycline and vitamin A. In addition, to the inhibition of growth, tetracycline may produce permanent discoloration of the teeth and enamel hypoplasia, due to diminished calcification in the areas of drug retention. Nitrofurantoin may also cause permanent discoloration of the teeth in the primary dentition. These therapeutic misadventures have brought forcibly to the forefront, the problems of the therapeutic implications of immaturity and that the clinical investigator must be aware of the differences in drug responses by the immature and the mature.

This type of knowledge must keep pace with pharmaceutical advances, and until it does we will undoubtedly continue to do harm with well intentioned efforts.

The Physician
When we realize that in the United States about four hundred new brand-name drug products are placed on the market every year and that a goodly number of these are also marketed in Canada, it is no wonder that the physician is bewildered. We all know that these drugs are promoted with claims of unique and compelling virtues by advertising literature that floods our desks daily. Persuasive detail men urge us to prescribe their particular group of wonder drugs. The worthy physician wants to give his patients the advantage of any significant improvements in drug therapy without delay, but certainly the increasing evidence that many of these new drugs do not produce the desired effects or have serious side effects should make him pause and question his critical awareness to prescribe a drug that has not as yet been properly evaluated despite the claims of the pharmaceutical companies.

Let us assume that four hundred new products are placed on the market. It stands to reason that only a few of the four hundred products offer fundamental advances in treatment. Actually, only about twenty are even new basic chemical compounds, the remainder are new salts or minor derivatives of existing drugs, compounded mixtures of old or new agents, different dosage forms, and the various brand names of the same drug. The doctor’s problem is to recognize the really new parent drugs among this profusion, and to learn their true value or if they really are an improvement over the old. How can he obtain the necessary, accurate and authentic information—where can he look for guidance?

There are certain brochures and articles that are received that are informative and helpful and should be read, but it is always important that the physician make a habit of using other means for preserving independent objective professional judgement. The first aid to be mentioned is that preparatory to marketing a drug product, the manufacturer takes great pains to develop a concise description of the product, indications and precautions in clinical use, guidance for dosage, the known adverse reactions, and pertinent pharmacologic information. By federal law this brochure must accompany each package of the product, and must be approved by the Food and Drug Administration. Therefore, a logical first step in prescribing a product is to become thoroughly familiar with the contents of the package brochure.

Up to recently, the Food and Drug Administration has been interested only in the safety of the drug. Acceptance of the product has not constituted endorsement of the claims made for clinical usefulness and effectiveness. The important thing to remember is that the material in these brochures has generally been restrained and more honest compared to the portrayals in promotional material. The New Drug Act of 1962 in the United States contains an amendment authorizing the FDA to insist upon substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof. This latter provision will enable the physician to have even greater confidence in the claims for clinical usefulness set forth in the package brochure. These are still the claims of the manufacturer, and so the discriminating clinician will turn to other sources for aid in the proper evaluation of drugs. One has to remember that at the time a new drug product is introduced on the market, an energetic programme of promotion is launched to stimulate to prescribe it. Aside from the
package brochure, there may be little or nothing about the drug published in professional medical literature. We all know that months or years will pass before an adequate appraisal of a drug can be expected in medical journals and textbooks, and authoritative committees of medical societies are slow and cautious in rendering their opinions. Meanwhile, the physician shares a natural desire to try the new and bring any benefits to his patients as soon as anyone else.

In recognition of the need for independent and pointed comment to appear promptly after a new drug product begins to be promoted, a plan was inaugurated in 1959 for the fortnightly publication of The Medical Letter. Each eight page issue contains brief comments on newly released drug products and related topics. These are published soon after the drugs appear on the market and are prepared under the supervision of an editorial board of competent authorities who call freely on specialists in various fields. No advertising is accepted by The Medical Letter and all available data on the actions, comparative efficacy and costs are analyzed forthrightly.

Because of the attempt to give information as quickly as possible and when it is most needed, most of the comments reveal the poor quality of supporting evidence for claims in behalf of a drug product and the reader is left with the warning to proceed cautiously in prescribing the new drug or to stick to a well-tried established drug for the same purpose. It does serve a purpose, but the views are only tentative and early conclusions may be revised or confirmed in subsequent letters.

The next important aid is the bimonthly publication Clinical Pharmacology and Therapeutics. Instead of searching through other medical journals to find something about a newly released drug, each issue of this journal has a solid core of reports of studies of newer drugs, reviews of the present knowledge of classes of drugs or advances in therapy of various disorders, symposia and lively editorial comment. Best of all are the articles at the end of each volume discussing poor prescribing of drugs, the use of drugs in angina pectoris, etc. A very useful contribution has been the continuing publication of abstracts of reports of adverse reactions to drugs appearing in the world literature. From these the clinician can be forewarned or prepared to distinguish perplexing drug effects from manifestations of the disease under treatment.

Many are finding this Journal fills a gap between the earlier tentative appraisals of The Medical Letter and the later statements in Monographs and Textbooks. To me this Journal not only offers a valid continuing education regarding drugs, but also an excellent source of reference. Always at hand one should have Goodman & Gilman’s Classic, The Pharmacologic Basis of Therapeutics, because the general principles of drug therapy are always worth reviewing whenever a particular field of drug therapy is experiencing a boom in new products or a ‘breakthrough’ is proclaimed. Another publication, Drugs of Choice, has many features to recommend it. It contains excellent contributions from forty-seven outstanding specialists and gives comprehensive coverage to the clinical use of drugs. The editor is an eminent clinical pharmacologist and the outstanding feature is that it is practical and convenient. A revised edition is published regularly every two years, to keep the contents remarkably current and yet allow time for newer drugs to have had widespread usage before an evaluation is attempted. The appraisals of new drugs are candid and there is an honest attempt to compare those worth while with older drugs. The drugs are grouped for discussion according to the clinical situation calling for their use, e.g., relief of pain, hypertension, etc., which is a natural approach for the doctor
seeking suitable treatment. An important feature is the description of the basic pharmacology and pathologic physiology which enables the physician to use the appropriate drugs intelligently. With regard to Hospital Pharmacopoeias, these are being used in an increasing number of medical centres with a view to including those drugs which we believe are of definite value. The one compiled here is the work not only of the Pharmacy Committee, but of Chiefs of various departments. We must not be pressured into adding inconsequential drugs and superfluous mixtures. There must be developed habits of discrimination in therapy. We realize that they are a guide to choice of drugs and it is up to the individual physician to help us by being aware of the difficulties involved in trying to keep the Pharmacopoeia from becoming the Drug Manufacturer’s Vade Mecum.

Finally, the American Medical Association is now trying to help physicians evaluate drugs and keep abreast of advances in therapeutics. They publish an annual Therapeutic Number of the Journal of the American Medical Association which contains general articles on drugs, principles of pharmacology and therapeutics, treatment of diseases, etc. Here in Canada, we are dependent on these outside sources for our information regarding drugs. A positive approach is needed here to find qualified investigators, encourage some of the younger men to become clinical pharmacologists and improve the status of our knowledge of drugs by postgraduate programmes with emphasis on drugs.

Conclusion

In conclusion, I am sure that we are all aware that the clinical evaluation of drug therapy, with which this Society is most concerned, is of importance to all of us and that what we need is a sound programme.

The pharmacologist has to depend heavily on guidance from the clinician. New clinical findings or an observation which may appear trivial to the clinician may well be the one clue which will lead the astute pharmacologist to develop or reject an entire line of drugs.

The clinical investigator needs to have accurate and reproducible methods of patient examination and classification. These are essential whether these trials are to be conducted independently by individual investigators or as some type of cooperative or group undertaking. Will a given patient examined in two different institutions always be placed in the same category by each? Will two examiners give the same rating of improvement? What is the natural course of the disease in the untreated or control case? These questions must be resolved if meaningful answers are to be derived from either individual or co-operative investigations.

The physician should take pains to prescribe more intelligently. He should not delegate his authority to the news media or be pressured by overenthusiastic promotional advertising. A large number of new drugs are introduced every year, but it is his duty to learn about them from authentic sources so that he can pass the benefits on to his patients.

I sincerely hope that you will find the proceedings of this meeting interesting and fruitful and that this Society will be able to contribute to better methodologies thus aiding the pharmacologist clinical investigator and the physician and contributing to the health of our citizens.