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COOPERATIVE RESEARCH: A CASE REPORT

COOPERATIVE scientific research among different major departments of different institutions is so rare and of such significance for the future development of American science that the story of the successful accomplishment of such an undertaking for now six years may prove to be stimulating as well as interesting. As a sequel to the growing complexity of scientific technique, it is probable that there will be an increase in the number of cooperative researches of the type to be described, since this form of scientific work possesses a distinct advantage in the pooling of knowledge and resources. Individual scientific achievement, of course, may always be expected to develop whenever genius and opportunity are in proper conjunction. As the specialties will continue to diverge, however, the organization of science will imply greater liaison and cooperation between the specialists, in order to advance the common front of scientific knowledge.

In the case to be described, the mutual incentive to productive effort has been so fruitful that a morale and enthusiasm has developed which is astonishing. Individual ambition has been disciplined to team work for the success of the endeavor as a whole, and instead of engendering the slight jealousies and friction which often arise between workers on the same scientific problem, friendships have been created and cemented which seem impossible of dissolution.

This particular cooperative venture originated with some of the scientists engaged in the Chemical Warfare Service during the war. Among those associated together at the American University Experiment Station at Washington were Professor A. S. Loevenhart, of the University of Wisconsin, and Professor W. Lee Lewis, of Northwestern University. Professor Lewis is the chemist who developed "Lewisite," about which so much romance arose at the end of the war, and Professor Loevenhart is the pharmacologist who directed the study of the action of this and other substances on the human body.

Professor Loevenhart became impressed with the significance of their cooperative researches. In discussing "an institute for research in synthetic organic chemistry" at a meeting in 1918, Professor Loevenhart said:

In my work at the American University Experiment Station I have seen how satisfactory and effective research work in close cooperation between chemists and

pharmacologists may be. The object toward which we are working there is the development of materials destructive of life, but the thought naturally presents itself that if this cooperative work is so effective in war time for the development of offense weapons, in peace time such cooperation would be of enormous value in promoting the security of life and its comforts.

I may briefly recount the way in which the work at American University has been conducted. Most of the materials are produced by chemists working in the station. Formal conferences are held twice a week between pharmacologists and chemists, and there are informal conferences each day. At these conferences it is decided what substances should be prepared. When the materials are synthesized they are turned over to the pharmacological section for every sort of test. The results of these tests are then made known to the chemists and the possibilities of improving the materials are then discussed. I may say that the work has been eminently successful from every standpoint, and that the cooperation has been delightful. One can hardly realize until he has experienced it how the pharmacologist and chemist working together mutually stimulate one another.

I am therefore prepared to testify that cooperation of the kind proposed is not only practicable, but is the ideal condition for productive research. . . .

The need for an institution of the type proposed is obvious when one realizes that there is no institution in America to-day where the therapeutic value of a drug can be determined in a manner acceptable alike to scientific men and physicians. To my mind such an institute should not only foster the production and testing of remedial agents, but every phase of synthetic organic chemistry should be considered within its domain. This is necessary because remedial agents may be found among any group of organic chemical products.

Professor Loevenhart and Professor Lewis have partially realized this general scheme in the work to be described, in spite of the difficulties of operation with inadequate equipment and resources, and in spite of the great inconvenience of a wide geographical separation of the various phases of the work.

THE U. S. INTERDEPARTMENTAL SOCIAL HYGIENE BOARD

One of the minor consequences of the war was the creation in 1918 of the United States Interdepartmental Social Hygiene Board, which enlisted the forces of the War, Navy and Treasury Departments in a comprehensive campaign against venereal disease. The functions of the board included

> medical measures for the prevention, treatment and control of venereal diseases; protective measures primarily directed to the problem of safeguarding the Army and Navy; scientific research for the discovery of better medical methods for the prevention and treatment of venereal diseases; and educational measures for the discovery or development of better educational methods in the prevention of venereal diseases, or for psychological or sociological research related thereto.

The work of this board involved cooperative research on a grand scale, and however disorganized and unrelated the specific accomplishments of the various workers supported by grants from this board may seem, the results as a whole were magnificent.

During 1919, 1920 and 1921, the division of scientific research of the board distributed some $285,000 for some forty separate researches in twenty-three different institutions. Of this sum, $12,000 was given to Northwestern University to be administered for two purposes: (a) "A synthesis of organic compounds containing arsenic of possible value in the treatment of syphilis of the central nervous system," under the direction of Professor W. Lee Lewis, and (b) "a synthesis of new organic compounds of mercury for use in the treatment of syphilis of the central nervous system," directed by Professor Frank C. Whitmore. To the University of Wisconsin, $26,800 was given during the three years for the object of preparing and studying "mercurial and arsenical compounds which have a predilection for the central nervous system, in the hope of finding drugs more useful than any known in the treatment of syphilis of the central nervous system." It was the understanding between all parties concerned that whatever compounds were produced by the Northwestern group were to be submitted to the Wisconsin workers for biological study, and that the closest cooperation between the two groups was to be maintained. A total of twenty-three scientists and assistants engaged in this work at the two institutions during the three years it was supported by the grants from the U. S. Interdepartmental Social Hygiene Board.

Appropriations from the board were discontinued in 1921. In a recent report, it is stated that many of the research men operating under grants from the board indicated at that time that their studies were completed and that nothing could be gained by further appropriations. To quote from this report, it is said that this statement

> illustrates so admirably the honest spirit in which these investigations were conducted. But inasmuch as the best workers of the country were engaged in the work, it also suggests that a continuance of the fund, with the inevitable insistence of money—especially government money—to get itself spent, would have seen a deterioration in the product and a final degeneration of the whole mechanism into an official routine quite incompatible with free research. The scientific work of the Interdepartmental Board was conceived and executed in that spirit of ideal-

ism on the part of the government officials in charge which was calculated to meet the scientists on their own ground. That youthful idealism which the war inspired has gone, and gone with it is the probability of reproducing the circumstances necessary to the successful continuation of this work at the present time. The scientist, like the rest of us, must return to the humdrum of peace.

While these interesting observations may have been true of the general work of the board, thus justifying its demise, they were not at all true of the close cooperative work between Professors Lewis, Whitmore, Loevenhart and their associates at Northwestern and Wisconsin. Their effort was just beginning to get a good start when its support was withdrawn. The threatened collapse of their venture was averted by the financial help of a private organization which undertook to do in a large city what the Interdepartmental Board tried to do for the country as a whole.

THE PUBLIC HEALTH INSTITUTE OF CHICAGO

One of the medical officers in the army who had been impressed with the campaign against venereal disease started by the Interdepartmental Board was Dr. Joseph C. Berkowitz, of Chicago. Upon discharge from service, he conceived the idea of undertaking to handle the civil population of a large city with respect to venereal disease in somewhat the same manner which had been used with success in the army, and by using methods of advertising similar to those employed by the Public Health Service of the U. S. government. This idea involved treatment at a nominal cost.

The Public Health Institute was organized in February, 1920, by Dr. Berkowitz and Myron E. Adams, an experienced sociologist, with the support of many prominent men of Chicago, among whom were A. A. Sprague, Harold F. McCormick, T. R. Gowanlock, General J. A. Ryan, Samuel Insull, H. M. Byllesby, A. A. Carpenter and N. W. MacChesney. R. A. Gardner, J. M. Dickinson, Jr., N. B. Judah, Lester Armour and Marshall Field were later added to the trustees. These public-spirited citizens have taken a direct part in the management of the institute and have always decided its policies. This has assured to the institute the application of the best business intelligence available.

The immediate object was to provide adequate medical service for those sufferers from venereal diseases who belonged to the great middle class and who were therefore either too proud to avail themselves of free treatment at the dispensaries of medical schools or financially unable to afford the expense of proper examination and lengthy treatment at the hands of a qualified specialist. In order to make its presence known to the vast number of people who needed its services, it was necessary to advertise in the newspapers. These notices were carefully worded to emphasize the fact that the institute was organized for public service and not for profit. The names of the lay directors were published to guarantee this function.

Unfortunately, the Public Health Institute incurred the antagonism of a small group of Chicago physicians, who, vehement in their disapproval, took opportunity to attack the institute on the convenient grounds that it violated medical ethics by its adverising. Their expressed objections do not seem to have been well advised, but they served as a cloak to reality and as a placebo to conscience. It appears to be only a question of time when the leaders in the medical profession will discountenance such criticism on the part of their less magnanimous associates.

This digression may seem uncalled for, but it is introduced to illustrate the non-technical troubles which may arise in the progress of cooperative research. The problem of financing such a large undertaking brings contact with many different types of people. In order that the necessary harmony may prevail, it is essential for those engaged in the venture to understand each other, and to have full confidence in one another. Only under these conditions may possible antagonism be met with equanimity.

Venereal disease affects not only the present generation, but also innocent members of generations to come. Its treatment, therefore, becomes essentially a matter of public health. If this service can be rendered by a private institute, it relieves the state of assuming the burden. It is the ideal of the Public Health Institute of Chicago to make high-grade medical service of this character accessible to the mass of the people from the standpoints of time, place and money; in other words, to make it cheaper for a person to be cured than to remain ill of venereal disease. Even with the nominal charge which is made for this service, a surplus has accumulated. Since the institute is a non-profit organization, this can only be disposed of in an effort to improve its service to its clientele, in educational measures or in promoting research.

When the U. S. Interdepartmental Social Hygiene Board failed to continue the necessary funds for the continuation of the cooperative research at Northwestern and Wisconsin, the Public Health Institute came forward and granted the money each year to the present time. This support of scientific research in a field bearing upon its own problems was made an integral part of the program of the institute, and will continue to be so. Patronage of this sort is of national significance.

The cooperative effort between Professor Lewis and Professor Loevenhart and their associates has been, therefore, an uninterrupted affair since 1919, and it has produced important results. Before describing these, it may be of interest briefly to discuss the organization under which the research has operated.

ORGANIZATION

The research involves three major phases: (a) the chemical, (b) the pharmacological and (c) the clinical. The actual work in the first two phases is done by graduate students who are studying upon what is essentially a fellowship basis for their doctorates, while the clinical studies are handled by thoroughly trained and properly qualified physicians. The production of organic arsenical substances is under the direction of Professor W. Lee Lewis, and the synthesis of organic mercurial compounds is guided by Professor Frank C. Whitmore, both at Northwestern University. Some synthetic organic work and all the pharmacological part of the effort is under the supervision of Professor A. S. Loevenhart, of the University of Wisconsin. The clinical investigations are managed by Professor W. F. Lorenz, the director of the Wisconsin Psychiatric Institute.

An interesting feature of the chemical phase of the research has been the development of the Intermediate Laboratory. It occurred to Professor Whitmore that at least 90 per cent. of the research chemists' time was employed in making intermediate chemical substances necessary for the synthesis of the compounds desired. These intermediates are usually impossible to obtain, even from such specialized dealers as the Eastman Kodak Company. Accordingly, Northwestern University erected a small laboratory building in which two men devote their energy to making such intermediates as may be required by the synthetic chemists. This has resulted in a tremendous saving of money and time and insures a purity of intermediates impossible to obtain otherwise. With the increasing interest in this line of work, the large scale production of intermediates by this laboratory may become of great assistance to chemists outside of this particular group.

The actual chemical work in this cooperative research is proceeding in an exceedingly comprehensive and orderly manner. No compound is submitted for pharmacological study until its composition and structure has been accurately determined, until it has been purified with scrupulous care and until its physical and chemical properties are known.

The pharmacological investigation of compounds received at the University of Wisconsin involves several steps: (a) determination of toxicity on mice, rats, rabbits and guinea pigs; (b) estimation of therapeutic value in trypanosome infections in rats and rabbits; (c) estimation of therapeutic value in experimental rabbit syphilis and (d) determination of distribution in the tissues and rate of elimination from the body. If a compound is found to have therapeutic value, it is administered to the laboratory workers and to the director, in order to determine its rate and form of excretion and in order to ascertain whether or not it has any untoward effects in humans, before it is submitted to the clinical group for trial.

Upon reaching clinical service, a compound is again subjected to most careful study, of a somewhat different type. Hospitalized patients are selected for trial use of the drug. Attention has been paid generally to patients suffering from one of the many manifestations of syphilis of the central nervous system, but patients in other stages of syphilitic infection are also studied. The dosage to be employed is calculated from the experimental work, and the minimal amount from which therapeutic effects might be expected to result are used at first. If this is inadequate, the dosage is cautiously increased. Animal experimentation indicates the organs or tissues which are first affected by the drug when used in toxic amounts. The attention of the clinicians, therefore, is riveted upon the function which will first show any deleterious effects of the drug. In order to do this, specialized functional tests are employed. By such precautions, drugs may be excluded from human therapy without injuring a single patient.

The clinical and serological picture of these hospitalized patients is carefully watched, and special methods have been devised for detecting changes in the mental or physical condition. If the drug is successful in bringing about improvement in a large series of such cases, its indications and limitations are thoroughly considered and it may then be used upon selected ambulatory patients under the personal supervision of Professor Lorenz. When a year or more of painstaking clinical experience has been obtained with the use of the drug, it may be released, under control, to certain syphilographers, for use with patients for whom it may be indicated. If these confirm the previous findings, it may be considered for release to the general practitioner.

Complex organization of this sort requires frequent conferences for discussion of results and outlining of plans. The syntheses attempted by the chemical group are largely determined by the manner in which the compounds already studied may act pharmacologically. Fundamental problems on the relation between chemical constitution and pharmacological be-

havior must be attacked and solved. The many technical details connected with the use of a chemical substance in medical practice must be studied and met in the best possible manner. The question of solubility and stability is of utmost importance in work of this kind, and the resources of the chemist are often taxed to the limit in the effort to solve such difficulties.

Frequent conferences and open discussions are most helpful and inspiring in these matters. Those engaged in each phase of the work in this cooperative effort hold a weekly meeting, while monthly gatherings are called for the general force. The officials of the Public Health Institute try to meet with the research staff at least quarterly. This sounds almost like big business, but in this way the general effort is kept together, and mutual stimulus and inspiration are secured. The myopic vision of the individual is broadened by the use of the spectacles of his neighbor. The chemist feels he is doing something, when he actually sees a sufferer from general paralysis improve mentally and physically under the influence of the compound he has synthesized in consultation with the pharmacologist, who believes he knows how to improve the action of a substance previously made. When the Public Health Institute can help its patients in a manner previously impossible, it knows that its money has been well spent.

RESULTS

The results of scientific research are judged by the quality of the publications describing it. The results of this cooperative research have appeared in twenty-nine papers, published in the *Journal of the American Chemical Society* and in leading medical journals. Two more papers are in print, and at least a dozen articles are in preparation, including a comprehensive monograph describing the effort as a whole. Nine graduate students have obtained their doctorates partially through the research involved in the problem, while seven others are at present candidates for their doctorates on the basis of their work in this field.

It took about a year for the chemical staff to become oriented in this particular study and a somewhat longer time for the pharmacologists. The latter had to devise standardized quantitative methods for comparing the activity of one compound with another. This was an exceedingly important proposition and has been worked out so there can be no uncertainty about the relative merits of the substances studied. Qualitative comparisons are readily enough secured, but scientific men in general will appreciate the advantage of placing such comparisons upon a quantitative basis.

The most important achievement of this cooperative research which has been published to date was the finding that tryparsamide—the sodium salt of N-phenyl-glycine-amide-p-arsonic acid—is of great value in the treatment of syphilis of the central nervous system. This discovery has been heralded as the greatest advance in the therapy of syphilis since Ehrlich introduced salvarsan.

The steps leading up to this discovery are interesting. It occurred to Professor Loevenhart and Professor Lorenz that the therapy of neuro-syphilis might be an entirely different proposition from the therapy of general syphilis. Ehrlich's preparations (arsphenamine and neo-arsphenamine) are of no value in neuro-syphilis, although they are excellent in general syphilis. On this hypothesis, then, it was not logical to assume that an arsenical preparation would be of no service in neuro-syphilis merely because it is not beneficial in other forms of syphilis. Accordingly, the Wisconsin group began to study various arsenical compounds which had been discarded for use in the general types of syphilitic infection, for the purpose of ascertaining whether or not they might be employed in the therapy of syphilis of the central nervous system.

Among such substances investigated was tryparsamide, which was kindly sent by the Rockefeller Institute, along with two other compounds, for this purpose. Tryparsamide had been synthesized by Dr. W. A. Jacobs and Dr. Michael Heidelberger, of the Rockefeller Institute, and was described by them in 1919. Dr. Wade H. Brown and Dr. Louise Pearce, also of the Rockefeller Institute, studied its toxicity, observed its tonic effect in animals and made an exhaustive study of its therapeutic action in animal trypanosomiasis and rabbit syphilis. They also investigated its therapeutic value in late human syphilis, and Dr. Albert Keidel and Dr. J. E. Moore studied its action in early human syphilis. While it was found very efficacious in sterilizing an animal infected with trypanosomes, it gave disappointing results in human syphilis. It was received for study at Wisconsin in October, 1919, and it was quickly apparent that it had great possibilities of being beneficial in neuro-syphilis. Later, Dr. Pearce tried it with great success in the treatment of human trypanosomiasis or African sleeping sickness. After more than three years of careful clinical study with the drug in neuro-syphilis, Lorenz, Loevenhart, Bleckwenn and Hodges published their surprising results with it in May, 1923. Since then the findings of the latter have been abundantly confirmed.

To a certain extent, then, the hypothesis upon which Professors Loevenhart and Lorenz proceeded was justified. Tryparsamide is apparently unique

in bringing about a resolution of syphilitic lesions in the central nervous system, leading to astonishing clinical recoveries from paresis and even maniacal mental disorders. The saving to the state of Wisconsin alone, through the discharge of patients suffering from various forms of insanity occasioned by syphilis, who have been apparently permanently relieved of their mental disability, has already many times paid for the total cost of the entire research.

While the chemical phase of the cooperative effort has not as yet produced such startling results, it has contributed information of a fundamental character in organic research on mercurials and arsenicals. In the employment of new synthetic methods, compounds of arsenic have been obtained in which the well-known "tonic" action of arsenic has been attenuated to a remarkable degree, so that these substances give promise of being very valuable in the symptomatic treatment of emaciated patients. Many new facts concerning the toxicity of mercury compounds have been found.

Among the most important results of the pharmacological phase of this cooperative research has been the working out of a quantitative method for the comparison of the therapeutic value of the many different compounds studied. Qualitative estimations can not be expected to yield accurate knowledge upon as complex a problem as this, particularly when such estimations are limited only to a single criterion of therapeutic action. In the method devised by Professor Loevenhart and his associates, a standardized inoculation or infection is made; each treated animal is followed with a corresponding untreated but infected animal, and the dosage of the compound used is calculated from the maximum tolerated dose; the course of the blood Wassermann, the exact character of the initial lesion and the number of infecting organisms present at any one time are all accurately determined, and then, by means of a formula, the therapeutic value of the drug as compared to neo-arsphenamine (which has been arbitrarily selected as a standard) may be calculated. This method has yielded information impossible to secure by ordinary qualitative technique.

The routine blood Wassermann, which has been performed on all experimental rabbits, has given surprising knowledge of a fundamental character upon immunological reactions in general, and in particular upon the significance of the Wassermann reaction itself. This is being closely studied by Professor Lorenz at the present time.

Another interesting contribution from the pharmacological phase of this general research has been one by Dr. Albert Young and Professor Loevenhart, on the action of organic arsenicals upon the optic tract. It had long been supposed that the deleterious effect of organic arsenicals on the optic tract was due to the presence of pentavalent arsenic in the compounds. This work rather conclusively proved that injury is due to the presence of either trivalent or pentavalent arsenic in the para position to an amino or substituted animo group.

In Conclusion

It is felt by the workers concerned in this cooperative venture that the real effort is just beginning. The hopefulness of undertaking to find arsenical and mercurial organic compounds which might be better than anything yet known for the treatment of syphilis of the central nervous system has been justified, and this is provoking greater optimism for the future. So much promising study is in sight that enthusiasm among the group is increasingly evident at each meeting. It is hoped that this plain recital of the story of a working cooperative scientific research, with its implied disappointments and reverses, as well as with its successes, may prove to be the needed stimulus to the inauguration of similar efforts elsewhere.

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THE ANTIQUITY PHANTOM IN AMERICAN ARCHEOLOGY

INTEREST in American antiquities has increased rapidly in recent years, and researches are extending to many fields heretofore untouched. So fascinating is the lure of great antiquity that numerous untrained explorers are entering the field, and the highly colored accounts of their discoveries are broadcasted with fanciful elaborations by predatory journalists. We hear, for example, of numerous pre-Columbian discoveries of America; of ancient races preceding the Indians; of civilizations antedating those of the Nile and the Euphrates; of glyphic inscriptions miles in length that await a translator; of skeletons of men twelve feet in length; of dinosaurs and ibexes engraved on rock surfaces; of the ruins of a Chinese city; of America as the probable birthplace of humanity; and so on, *ad infinitum*. These fanciful announcements by untrained adventurers in the realm of science, being without chronological or other support, are soon forgotten, but when geological chronology is appealed to by explorers, whose statements and conclusions find a place in scientific journals, the case becomes more serious and deserves more than passing attention.

Recently there has come to my notice a brief ar-