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THE IMPORTANCE OF FUNDAMENTAL PRINCIPLES IN DRUG EVALUATION*

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I am deeply honored for this opportunity to address the Rho Chi Society on the occasion of the Sixth Annual Rho Chi Lecture. Apart from my personal involvement, I feel that it is appropriate and fitting that a Society whose purpose is to promote scholarship and high attainments in the pharmaceutical sciences should be cognizant and in support of a movement intended to engender sound application of fundamental principles to drug evaluation.

We are living in an era where everyone and no one is an expert on drugs. The pharmacologist of today may be a molecular biologist studying drug effects on RNA synthesis or at the other end of the spectrum he may be a psychiatrist studying the effects of drugs on the electroencephalogram. However, most of these specialists from non-drug oriented disciplines are not totally aware of the multitude of factors which can influence drug responses. My objective in this presentation is to describe several examples in which neglect of application of fundamental principles results in essentially meaningless and uninterpretable experiments. Unfortunately, such approaches are the rule rather than the exception and a real need exists for improvement in our modus operandi.

Let's begin with experimental design: Ideally, this should take some form which will eliminate subjective bias and include enough subjects and controls to permit meaningful statistical evaluation when the experiment is completed; all too often this portion of the experiment is taken for granted. In practice, most experimenters tend to neglect any but the most primitive procedures for statistical analysis of data: considerations such as investigation of the character of the variability, biotransformation of variables, or the quantitative as opposed to quantal analysis of data are rarely considered. These aspects of the experiment are so fundamentally important that it is essential that the uninitiated scientist should consult with a biostatistician while he is planning his first experiments. Frequently a period of close collaboration is essential since the complexities of the resultant data may require the use of a computer for analysis.

One frequently abused problem area involving both experimental design and statistical analysis has to do with drug combination experiments. The usual pattern is for the investigator to use two drugs, drug "A" and drug "B". For example, when administered alone at a particular dose, drug "A" produces a 20 per cent effect; drug "B" when administered alone at a certain dose produces no effect. When the two drugs are combined, a 60 per cent effect is achieved; the investigator innocently believes this to be an example of genuine potentiation. If, however, the data were properly analyzed and the experiment were set up properly involving dose-response relationships, rather than single doses of each component, there is a good chance that this type of result could be proven to represent a simple additive effect.

Perhaps the most often neglected and misunderstood aspect of drug evaluation is concerned with drug dosage. There is an old adage in pharmacology that enough of any drug can be made to induce almost any effect, and that is not far from the truth. Therefore, in order for any experiment involving drugs to have relevance or implications regarding the drug, a parallel must be drawn between the concentration of drug in the experiment and the concentration which may be achieved therapeutically or toxicologically, whichever the case may be. The following examples illustrate the more important principles involved.

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The cyclamates were recently taken off the market on the basis of some experiments performed in rats in which the animals were treated with 2.5 Grams/kg./day. The rats developed tumors of the bladder, and in keeping with the provisions of the Delaney Amendment which require that a food additive must be removed from the market if it has been shown to cause cancer when fed to humans or animals, the cyclamates met their demise. We might first of all question the dose of drug used; in this case it happens to be approximately fifty times the maximum amount proposed for adult human consumption. Unfortunately, the Delaney Amendment is open-ended, it says nothing about dose. In other words, if any food additive causes cancer, regardless of dose, it is not acceptable for human consumption. I wonder what would happen if this type of experiment were performed on Capsicum frutescens, commonly known as cayenne pepper.

There is abundant evidence that drug dosage can seriously influence drug disposition and metabolism. Thus, it does not necessarily follow that the toxicity achieved at a very high dose of a drug is simply an extension of an effect which may occur at a low intensity or frequency at therapeutic doses. Drugs have been demonstrated to undergo qualitatively different pathways of degradation as dosage is increased; if under these circumstances the new metabolite happens to be carcinogenic and also concentrates in the urine, this could explain a carcinogenic effect in a drug which would ordinarily be quite safe even at many multiples of a therapeutic dose. It is especially important with a drug which has already been in use in man for years to ascertain that the factors responsible for causing tumors in rats can actually occur in man. In other words, if man should metabolize the drug in a manner different from the rat so that a carcinogenic substance is not formed, this fact must be taken into consideration by the investigators.

A second point regarding dosage and toxicity is concerned with a description of what constitutes an adequate margin between the therapeutic dose and the toxic dose. Acute doses of aspirin from 10 to 30 grams have proven to be fatal; the usual dose is 0.3 to 1.0 gram. This is really not much of a safety margin for a drug used as indiscriminantly as aspirin. Another interesting side issue about the cyclamates and the Delaney Amendment is the fact that, if the cyclamates had simply killed rats at 2.5 Grams/kg./day, this drug would probably still be on the market.

There are less pragmatic reasons for being concerned about drug dosage than those already mentioned. When considering the mechanism of action of a drug, for example, this generally refers to the mechanism of therapeutic action rather than the mechanism of toxic action; therefore, some effort must be exercised to conduct the experiments with concentrations of the drug which are *therapeutic* and not toxic. This is a very difficult and serious problem principally because many mechanism of action experiments are performed in situ or in vitro. In order to match the in vivo conditions the investigator must have knowledge about drug concentration at the receptor site, its state of ionic equilibrium, protein binding, and so on. By the same token, the investigator who works only with in vivo systems to determine mechanism of drug action is at the mercy of numerous variables intermediate between the drug he starts with and the intended receptor.

For example, many otherwise reputable scientists have drawn all sorts of conclusions about so called "analgesic receptor sites" in the central nervous system, based on nothing more than knowledge of the chemical structures of the drugs and their analgesic effect after systemic administration. The fact that differences in absorption, metabolism, distribution, binding, or other factors, could account for the observed differences in potency, rather than different affinities for a supposed receptor site was not considered. In certain instances, to make matters worse, analgesic efficacy has been estimated on the basis of an endpoint which confounds duration of drug action with intensity of effect. Under these circumstances an

alteration in the structure of a drug which would simply result in a slowing down of its metabolism could conceivably prolong its duration of action. By confounding duration of action with activity as an endpoint for analgesia, the investigator may draw the erroneous conclusion that the change in structure has altered the affinity of the receptor for the drug.

Species differences in reactivity to drugs are often attributable to variations in drug metabolism and/or distribution although some basic physical and anatomical differences may occasionally account for dramatic differences in responsitivity. The point is that it is not reasonable to establish therapeutic potency in one species and toxicity potency in another species. It is also quite unacceptable to establish therapeutic potency by one route of administration and toxicity potency by a second route of administration, albeit that both are performed in the same species. It is amazing how often therapeutic potency is estimated by the intraperitoneal route (which, of course, makes the drug appear very potent) whereas toxicity is measured by the oral route, thus providing for a maximum spread between the two effects.

I hope I have provided enough germane examples to establish the importance of this problem to the future of drug research. We are living in an era in which we are literally swamped with scientific publications and literature. Furthermore, there is a growing tendency for more and more specialization within disciplines. Both factors, I believe, have had a deleterious influence on the caliber of our scientific progress. Scientific progress is measured by the quality not the quantity of experiments performed.

In the early 1950's, a series of experiments was performed which were intended to shed some light on the mechanism of action of a drug as well as the mechanism of action of the central nervous system. Unfortunately, the theory behind this research was based on the supposition that the central nervous system was simply a homogeneous mass of amines and that the action of certain drugs depended on which amine was depleted and which was preserved. Whole brains were homogenized and scientific reports by the hundreds appeared which simply reported on the effect of this or that drug or treatment on norepinephrine or serotonin levels in whole brain. Now there is absolutely nothing wrong with this kind of an approach so long as it seeks out a correlation between two phenomena. Such an approach begins to get into trouble when one attempts to relate empirical correlations with causal phenomena. It is one thing to say that reserpine depletes the brain of serotonin. It is quite another to say, after finding this to occur in whole brain homogenates, that this is the mechanism whereby reserpine causes central nervous system depression. In the first place, such an approach is inappropriate in terms of discovering a mechanism of action due to the very fact that whole brain homogenates were used. The brain does not function as a single unit and it is naive to expect it to do so.

Although the aforementioned series of experiments were successful in stimulating a tremendous amount of research, they also had a deleterious influence on scientific progress because many scientists followed this pattern and glibly explained away the mechanism of action of other drugs based on such spurious experimentation. It would not take much to make the experiments entirely reasonable and rational, i.e., by working with a specific system within the central nervous system and investigating amine concentrations in specific neurones sharing similar functions. In retrospect it seems to me that a great deal more scientific progress could have been achieved had there been better collaboration at the outset between biochemists and neurophysiologists.

In conclusion, I would like to make some suggestions and recommendations which may help resolve the problem for the future:

1. Education – Formal courses should be offered routinely in pharmacodynamics and pharmacokinetics. They should essentially cover the type of material presented here. Ideally, experts in specific disciplines should handle their own areas of interest. Thus, the teaching staff should include biostatisticians, experts on drug metabolism, receptor theory, and other specialists. For the many post-doctorate specialists, formal symposia on fundamental principles should be made available at periodic intervals, certainly no less than once every two years.

2. Scientific Publications – With the trend moving in the direction of specialty journals in particular disciplines (drug metabolism, molecular biology, cancer Chemotherapy, to name a few), there is also a great tendency toward inbreeding on the part of referees. Rarely does an expert on biostatistics have an opportunity to review papers submitted to bioscience journals. A great deal of care and discretion must be used by editors in selecting referees in order to assure that all aspects of the research in question meet minimum standards of scientific acceptability.

3. Ongoing Research Programs – Every effort should be made to encourage research collaboration between specialists in different disciplines. It is a rare circumstance wherein a single research group working on a specific problem can boast enough of the diverse knowledge and specialized equipment necessary to pursue a problem in drug evaluation to completion. As previously mentioned, collaboration with a biostatistician is frequently essential at the inception of a new program.

You may reasonably inquire where Rho Chi fits into this scheme of things. If one of Rho Chi's raison d'etre is to promote high attainments in the pharmaceutical sciences, I can't think of any attainment more important and in urgent need of achievement than this one. The future of all drug research depends on it.

Dr. David H. Tedeschi (left), Director of the Pharmacology Department of Geigy Pharmaceuticals, is shown receiving the 1970 Rho Chi Award from Vice-President Raymond E. Hopponen at the Washington meeting of Rho Chi Society.

PHARMACY – SOME CHANGES ARE COMING*

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My title is a safe one because everything changes with time. The most remarkable aspect of our world over the past five centuries has been the constancy of change. Our present twentieth century has set some kind of a record for the rate at which major changes have occurred in society in general and how these changes have influenced the health sciences. As we enter the new decade some major changes in the health sciences appear imminent and for this reason I would like to spend some time reviewing the past. A look backwards is frequently helpful in developing a perspective in which upcoming changes can be accommodated with equanimity and our professional or career decisions can be projected with greater confidence.

Let me begin by defining some terms that appear to mean different things to different people and thereby lead to confusion. We have often heard the statement that to be human is one thing and to be scientific is quite another. Let me suggest that the natural contrast to human values is not scientific values but social values.

Human values begin as the qualities of a hypothetical completely free man. This man employs imagination and intelligence to survive. He accepts his human state and has confidence in his ability to cope with his environment. He recognizes no authority, is unhampered by convention, and his highly individualistic in all his dealings.

These human qualities become values only as the individual submits to some kind of social order. Without social discipline, he is arbitrary, willful, self-indulgent, and cruel. As he is forced to respect others in order to survive himself, he sees common human problems.

As he becomes sympathetic, considerate, and responsive to the individuality in others, he may gain insight concerning problems common to all men. This insight may, in turn, suggest a service necessary to all. As he strives to provide this service, he becomes altruistic. He freely uses his intelligence and imagination for the benefit of others. He may unite his efforts with those of other men and form an organization to provide the service more efficiently to more people.

At this point, human values and social values are ideally balanced and indistinguishable. However, as ideas become translated into practices, the ideas may become controlled by them. Unless the organization has provisions permitting flexibility, it may dominate the individual and force him to conform. Freedom becomes compromised, and practices established during, and valid for, one point in time impede the dynamic progress of a later era. The ideal balance between freedom and discipline is lost. Excessive discipline and insufficient freedom convert altruism and selflessness to sentimentality and regimentation.

A perfect balance between discipline and freedom, would, of course, do away with conflict. However, the elusive nature of such perfection always raises the troublesome question, "Where is the perfect balance between human values (freedom and individualism) and

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social values (discipline and altruism)?" Although this question is difficult to answer, it is the only valid one. We must not ask "Which are better—human values or social values?" It is dangerous to debate the relative merits of two "goods." It leads to the suppression of one or the other. We cannot have freedom without discipline because this is unacceptable to society and we cannot have discipline without freedom because that is intolerable to the individual. When these two goods become inbalanced, we must resolve the conflict by re-establishing an acceptable balance between the individual and society.

Human and Social Values in Historical Perspective

Although the individual in any era may approach the ideal balance of human and social values, historical periods can be defined by emphasis on one set of values as opposed to the other. Humanistic periods are characterized by free science and a striving for new knowledge. Socialistic periods are characterized by the use of knowledge for the benefit of society—that is, applied science with the development of new technology and organizational changes.

Throughout the Middle Ages, while monks preserved Galen's works with carefully hand-copied manuscripts, disease was considered a visitation of God. Observation of the patient was irrelevant, and treatment consisted in offering prayers. Medicine, like everything else, stagnated in a pool of sanctity during this authoritarian, anti-humanistic age when Ultimate Authority was invoked to explain all things.

The Renaissance represented a contrasting humanistic surge. Individual accomplishment and universal men such as Leonardo da Vinci emerged. Francis Bacon outlined the scientific method and encouraged us to follow the example of the child scientist in our quest for truth. In medicine the works of Paracelsus, Vesalius, and Paré in the sixteenth century and Harvey, Malpighi and Sydenham in the seventeenth century provided in the knowledge that finally broke the authority of Galen.

Social organization and social values were again uppermost in the eighteenth century. Only a few men such as Morgagni, Jenner, and Hunter added to medical knowledge. Theories and systems were the vogue. Systematists such as Haller, Ramazzini, and Frank formed complicated logical systems based on the knowledge obtained during the previous two centuries. Although their systems seem absurd to us now, they did assimilate previously acquired knowledge and provided the nineteenth century scientists with an organized—perhaps overorganized—foundation.

In the nineteenth century, a humanistic spirit returned and medical theories were forced to stand up to experimentation. The discoveries by Galvani, Priestly, Lavoisier, and Carnot gave medicine new research methods. Thus the two essential ingredients necessary for acquiring new medical knowledge were provided—methods and a free science without social restriction. The Paris Clinical School established physical diagnosis and made correlations between clinical and autopsy findings. Pasteur and Koch founded bacteriology. Virchow defined cellular pathology. Bernard redefined physiology. There was a tremendous expansion of knowledge and medicine began to assume the form it has today.

The expansion of knowledge in the nineteenth century imposed new obligations upon the medical profession. Synthesis was required to incorporate the new knowledge into the practice. Applied science was needed to extract from the new knowledge an improved technology and systematists were again needed to reorganize medicine and its practice. Therefore, at the beginning of the twentieth century the emphasis was again on social values.

Twentieth Century Emphasis on Social Values

Most aspects of life became highly organized during the first part of this century. The corner grocer was replaced by the supermarket, the small manufacturer was replaced by big

industry, Joe's Diner was replaced by chain restaurants, and the country doctor was replaced by the clinical specialists. In each case an individual was replaced by a smoothly operating, efficient, impersonal organization. The change in medicine during this period merely reflected this larger movement toward socialization.

The need for restatement of medicine's goals in terms of social values was particularly pressing in this country, where sudden growth and wide dispersion of population led to medical diploma mills and a low standard of medical practice. As a result of the Flexner Report, which provided irrefutable evidence of the poor quality of our medical practice and medical education, the diploma mills were closed and the remaining medical schools strove to justify their survival.

To produce a new physician better informed than his country doctor predecessor, medical education was first vastly improved and then standardized to maintain the improvement. Medical science stressed applied research, which led to new techniques and medical tools. In the hands of the new physician these tools were a formidable weapon against disease. Techniques became more complicated and further specialized training was required. Specialties sprang up and board certification insured high standards at this level as well.

Flexner had challenged the profession to provide the best medical care possible. That goal gave medicine the zeal of a "calling." It stimulated the development of schools demanding discipline and self-denial in the training of its doctors. Medicine's mission was to train doctors and care for the sick. The student was told, "Maintain a dignity that inspires confidence; utilize an objective approach toward the patient's illness and remenber medicine's obligation to society and be true to its highest principles."

This emphasis upon social values resulted in an almost unbelievable improvement in the nation's and the world's health. The population explosion is eloquent testimony of the achievement.

This emphasis upon social values also developed a medical profession primarily concerned with its duty to society. The individual physician is, as a consequence, measured by his profession on the yardstick of social values. The high premium placed upon discipline, objectivity, emotional stability, and dignity makes him guard against the human tendency to relax his discipline. The physician strives instead to acquire new skills and techniques and certification of his abilities in these techniques. This provides him with the prestige of being a specialist, or even super-specialist, and elevates him in the hierarchy of his society, the medical profession.

In the 1950's and 1960's we saw the reemergence of a humanistic, free medical research. With emphasis on "free" research has come a movement to liberalize medical education. Curricula change to stress concept rather than content and modern research techniques were incorporated into new teaching methods. Those who criticized this new direction in medical research did not sufficiently appreciate the impact of recent discoveries and they failed to make the distinction between socially dictated, "useful" applied science, and humanistic or "useless" free science, that seeks new knowledge for its own sake. This useless new knowledge will, of course, ultimately be useful, but it is unrealistic to expect the usefulness to follow immediately. We might just as well criticize Pasteur and Koch for their failure to discover penicillin and streptomycin. In the physician-patient relationship austere discipline has remained firmly entrenched. Individuality has been sacrificed to high standards and the objectivity of the physician has fostered distrust of natural human reactions. Physicians continue to have difficulty relating to people because the medicine they practice is right and proper and their posture is authoritarian. I am not convinced that we should change this pattern of activity for the physician and risk a lowering of the quality of health care. It might be much better to add paramedical personnel to the health team who can pro - vide the humanism which is now missing in the physician-patient relationship.

As we enter the 1970's, the balance between human and social values is shifting again. Free research is being de-emphasized and mission oriented applied research is in vogue. The social values will dominate the human values in research for some indefinite period. Our laboratories will direct themselves to solving the practical problems of society such as environmental pollution. Concurrently, society will demand more medical care with emphasis on improved delivery of that care to more people, especially the disadvantaged, the elderly, and the rural resident. Society will want that care delivered by people who are competent professionally, who are not overworked and who have time to relate to them individually as warm and understanding persons. Society does not want the stereotyped M.D., the authoritarian father-figure, unless they as individuals are very ill and thereby very dependent upon his professional skills for survival. Under these conditions most people are insensitive to the authoritarian manner of the physician.

The federal government has committed itself to training more health manpower and delivering more health care to society. How will it accomplish these objectives? A few years ago it was suggested that the answer to our problem was to train more M.D.'s. Special federal grants were initiated to increase enrollment in existing medical schools and construction funds were made available for building new medical schools to train more doctors. The record of increased federal expenditures and increased medical school enrollment has not been well coordinated. From 1962 to 1969 we increased total medical school enrollment (four years) from 31,491 to 35,833. This is an increase of about 1,000 M.D. graduates per year. During the same period the number of full time medical school faculty increased from 13,000 to 23,000 for a net increase of almost 10,000. Thus, for each new student added to our medical schools we added two plus new faculty members. We have now learned that adding faculty members is more expensive than adding students. From 1958 to 1968 the Federal government expenditure for teaching, training, and research grants to medical schools increased from $95 million to $615 million per year. The per cent of total medical school expenditures paid with federal funds has increased from 30 to 53 per cent in this period of the past ten years. It appears that the federal investment has been of primary value in the development and support of faculty and this has not produced a commensurate increase in M.D. graduates.

We can expect the government to redirect its funding to medical schools so that more money will be earmarked for health manpower training and less money will be available for research and research training.

I anticipate that the greatest emphasis in health manpower training will be directed toward paramedical personnel rather than a major increase in the number of M.D. graduates per year.

Since medical schools have not demonstrated that they can rapidly increase the number of M.D. graduates despite considerable financial aid from the federal government, I expect to see the rapid development of paramedical personnel who will provide direct health care to the population.

The Pediatric Nurse Practitioner (P.N.P.) represents one of several new approaches to achieve more effective utilization of existing paramedical personnel for the delivery of health care. The Pediatric Nurse Practitioner Program was developed at the University of Colorado. The nurses receive approximately four months of intensive theory and practice in pediatrics at the Medical Center in Denver. They learn improved interviewing techniques appropriate for their expanded roles and responsibilities. They become proficient in performing a complete physical examination, including the basic skills of inspection, palpation, percussion, and auscultation. They also learn to use such tools as the stethoscope and otoscope in order to increase their ability to gather data on which to base decisions. In seminars conducted by the medical and nursing faculty, the nurses learn about various aspects of the parent-child relationship, variations in growth patterns, physical and psychosocial development, and the essentials of infant nutrition. They also learn immunization procedures and

schedules. In addition, they work with a child psychiatrist and learn the essential features of personality development and directions for counseling parents in child-rearing practices. After four months of training at the Medical Center, the Pediatric Nurse Practitioner functions in the office of a pediatrician in private practice and in field stations in low income urban and rural areas, where they are readily accessible to the people. These nurses provide total well-child care and make significant contributions in the supervision of infants by giving mothers instructions regarding many items of child care. This includes formula preparation, infant feeding, bathing, toilet training, and accident prevention. They also counsel with the parents about a number of minor physical and psychological problems. The nurse's services are particularly meaningful in counseling young inexperienced mothers. Routine checkups of infants and older children, developmental testing, various screening procedures, and routine immunizations can be carried out by the nurse. The child who is ill also receives a complete evaluation including a history and physical examination. With a plan of management previously agreed upon, the nurses may handle the problem themselves or refer the child for immediate attention elsewhere. Special emphasis is placed on the importance of followup care. One recent survey has evaluated the functioning of the Pediatric Nurse Practitioner in actual practice. This survey was made in a health station in a low income urban neighborhood in Denver. It was found that 82 per cent of all the children who came to this health station (which was quite removed from any physician or medical facility) were cared for by the nurse. Seventy-one per cent were cared for by the nurse alone while in the other 11 per cent the nurse required consultation with a physician by telephone. Thus in less than one-quarter of all visits was it necessary for the nurse to refer the child to a physician or some other medical facility for additional diagnosis or care.

The pediatricians who employed Pediatric Nurse Practitioners as associates in their practices have found that such an association provides them with at least one-third more time than they formerly had for patient care, reading, attendance at meetings, and other purposes.

An attempt was also made to evaluate the professional competence of the Pediatric Nurse Practitioner. Records of 180 children who were seen both by the nurse and by a pediatrician were evaluated. One-half of the children were well, the other half were sick or injured. A significant difference in assessment by the two health professionals was noted in only two instances. In one, the nurse thought that the child had an inflamed throat; the doctor found pneumonitis. In another, the nurse also found an inflamed throat and several hours later the child was seen by a doctor who diagnosed meningitis. The child was hospitalized but the cerebrospinal fluid obtained for examination was entirely normal. In this case the nurse had probably been correct. The potential impact of the Pediatric Nurse Practitioner Program in meeting the health needs of the child population of this country has been evaluated. Since each nurse allows the pediatrician to increase his potential by at least one-third, the training of twenty nurses a year for a period of five years at each of 100 pediatric centers would more than double the amount of health care available to children.

Another type of paramedical personnel who is entering the health profession is the Physician Assistant (P.A.). Duke University School of Medicine has graduated twenty-nine P.A.'s from this program. The Duke Program recruits its students from those who have had previous health care experience, either in the Armed Forces as Medical Corpsmen, or in civilian life as practical nurses. About 90 per cent are men and the large majority of these are from the Armed Forces. This experience requirement is important in the recruitment philosophy. The candidates are usually in their mid-twenties or older and most have families. They are mature, have worked with patients, and have decided they want to pursue a career in the health field. A high school diploma is the minimal educational requirement but most have had one or more years of college. The course is two years in length with a total of about one month off during the training period. A certificate rather than a degree is now awarded; however, it is hoped that the degree option will be made available so that the graduate may complete work for a Bachelor of Science degree after the awarding of the certificate. The first nine months of the course are primarily didactic. Lectures in medical terminology, medi-

cal history, ethics, and basic laboratory procedures are given initially. Six months are spent in an integrated series of lectures arranged by organ systems and covering physiology, anatomy, disease states, and principles of therapy. During the last half of the initial nine-month period, instruction is given in history-taking and physical examination. The last six weeks are spent in an introduction to radiology, electrocardiography, and discussion of the public health system. The remaining fifteen months are spent in a series of clinical rotations. An inpatient ward rotation, an outpatient rotation including emergency room experience and a rotation in the office of a community practitioner are all required. The duties of the Physician Assistant vary according to the activities of the physician for whom he works. In the office of an internist he performs and records histories and physical examinations, helps with patient instructions, records laboratory data, completes forms, follows the patient in the hospital setting, and so on. In the office of a general practitioner he may also suture minor lacerations, change dressings, and remove casts. Any duty which the physician does repetitively might be assigned to a well-trained assistant. The assistant works fifty or more hours per week, and his beginning salary is approximately $10,000 per year. It is the impression that physicians are supportive and enthusiastic in the development of this kind of assistant. Perhaps their attitude is related to the fact that they realize that few other solutions are readily available for reducing their workload and permitting them to see more patients. It will be necessary to provide refresher courses for the P.A. so that he can learn new techniques or review areas previously learned but not used. In this respect he is the same as the physician. His education is never complete, he must always be a learner. The question of licensing has come up in many areas and it appears that the best approach will be to provide a minor revision of medical practice acts to authorize delegation of tasks by physicians to trained assistants. For many Physician Assistants the obtaining of an M.D. seems too difficult and too remote to be a practical goal. A career as a Physician Assist seems to be an attainable and satisfying alternate for them. In the opinion of the people who have developed the program at Duke, the use of such personnel as the Physician Assistant will become an obligatory part of any practical future modification of the health care system. It is only through the use of such personnel that we will be able to make maximal use of scarce and expensive professional manpower. Undoubtedly the physician must take an active role in the training of his own assistants just as he must be responsible for their correct use.

Medical educators and health administrators in government have accepted and are now promoting programs of training for paramedical personnel. There is still room for further innovation and I expect that pharmacy as a profession will promote new programs for increased utilization of the pharmacist in the health team. Before turning to the future role of the pharmacist, let me review the future projections of the business community with respect to the marketing of drugs and health care products.

It is projected that a system of inexpensive motel-type parahospitals for ambulatory and convalescent patients will be in existence within ten to fifteen years. This system of parahospitals will care for at least one-half of the total patient population now found in major intensive care hospitals (currently 28 million patients per year). It is also projected that one-third of nonhospital patient visits will be for routine screening, immunizations, and well-patient care. These visits will take place in the M.D.'s office, decentralized satellite health centers, and/or parahospitals. All of this represents a substantially increased market for diagnostic equipment, materials and supplies, laboratory equipment and supplies, and immunization medications. Rapid automated methods for performing and evaluating most diagnostic tests will be in widespread use. Paramedical personnel will be utilized in increasing degrees to provide diagnoses and prophylaxis of disease. Some authorities predict that over one-half of the visits by patients outside the hospital will be specifically to non M.D. paramedical personnel (the M.D. will not see these patients). Few, if any, M.D.'s will be in private practice. There will be ultraspecialists who do only single procedures and who have limited breadth of training. Virtually all M.D.'s will be in clinics or prepaid health care groups located in local or regional medical centers. The typical M.D. will spend less than one-quarter of his time on direct patient care. The new intermediate type of practitioner whose training lies between the M.D. and the nurse will constitute the majority of practicing medical personnel.

Medicine of the future will be compartmentalized into ordinary and serious illness categories. The ordinary illnesses will be cared for mainly by paramedical personnel; the serious diseases will be handled by the M.D.'s and ultraspecialists. Prepaid health care groups will not only attend the ill but will also conduct a significant well-patient care program for the prevention of disease. The delivery of health care will be oriented to keep people out of the hosptials. The existence of organized health care satellites and parahospitals will make it possible to assure good health care in physically dispersed centers.

The marketing analysts also have some specific projections with respect to pharmacy. They project that there will not be very many independent pharmacies in the future. Pharmacists will be employees of group practice, of clinic health centers, parahospitals, and intensive care hospital pharmacies. A major activity for the pharmacist in these places will be to stock and dispense those drugs contained in the computer formulary. The future computer may well match up diagnosis to the choice of treatment and represent in effect an automated formulary and treatment guide. In the large hospitals we can be sure that clinical pharmacists will make ward rounds with doctors and act as consultants. In a recent article in Modern Medicine the future role of the clinical pharmacist was described in the following way: The pharmacist will look up the code number of the drug decided upon for a case and step to the bedside console and dial the pharmacy. This will connect him with the automatic drug dispensary and he can then dial the code number of the prescribed drug. This will activate a computer directing a pickup device in the pharmacy to select the prepackaged medication and deposit it in a pneumatic tube that sends it swiftly to the console in the room from which the call originated. In a matter of seconds the clinical pharmacist will have the package medication in hand, check the labeling and confer with the attending physician concerning the dosage directions. He may then hand the medication to the nurse for administration or possibly he may administer the drug personally. A prototype of this kind of hospital unit which makes use of the clinical pharmacist has already been exhibited at a recent meeting of the American Hospital Association. The automated computer controlled drug dispensing system will save the pharmacist's time and will also reduce the workload of the doctor and nurse.

The Future Role of the Pharmacist

I have referred to the clinical pharmacist as a new member of the future health team. You have such a program in operation at the University of Wisconsin for the training of clinical pharmacists. Your curriculum committee has also recommended new courses with a clinical orientation; a survey of disease states, two semesters of pharmacology and a semester of toxicology. Such developments suggest to me that the pharmacist will be better trained in theoretical knowledge about drugs than his M.D. counterpart. The important missing link in the training of the pharmacist which would qualify him to deliver health care to the patient is that he lacks clinical experience in the use of drugs.

The Physician Assistant and the Pediatric Nurse Practitioner are examples of health professionals who will assume some responsibilities in drug administration and monitor the response of the patient to drugs. I think the pharmacist could assume comparable or greater responsibilities in the administration and monitoring of patient responses to drugs if he received some additional clinical training. I feel that all pharmacists should receive some clinical training and new programs should be developed so that pharmacists can become more involved in the delivery of health care to the public. Your current academic program of two years of liberal arts training plus three years of pharmacy provides an excellent preparation for further training in clinical medicine. One year of clinical training could expand the role of the hospital pharmacist or clinical pharmacist to include the administration of drugs to hospital inpatients as well as monitoring the response of the patient to his medication by physical measurements or chemical measurements.

With two years of clinical training I would expect the pharmacist to be able to develop some diagnostic skills in addition to enhancing his ability to administer and monitor drug

responses in an outpatient population on chronic drug therapy. Such patients would require only occasional visits to a physician for evaluation. I could envision this kind of pharmacist working in a health clinic where he supervised the work of a medical technologist who performed routine clinical laboratory determinations on blood and urine as well as x-ray and ECG tests. Such facilities would permit the local population to be periodically evaluated for the detection of disease. A nurse or Pediatric Nurse Practitioner could provide well baby care and immunization programs in this setting as well as limited emergency room care for minor injuries. The pharmacy could emerge as the neighborhood or rural health clinic of the future and provide diagnostic as well as treatment facilities for an expanding population that finds it inconvenient or too costly to obtain these services through existing personnel and facilities. The pharmacist of today can expand his professional skills beyond the dispensing of medication to include some diagnostic skills and provide multiphasic screening procedures for the detection of disease as well as monitoring the response of outpatients receiving chronic drug therapy. The pharmacist can also supervise public health programs involving immunization procedures and periodic health examinations for children and adults. He has the basic training to expand his role in the delivery of health care and I personally hope that the profession of pharmacy will move ahead rapidly to provide personnel to fill some of the needs I have described. The present training programs for Physician Assistants and Pediatric Nurse Practitioners suggest to me that the pharmacist with five years of university training is being underutilized in the delivery of health care to society.

Sources:

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