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**Cover:** Drugs—Old and New. See Symposium on Clinical Pharmacology

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There is a similarity in the approach taken by Dr. Wolf (Dr. Stewart G., the 1967 Stoneburner Lecturer) and Col. Moser to the one I will present to you. Dr. Wolf is interested in why some people die suddenly and why others do not. What are the factors responsible for predisposition? The major theme of our studies on the epidemiology of adverse drug reactions has been to gain understanding of why some people will have trouble and others will not when given the same drugs in essentially the same way and for the same reasons. Col. Moser spoke to the problem of adverse drug reactions, i.e., their recognition, identification, and documentation. Epidemiological methods allow us to identify reactions, when they occur, and to establish the risk involved in administration of drugs to patients.

In any epidemiological study there are two pieces of information that must be accumulated. One is denominator data and the other is numerator data. When we began our studies about five years ago, our initial attention was directed toward assembling denominator data. How many drugs are used? What patients receive them? Under what circumstances? These data identified the population at risk. One should also know the dosage form in which the drug is administered, and have information on the duration of therapy. Unfortunately, the latter two pieces of information are difficult to obtain, because, as Col. Moser has pointed out, the accumulation of masses of information on patients at risk and the drugs they receive is an overwhelming task requiring automatic data processing. At present, in most hospitals, it is impossible to retrieve information on dosage form or duration of therapy, although in most instances it is possible to identify the population at risk receiving given groups of drugs.

Drug Usage in Hospitals

I will summarize some of the pertinent observations that we have made during the course of our investigations.

The most frequently used drugs in a hospital, as you might expect, are tranquilizers and sedatives. It is interesting, however, in reference to Col. Moser’s paying particular attention to tetracycline, that in one survey at the Johns Hopkins Hospital, five of the ten most commonly prescribed drugs were antimicrobial agents.

The studies that I will speak about were confined largely to an evaluation of drug usage and adverse reactions to drugs on a medical service at the Johns Hopkins Hospital. This included an evaluation of private and public patients. The results were in essence identical, so there is no point in differentiating them.

On the medical service at the Johns Hopkins Hospital the average number of drugs given to a patient during hospitalization was 11. This ranged from zero to 42 different drugs. We have identified only one patient who received no medication during hospitalization. It is interesting to evaluate the kinds of drugs patients receive. In one study, evaluating all the patients in the hospital receiving methicillin, we identified a patient who received 37 different drugs, and this patient received five different antimicrobial agents during the course of hospitalization. In other university medical centers, the average number of drugs administered to patients on medical services is about 10 to 14 different medications during hospitalization.

Examining drug usage can be a useful exercise. It’s not just a collection of meaningless data. I would like to point out one example of how this was important at Johns Hopkins Hospital.

During the initial phase of our study on drug usage, we became aware that the surgical service used the most chloramphenicol in the hospital. We investigated the patients on the surgical service who received chloramphenicol. Most of the patients received the drug prophylactically, in an attempt to prevent wound infections. But the interesting thing was to determine why chloramphenicol was being used as a prophylactic drug, when this is not considered advisable. Two years before, one of the surgeons on the staff had done a study...
of the effectiveness of chloramphenicol in prevention of postoperative wound infections. He had instituted a study with a double-blind placebo and the housestaff administered the drugs in random fashion to the patients on the service, some getting chloramphenicol and some getting placebo. The study was conducted for six months. The surgeon evaluated his data, found no difference in the frequency of wound infections, and terminated his study. By this time, the surgical staff had become accustomed to using chloramphenicol prophylactically, however, and the practice was perpetuated. When this was brought to the attention of the surgeon-in-chief, some curtailment in the use of chloramphenicol was possible.

Detection of Adverse Drug Reactions

Identification of adverse drug reactions, when patients receive 11 different drugs, is a problem. When a reaction occurs or when some anticipated illness develops how can the physician 1) be certain that it is an adverse reaction to a drug, and 2) identify the specific drug responsible for the adverse effect. When a patient develops a febrile reaction or granulocytopenia during hospitalization, and he is receiving 42 different drugs, you tell me which one is involved! We can go to the literature and identify those drugs incriminated previously, but we may overlook the one that is specifically involved.

Methods of Detection

What are some of the methods that can be employed for detection of adverse reactions? The AMA Registry on Drugs and the Food and Drug Administration are using voluntary reporting, the system we initially adopted. In epidemiological studies, however, one needs a complete numerator and denominator. Otherwise incidence and rates cannot be accurately determined. We instituted a voluntary reporting system throughout the Johns Hopkins Hospital for one year. The average number of adverse reactions reported initially was 15 per month. It gradually went up to 25 per month at the end of the year. We thought this was under-reporting, so an effort was made to examine the records of patients upon whom reports had been obtained, as well as those on whom reports had not been obtained. Only one-tenth of all significant adverse reactions had been reported voluntarily. Obviously voluntary reporting is incomplete. Its greatest usefulness is in the identification of previously unrecognized ill effects of a drug.

The only way to collect complete data is by personalized surveillance. This can be done, prospectively or retrospectively, and we have done both. A retrospective analysis is notoriously inadequate. To evaluate this we selected the records of patients who had been given Warfarin. The ill effects of anticoagulant drugs are readily identifiable. In a retrospective analysis 10% of the patients who received this anticoagulant drug had some manifestation of bleeding, gross or microscopic. The commonest site of bleeding, of course, was in the urine. Most commonly the bleeding was microscopic. Occasionally, blood was found in the feces, but subarachnoid hemorrhage and massive bleeding into the pleural space following thoracentesis was demonstrable. This method too, however, was an inadequate way of obtaining data, because doctors are not good at recording reactions in patients' charts. This is illustrated by the fact that the majority of the patients receiving Warfarin had one urinalysis and had one stool examination for occult blood done during hospitalization and that was the day of admission. Generally these examinations were not repeated. The necessary tests were not done to detect the most common sites of bleeding in patients receiving anticoagulants.

Personalized prospective surveillance was the only way to obtain complete information. Three methods have been evaluated: 1) surveillance of all patients receiving a particular drug in the hospital; 2) surveillance of all patients with a particular disease in the hospital, the drugs they receive, and the reactions they may develop; 3) surveillance of groups of patients, such as those on a medical service or surgical service. The latter is the one that has proven, in our hands, the most useful in uncovering information relevant to the factors that predispose patients to reactions.

Definition of a Reaction

Another problem is the definition of a reaction. It can be defined by mechanism involved, clinical features, or in terms of severity or probability. Severity is relatively easy to note: 1) fatal or life-threatening; 2) requiring an antidote or long hospitalization; and 3) an annoyance. The real difficulty is documenting the probability of a reaction. These are the systems that we have employed: 1) A documented reaction is one known to occur, with a clear temporal association with the administration of the drug; on re-challenge the patient has a recurrence of the reaction; or there is some confirmatory laboratory test establishing that the drug is incriminated in the patient's illness. 2) Probable reactions that have a temporal relationship, are known to occur and disappear on withdrawal of the medication. We have ignored other reactions which are possible, because we cannot in those instances establish this as an adverse drug effect. I would like to show you examples of problems in identifying drug reactions. A 6-year-old boy with a tetralogy of Fallot was seen in the hospital for surgical cor-
resection of his cardiac defect. He was put on penicillin and streptomycin prophylactically. Following operation he developed progressively increasing fever, leukocytosis, mild anemia, weight loss, and anorexia. He had multiple blood cultures taken which were negative. He had no splenomegaly, nor did he have microscopic hematuria or petechiae, but the surgeons felt that he must have a post-cardiotomy infection. The dosages of the anti-microbial drugs were increased, and others were added. The therapy was continued for seven weeks at which time I was called in consultation. It was suggested that the patient might have drug fever. Streptomycin, tetracycline, and erythromycin were stopped without any termination in the patient's course. Eight hours after the penicillin was stopped, the patient was afebrile and left the hospital four days later. This boy had fever as the only manifestation of the ill effects of a drug, and this was confused with infection. A young woman was seen in the emergency room because of a streptococcal sore throat. She was given penicillin. Within 48 hours, she returned to the emergency room with a florid confluent erythematous rash, and a diagnosis of scarlet fever was made. The girl did not have scarlet fever. Following recovery, after discontinuing her treatment, she was given penicillin again and had a recurrence of the reaction. Again identification of a reaction and differentiating it from a naturally occurring disease complicated the identification of a drug reaction.

**Adverse Reactions Occurring in Hospitals**

With this as background, let's look at the overall problem of adverse drug reactions in the hospital. On the medical service of the Johns Hopkins Hospital 5% of all the patients are admitted to the hospital with an adverse drug reaction. Four percent of the patients are admitted to the medical service, because of adverse effects of drugs. Adverse drug reactions as a cause of hospitalization represent the seventh most common reason for admission to the medical service. Of those patients admitted to the hospital who have a reaction at the time of admission, 30% will have a reaction to another drug during the course of hospitalization. This contrasts with an overall rate of reactions to drugs of 10% in all patients on the medical service. This means that the patient who has had a reaction to a medication has a three-fold greater likelihood of having a reaction to another drug during the course of hospitalization. This identifies patients with a pronounced predisposition to the occurrence of reactions.

A patient with miliary tuberculosis who was comatose when admitted to the hospital, was put on INH, PASA, and streptomycin. During the course of the first five or six days of hospitalization she defervesced, and regained consciousness. She developed an exfoliative rash and because of this it was necessary to stop all of her medication. At that time her temperature declined and her exfoliative rash disappeared. She still had her miliary tuberculosis, so she was put back on INH, but this time she developed a follicular rash over the face. An industrious intern aspirated one of these and grew a Staphylococcus albus. He was alarmed that the patient might be developing staphylococcal sepsis, and gave the patient an injection of penicillin. She went into anaphylactic shock, requiring hydrocortisone and norepinephrine. All drugs were again stopped, except that steroid and digitalis were continued. Again, the patient required treatment for her tuberculosis. While on prednisone she was given a single dose of PASA, and had a frank chill with a prompt rise in temperature. Subsequently, she was given a single dose of streptomycin, and again had a prompt chill and recurrence of fever. During the course of these 70 days of hospitalization, this patient had documented reactions, to paminosalicylic acid, penicillin, streptomycin, and INH.

I would like to return briefly to the problem of severity. Not all reactions to drugs seen in hospitals are mild. Mild reactions account for almost half of those observed. Correspondingly almost half of the patients had reactions sufficiently severe to warrant the physician's giving an antidote, prolong hospitalization or to threaten life. Seven percent of the patients with adverse reactions had life-threatening or fatal reactions.

Gastrointestinal reactions to drugs are particularly common in women. In a report by Jordan and Dingle, women with colds also have an increased frequency of nausea, vomiting, and diarrhea. Whether this is a specific effect of drug reactions or whether it is a peculiarity of females, I don't know. Nevertheless, in all of our subsequent studies we have eliminated the minor gastrointestinal reactions, because we cannot be certain of the relationship to the drug itself. It should be emphasized, however, that adverse effects of drugs frequently mimic natural disease.

Tranquilizers and sedatives rank far above any other drugs as causes of ill effects in patients. Antimicrobial and cardiac drugs, however, are near in importance of ill effects in hospitalized patients. There is wide variation in rates of reactions to different drugs. The range was from 27% (probenecid) down to 3.1% (mercaptomerin). Col. Moser made the point that before the physician can significantly weigh benefit with risk, he must have such data as this, citing incidence as well as severity. Unfortunately, such data is usually lacking at the present time. In contrast to Col. Moser, however, I do not believe the present systems of the
AMA Council on Drug and the Food and Drug Administration will get us to the point of determining the exact risk.

Severity of Reactions

Patients do die of drug reactions in the hospital. During one three-month period on the medical service of the Johns Hopkins Hospital, there were five deaths due to drugs in hospitalized patients. It is possible for the physician to avoid some of these lethal effects as illustrated by these patients. A middle-aged man admitted to the hospital with chronic pulmonary disease had a coin lesion in his lung. During the course of his hospitalization it was decided that he should be bronchoscedoped. The pre-bronchoscopic medications were promazine, pentobarbital, and morphine. This medication was given and he was taken to the endoscopy room where he developed respiratory arrest. He was given artificial respiration and returned to the ward without bronchoscopy with the advice of the endoscopist that the patient should not be bronchoscedoped because of the problem of premedication. Two weeks later there was a change of physicians on the ward. They were fully aware that the patient shouldn't be bronchoscedoped, but they needed a study to identify the nature of his pulmonary disease. A bronchogram was decided upon. The pre-medica-tions for bronchography were promazine, pentobarbital, and morphine, of which the physicians on the ward were unaware. The pre-medication was given, and within a very short time the man went into shock, cardiac arrest, respiratory depression, and died. Another patient was a young woman who during her prepartum period on the obstetrical service had been found to have a minor urinary tract infection and was given sulfisoxazole. Her bacteriuria cleared, but she developed an urticarial and erythematous rash. A note was written in the progress notes by the obstetrician that the patient was allergic to sulfonamides and the drug was discontinued. Following delivery, the woman was again found to have bacteriuria. She was now no longer an obstetrical patient and was referred to the medical clinic for evaluation. The obstetrical records were kept in a different part of the chart from the medical records. Frequently the internist doesn't read the obstetrician's notes. Nevertheless, the internist recognized the bacteriuria and re-prescribed sulfisoxazole. Very shortly thereafter she had gross hematuria. She was admitted to the hospital hypertensive, had sulfona-mide crystalluria, and died in renal failure. Autopsy revealed she had typical sulfonamide crystals in the tubules of her kidney. She undoubtedly died of sulfonamide-induced allergic vasculitis. This illustrates some of the settings in which lethal effects of drugs can be observed and how they can be avoided.

We have been unable to confirm any relationship in the patient with atopy and the subsequent development of allergic or other reactions to drugs. However, history of an adverse reaction to any drug is associated with a significant increase in the frequency of reactions to other drugs subsequently administered. So there is something peculiar about people who have trouble with drugs. Whether this is heritable or what the factors are that are particularly involved remains to further study.

Number of Drugs Administered

An important factor related to the occurrence of adverse reactions to drugs in hospitalized patients is the number of drugs administered. When one exceeds a total of six drugs there is a logarithmic increase in the likelihood of the patient's having an adverse reaction to at least one drug. Of the patients receiving 16 drugs during the period of hospitalization, 45% of them will have an adverse reaction to at least one drug that they have during the period of hospitalization. If I were to recommend one thing that would significantly reduce the problem of the ill effects of drugs, it would be to curtail the use of innumerable drugs. This is undoubtedly the most important factor we have thus far identified. Why this curve is logarithmic I don't know. Our present feelings are that much of this is a problem of drug interaction, interactions that conceivably have not been identified and are unrecognized.

In studies of pneumonia the rate of allergic reaction to penicillin rarely is less than 10%. Yet in patients receiving penicillin in V.D. clinics, the rate is usually less than 1%. Is there a relationship between the presence of infection and the occurrence of allergic reactions to drugs? We have shown such a relationship which I think deserves further study. It's our present supposition that a severe infection may serve as an adjuvant to an immunological response to a simple chemical agent.

Over three times more men than women receiving penicillin in the hospital will have allergic reactions to this drug. By history the men in this study had received penicillin in the past no more frequently than women.

Conclusion

I would like to conclude by citing two other rather interesting observations we have made. Three-quarters of all the patients in all our surveillance who have allergic reactions to drugs have had peptic ulcer, ulcerative colitis, or neo-
plastic disease of the gastrointestinal tract. Of these patients, three-quarters of the drugs producing allergic reactions are administered orally. The rates of allergic reactions to individual drugs in patients with gastrointestinal disease as opposed to those without gastrointestinal disease receiving the same medication, are significantly increased. What the impact is of inflammatory gastrointestinal disease 1) upon the absorption of the drug, 2) upon its metabolism, and 3) upon its antigenicity has not been investigated before. But from these studies it is suggested that inflammatory disease of the gastrointestinal tract may be an important factor predisposing patients receiving oral drugs to occurrence of allergic reactions. It has commonly been supposed that patients with autoimmune disorders, e.g., systemic lupus erythematosus, may have a predisposition to multiple allergic reactions to drugs. In our evaluation of this problem, there is no significant increase in the occurrence of allergic reactions to drugs in these patients.

I would like to end with some unresolved questions. We obviously need more information on rates of reactions to drugs. Without this the physician is ill prepared in estimating risk as opposed to benefit. As Col. Moser pointed out, we can go 20 years before identification of a possible relationship of thrombocytopenia to tetracycline. It took six years to identify aplastic anemia in relation to chloramphenicol. There must be some better way to identify the ill effects of drugs than just by the casual, incidental, periodic reporting in the literature by physicians who suspect or identify relationships. I happen to think this is the greatest value of the Food and Drug Administration and the AMA Council on Drugs Registry on adverse reactions. Unfortunately, however, most of the reactions reported are those that we know exist. As far as I am aware, in the FDA program in operation in a multiplicity of hospitals voluntarily reporting adverse effects of drugs has not identified a single previously unrecognized ill effect of a drug that would not have been detected as promptly otherwise. We need a great deal more information about how drugs are used outside of the hospital by patients who can buy them in the drug store without prescription. I was recently amazed when a pharmaceutical representative came into my office, and I commented about how many drugs patients kept in their cabinets at home. The pharmaceutical representative was intrigued and came back the following day having counted the number of drugs in his cabinet—90! It is my impression that most of the patients who developed Fanconi syndrome from outdated tetracycline were children whose mothers had been given tetracycline by the physician, had kept it on the shelf, and then when the child got ill had given it to him. I think it’s critically important that the public be informed as much about the problem of drugs as the medical profession.

We do it poorly. We let journalists write about how horrible hospitals are, but I have yet to see anybody in the medical profession make any exertion to inform the public about the use of non-prescription drugs. We need a great deal more information about what heritable factors cause reactions to drugs. I have indicated some factors that suggest this may be far more important than we have previously recognized. We need more information on other factors—diseases and organ function—which influence predisposition to drug reactions. Most studies done on the metabolism, absorption, and excretion of drugs are performed in normal people. They are not comparable to patients in the hospital who have fever, renal failure, minor abnormalities of liver function, who have respiratory embarrassment and are in heart failure. We need a great deal more information about the reactions to drugs in patients who are sick, as well as we need increasing information about the problems of drugs in people who are well. Thank you.
Pharmacology of Anti-Anginal Agents

MAURICE McPHERSON

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For me, 1967 is a double centennial year; it commemorates both the year of Canadian Federation and the first use of nitrites for angina pectoris. It was in 1867 that Lauder Brunton published his paper in the Lancet on the use of “Nitrite of Amyl for Angina Pectoris” (Brunton, 1867). It is sad to reflect that apart from this one lucky break this is really the only significant progress we have made in the treatment of angina pectoris in the last hundred years. The reason for this lack of progress is that we did not understand why nitrites were so beneficial and, consequently, we supplied explanations which were incorrect. Having done that, we subsequently have tried to produce better drugs with the same presumed action. When Brunton wrote his paper he deduced that the pain of angina was related to an elevation of blood pressure. He knew that nitrite of amyl could produce prostration and a thin thready pulse, and he thought it probably worked by lowering the blood pressure. For some time thereafter other drugs that were supposed to lower blood pressure were given therapeutic trial. Then, it was discovered that injection of nitrites into the coronary artery of an animal caused an increase in coronary flow. From this time on it was assumed that nitrites relieved angina pectoris by increasing coronary flow. It is for this reason that, if you want to look up anti-anginal drugs in any contemporary textbook, you must look them up under the title of “Coronary Vasodilator Drugs.”

For the last 40 years or so manufacturers have continued to produce more potent vasodilator drugs as judged by their ability to increase coronary flow in the normal heart. Unfortunately none of them has worked. The drug that drew my attention to this dilemma is one of the most potent of these preparations, dipyridamole (Persantin). While nitroglycerin produces only a small increase in coronary flow, lasting from 30 seconds to 1 minute, dipyridamole, given in a reasonable dose intravenously or by mouth, may double coronary flow for 20 to 30 minutes. It will do this without increasing myocardial oxygen consumption, so that the whole myocardium and the coronary sinus blood oxygen content increase proportionately. This ought to be beneficial if increasing coronary flow is going to relieve angina, and for this reason we carried out a careful clinical trial of this agent (Kinsella, Troup, and McGregor, 1962). We could find no therapeutic effect at all. Following this experience we decided to pause and try to review the pathophysiologypathy of angina and to consider in what ways it might theoretically be influenced by therapy.

Pathologic Physiology of Angina Pectoris

Firstly, we now know that angina pectoris is not just a sensation of pain and discomfort. It is a syndrome which includes not only pain, but also electrocardiographic changes, a shift to anaerobic me-
tabolism with production of lactate and acute left ventricular failure, when the involved muscle mass is large enough. We also know that this syndrome occurs whenever there is a discrepancy between the demand for myocardial oxygen and its supply. This discrepancy may, therefore, be correctable by reducing oxygen consumption or by increasing oxygen supply.

Normal oxygen supply demands fully oxygenated blood and normal hemoglobin. When the anginal patient suddenly gets worse it must not necessarily be concluded that one of his coronary arteries has become occluded, though this may of course be occurring. It could well be that his hemoglobin has dropped due, e.g., to bleeding piles or a peptic ulcer. Alternatively he may have become anoxic due to pulmonary embolism or pneumonia; or he may have inactivated up to 20% of his hemoglobin by smoking excessively. Likewise, his coronary flow may be very dependent on an adequate arterial pressure. Thus angina may be precipitated in the hypertensive patient with coronary disease by the successful treatment of hypertension. Whenever angina becomes exacerbated, these possibilities should be considered first.

The discrepancy between oxygen supply and demand can also be influenced, of course, by changes in myocardial oxygen consumption. Dr. Richardson (Dr. David W., an earlier speaker at the symposium) has been telling us that the amount of tension developed by the muscle fiber and the rate with which it is developed are the two critical determinants of oxygen consumption. However, the tension developed is influenced by two major variables. One is the amount of pressure developed in the ventricular chamber, and the other is the ventricular volume. According to the relationship between tension, pressure, and radius described by Laplace, the tension necessary for each fiber to develop a certain pressure will increase with the radius of curvature of the ventricle. A small ventricle can thus produce the same pressure with a smaller wall tension. It is more efficient. All other things being equal then, one might expect angina to be exacerbated by ventricular enlargement and improved by reduction in ventricular size. Fear or emotion causing increased sympatho-adrenal activity will increase both the force of contraction, the rate of development of tension, and the heart rate. These are good reasons why the blocking agent Propranolol, referred to earlier in this symposium, ought to raise the anginal threshold. The disappointing thing is how relatively poorly it does work, and I think, used at random in an anginal population, this drug is probably going to have more dangers than benefits. There are people, however, such as the thyrotoxic and the patient who gets pain associated with emotion, in whom I suspect this drug will prove to be extremely beneficial.

**Mechanism of Action of Nitrites**

Let us now consider the possible mechanism of action of the nitrite drugs, because these are the only really useful group of drugs available to us. First of all, it is clear that they do not just act by relieving pain. They are capable of lowering ventricular end-diastolic pressure, of abolishing the lactate production in the myocardium, and of abolishing the electrocardiographic changes of angina. The question is how they achieve this effect. Theoretically, they might either decrease myocardial oxygen consumption, or increase oxygen supply, or do both at once.

The prime effect of the nitrates is on vascular smooth muscle, and they cause an increase in large vessel diameter with verno-dilatation. When administered to a resting subject or to an anesthetized animal there is a fall in venous pressure, venous return to the heart, ventricular volume, cardiac output, and blood pressure. As we have seen, these effects should reduce myocardial oxygen consumption and may well explain the relief obtained by this drug in the resting subject. However, nitroglycerin will also produce relief in the exercising subject, and it is unlikely that the same mechanisms operate. For example, we have found that when patients are cycling on an ergometer a nitroglycerin tablet may actually increase the cardiac output, and the hypotensive effect of the drug is almost completely abolished (Hoeschen et al., 1966). Thus we have turned again to the possibility that nitrates may indeed exert their effect by changing coronary flow.

Now I would like to distinguish carefully between increasing coronary flow in a normal heart and re-distributing flow to the most ischemic areas of a chronically diseased heart. On consideration it would seem that the very last drug that you would choose to relieve angina pectoris is one which increases coronary flow in the normal heart. There is already present an extraordinarily effective mechanism which will increase or reduce coronary flow according to the local metabolic need, and as far as we can see it is geared very closely to oxygen tension. Any substance which increases coronary flow in the normal heart must do so by interfering with this autoregulatory mechanism, and it has been shown that this mechanism is completely paralyzed following a dose of a potent vasodilator drug such as dipyridamole (Farn and McGregor, 1967). This cannot be beneficial if local hypoxia is already causing maximum flow to the most ischemic areas of heart muscle. Indeed, in the presence of coronary narrowing it might even have an adverse effect by increasing flow to non-ischemic areas of heart muscle.

In atherosclerotic coronary disease it is the large coronary vessels
which are narrowed. Studies which Dr. W. Fam and I are carrying out at present indicate that these vessels take no part in autoregulation. Thus to increase flow through them it is necessary to use a vasodilator substance which will act at this site in the coronary tree. It may well be that the diseased vessels themselves are incapable of vasodilatation, but as you well know the ischemic areas of muscle may be partly or wholly supplied by collateral vessels arising from healthy neighbouring coronary arteries. A drug which acts on these arteries may be expected to increase flow into the ischemic areas of the heart through collateral channels. It is probably significant that this is precisely the site of action of nitroglycerin.

Angiographic observation tells us that a nitroglycerin tablet will increase the size of all the larger coronary arteries for several minutes, and we have found that the effect of nitroglycerin is almost completely confined to the larger vessels (McGregor and Fam, 1966). Furthermore, when a coronary branch of a dog is gradually narrowed, thus creating obstruction, nitroglycerin can be shown to augment the collateral flow into the ischemic area. Dipyridamole, which acts principally on the small coronary vessels does not have this effect (Fam and McGregor, 1964).

Conclusion

In conclusion I would like to stress that these observations do not constitute direct evidence of the mechanism whereby the nitrates relieve angina pectoris. It is probable that they are capable of causing some reduction of myocardial oxygen consumption. However, there is increasing indirect evidence which suggests that the site of action of these drugs is principally on the large coronary arteries. Their administration may thus relieve coronary spasm, if this ever causes angina, and more importantly will increase collateral flow into ischemic areas of myocardium when collateral channels have become enlarged. Drugs such as dipyridamole which seem to act on the small vessels, which are the site of autoregulation, are unlikely to have this effect. Indeed, if the autoregulatory mechanism is necessary to direct a limited blood flow to the most ischemic areas of myocardium, such drugs may theoretically be harmful.

References


Some Perspectives on Immunosuppressive Drugs

ROBERT S. SCHWARTZ

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My coming here to Richmond to discuss immunosuppressive drugs is surely carrying coals to Newcastle, because the Medical College of Virginia has been a leader in this field, particularly with reference to transplantation of the kidney. I don't know what I can tell you that you already don't know about immunosuppression; nevertheless, you might be interested in learning of our own experience with these drugs.

The four main classes of cytotoxic drugs of interest to the immunologist are the alkylating agents such as nitrogen mustard and cyclophosphamide, purine antagonists (6-mercaptopurine and azathioprine), the pyrimidine antagonists such as 5-fluorouracil, and finally the extremely interesting and potentially versatile agent methotrexate, a folic acid analog. Our laboratory has chosen to focus its attention on a single class of these compounds, the purine antagonists, in an attempt to find out as much about their immunological properties as we can. I plan to discuss two aspects of this work: 1) Some of the effects of 6-mercaptopurine (6-MP) in experimental animals, and 2) some of the effects of its analogue, azathioprine, in man.

### Purine Antagonists

6-Mercaptopurine, a rather simple analogue of hypoxanthine, has very powerful effects on cellular metabolism. Azathioprine was synthesized with the hope that it would have a higher therapeutic index than the parent compound. Its imidazol ring was attached to the sulfur atom in the expectation that this would slow down the metabolic degradation of 6-MP. Azathioprine does in fact appear to have a higher therapeutic index when compared to 6-MP in mice, but this has not yet been established in man.

6-Mercaptopurine has two major immunological properties that can be demonstrated in experimental animals. The first of these is suppression of humoral antibody synthesis. Animals given only a one-week course of 6-MP fail to elaborate a normal primary immune response. The second major effect of this material is on transplantation immunity; a significant prolongation of homograft survival can be obtained in a variety of animals treated with 6-MP.

One of the fundamental problems in this field, in fact the problem which I believe to be central to rational and successful immunosuppressive drug therapy, is that despite the very specific biochemical sites of action of various antimetabolites, the final result in an organized cell is its death. Regardless how specific the biochemical effect of an antimetabolite may be, the end result is disintegration of the metabolic cycles of the cell. Therefore, the central question is whether any specific immunological effects can be obtained by the use of materials which are really cell poisons. In my view, it is worthless to pursue a generalized destruction of the immune capability of an individual in order to achieve immunosuppression, whether in the treatment of an immunological disease or in the establishment of a functioning tissue graft. We would be trading a possible clinical effect for an immunological cripple.

### Immunological Effects of Cytotoxic Drugs

Quite surprisingly, specific immunological effects can in fact be obtained by cytotoxic drugs. Depending upon the experimental design, it is possible to delete a specific immunological reactivity without affecting an immune response to a randomly selected antigen. Such an animal is not an immunological cripple. It has acquired immunological tolerance of an antigen used during the period of chemotherapy. If this can be obtained in an experimental animal, there is every reason to believe that it can be also achieved in man.

One other effect of 6-mercaptopurine, and probably of other agents, which is of considerable importance in attempting to assess the reason for their clinical effectiveness, is illustrated by experi-
ments on suppression of the Arthus reaction in hyperimmunized rabbits. In these animals the peripheral expression of immune injury has been eliminated without an effect on the synthesis of antibody. Or, to put it differently, 6-MP has, in addition to its capacity to suppress antibody synthesis, a very potent anti-inflammatory effect. This will be seen time and again in clinical material.

**Mechanism of Action of Cytotoxic Drugs**

The mechanism of action of these drugs in patients with diseases presumed to be on an immunological basis is far from clear. Some of the questions we have posed include: 1) Does immunosuppression in fact occur in patients treated with these agents? 2) Can selective immunosuppression be achieved in man? 3) Is there any correlation between the degree of immunosuppression achieved with these agents and the clinical response? In order to gain some insight into these questions, the immune responses of a group of patients treated with either azathioprine or amethopterin were measured. Keyhole limpet hemocyanin (KLH), a powerful antigen long used in experimental animals, but never before applied to the study of human immunity, was used to evaluate the primary response. In normal subjects it provokes both a circulating antibody response and classical delayed hypersensitivity. Diphtheria toxoid was used to study the secondary response. In about a third of the patients, both primary and secondary immune responses were completely ablated during chemotherapy. In another third of the patients the primary immune response was completely suppressed, but a relatively normal secondary immune response occurred. Another third of the patients had a most interesting type of immune response while on continuous or even intermittent drug therapy. This can be called the "accordion" effect. When compared to the normal immune response, the induction period is greatly prolonged. However, once antibody synthesis occurs, there is a very rapid burst of antibody formation. This occurs even while the patient is on continuous immunosuppressive drug treatment.

One of the interesting observations that came out of this study was the effect of these drugs on two classes of immunoglobulins, IgM and IgG. In two-thirds of the patients on immunosuppressive drug therapy a greatly prolonged, but quantitatively normal IgM response occurred in the absence of any detectable IgG antibody synthesis. Thus, an apparently selective suppression of one molecular class of antibody may be obtained with both azathioprine and methotrexate in man.

**Clinical Results**

The question whether continuous immunosuppression is required to maintain a clinical remission in patients with immunological diseases probably has a negative answer in light of the "accordion" effect mentioned previously. This is another reason for believing that treatment with the currently available immunosuppressive drugs need be pushed to the point of destruction of all immune capabilities of the patient.

The third question, is there any correlation between the degree of immunosuppression and the actual clinical result, is extremely difficult to answer. In many patients there is no such correlation. Extensive depression of immunity does not indicate that a patient will respond clinically. Furthermore, some patients with a minimum or no immunosuppression have dramatic improvements. We believe that many of the effects of antimetabolites we have seen in man may be due to their important, but poorly understood, anti-inflammatory actions.

**Conclusion**

In conclusion, the antimetabolites have proven extremely interesting in the laboratory for the exploration of the mechanism of antibody synthesis and related problems. They have also proven to be extremely useful and interesting materials in the clinic. Whether they are going to replace any other standard forms of therapy, such as the corticosteroids, is, in my view, doubtful. Their use at the moment is experimental and their ultimate place in clinical medicine is by no means settled. They appear to have two important effects in man: 1) Suppression of antibody formation which can be, in many individuals, selective; and 2) Very important anti-inflammatory properties which may account for their effects on immune injury and for some of the very rapid responses seen in individuals treated with these agents.
The Pharmacology of Newer Diuretics

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Diuretics continue to be among the commonest of all prescribed items. Until recently, the physician needed to have little concern about the dose of the agent he was choosing because firstly, the dose-response curve tended to be startlingly flat, and secondly, there was little chance of inducing an excessive diuresis, regardless of dose. Now that furosemide (Lasix) and ethacrynic acid (Edecrin) have become available, we find that one must indeed titrate the dose to the particular patient, and must appreciate for the first time the complications which can result from an excessive diuresis. Finally, with the availability of triamterene and MK-870 (Colectril, not yet available), one must appreciate the importance of the distal tubular mechanism for potassium for sodium exchange. The additive effect of these exchange inhibitors can be of considerable clinical usefulness.

Adverse Effects of Diuretics

Figure 1 illustrates the excessive diuresis which can result from the newer, more potent diuretics. This patient was hospitalized and started on what seemed like a reasonable dose of ethacrynic acid, but she lost 35 pounds in four days. Fortunately, this patient had no adverse effects, but this is the very circumstance in which the series of adverse effects shown in table 1 can occur. The most important of these is hypovolemia. This is particularly likely to occur in the patient with cirrhosis or nephrosis.

The problem is one of developing circulatory collapse, shock. The only treatment advisable then is the infusion of salt-poor albumin. Such episodes have been reported with some real frequency. The problem of inducing excessive potassium loss is primarily related to the patient who is also taking digitalis and who becomes much more susceptible to the ectopic activity of the cardiac glycosides. Hypochloremia will induce diuretic refractoriness to mercurials, but not to these new agents. In spite of electrolyte derangements and in spite of reduction in renal blood flow, furosemide and ethacrynic acid will continue to exert diuretic effects. Hyponatremia may develop, particularly in the patient who is having a marked saluresis and who replaces the volume with tap water. The cause of muscle cramps, the weakness, the "washed-out" feeling, is still not clear, but the symptoms are well-recognized in patients in whom a marked prompt diuresis ensues. The relationship to thrombosis and the development of gout are not clear, but there is some circumstantial evidence suggesting that these can occur during diuresis. In summary, one must avoid having too rapid and too massive a diuresis.

Table 2 suggests some measures to avoid adverse effects of diuretics. The most important is the first: choose a sub-maximally effective dose. This requires knowing something about the dose response to these new agents. The only way to judge the response, of course, is to
TABLE 1
Results of Excessive Diuresis

1. Hypovolemia
   a. Reduction in renal blood flow
   b. Circulatory collapse
2. Hypokalemia
   a. Digitalis intoxication
3. Hypochloremia
   a. Mercurial refractoriness
4. Hyponatremia
   a. Water intoxication
5. Muscle cramps
6. Weakness
7. ? Thromboses
8. Acute gout

TABLE 2
Routine Measures on Initiating a Diuresis

1. Choose a submaximal diuretic dose.
2. Record weights and fluid balance.
3. Restrict activity.
4. Reduce sodium intake.
5. Restrict fluids to 1 to 1.5 liters, especially the day after diuresis.
6. Watch blood Na, K, Cl, HCO₃, urea and hematocrit.

record weights and fluid balance. Weights must be recorded by every out-patient who is taking diuretics for their diuretic properties. If a poor response from the diuretic occurs, restricting the patient’s physical activity during the day will often enhance the diuresis, since in heart failure, physical activity reduces renal blood flow. Fluids need be restricted only if the patient appears to be one who has the habit of ingesting water following a marked diuresis. No simple rule can be offered for the frequency of determining serum electrolytes. If the patient is having a marked response, they should be checked. Obviously, if he is having a poor response, they should be checked. With the new agents which continue to be effective even in the face of electrolyte abnormalities, it is necessary to check them with some regularity, like once every week or two.

**Quinethazone**

The first new agent to consider is quinethazone (Hydromox). Figure 2 shows the structural formula for quinethazone. Note the similarity to chlorthalidone (Hydroton) and to chlorothiazide (Diuril). Quinethazone is thus another one of the large group of thiazide derivatives. It has no particular advantage with the exception of a more prolonged activity. In this sense it more closely resembles chlorthalidone. It has no other advantages and no other disadvantages.

**Furosemide**

The structural formula for furosemide (Lasix) is shown in figure 3. Furosemide has also been called fursemide and frusemide. This is an agent whose activity-structure relationship is still not clear. Some would suggest that it is the common grouping with the thiazides; others would suggest that it is the free carboxyl group which is re-

Fig. 1—An excessively rapid response to ethacrynic acid.
PHARMACOLOGY OF NEWER DIURETICS

Fig. 2—Structural formulae of quinethazone (Hydromox), chlorthalidone (Hygroton), and chlorothiazide (Diuril).

Fig. 3—Furosemide (Lasix), 4-chloro-N-(2-furylmethyl)-5-sulfamoyl-anthranilic acid.

It is clear that it is different from the thiazides in several ways. Firstly, it is active in an animal in which there is no liver. The thiazides require the presence of the liver before diuresis will ensue. Secondly, furosemide causes a decrease in bicarbonate excretion in contrast to the typical thiazides. Thirdly, there is a markedly different order of efficacy. Furosemide clearly works in the ascending loop of Henle. It probably works in the proximal tubule, although animal micropuncture studies give contrary evidence. It has been said, though, and we have all been taught, that some 80% of the normal glomerular filtration is reabsorbed in the proximal tubule. If a diuretic were 100% effective, theoretically it could only increase urine output to 20% of the filtration rate if it had no activity in the proximal tubule. Furosemide can produce a diuresis of as much as one-half of the glomerular filtration rate, and this has been used as evidence that it must alter the proximal tubular reabsorption of salt and water.

Figure 4 shows the human response to furosemide contrasted with hydrochlorothiazide at 50 to 75 mg of each. Note that furosemide produces a larger diuresis, natriuresis and chloruresis, but importantly, no greater kaluresis. For each milliequivalent of sodium excreted, furosemide causes less potassium excretion than do the thiazides.

Furosemide is very rapidly effective, acting in minutes when given intravenously. Its maximum effect occurs within two hours when given orally. The duration of effect is correspondingly short. The dose response curve is shown in figure 5. In the case of hydrochlorothiazide, increasing the dose from 50 to 100 mg causes only a modestly increased natriuresis, whereas increasing the dose of furosemide from 50 to 100 mg causes a very considerable difference. Furose-
mide, therefore, differs in potency, that is, more diuresis per milligram, but more importantly, it differs in efficacy, giving a maximum response beyond what can be achieved with any of the thiazides.

The toxicity of furosemide is still under investigation. Table 3 lists the toxic reactions. Rare hypersensitivities, usually rashes and rare, not definitely causally-related alteration in blood counts have been reported. Nausea and vomiting appear to be clearly dose-related and will occur quite frequently at single doses exceeding 200 mg. Furosemide causes hyperuricemia regularly and will precipitate acute gout occasionally. Pancreatitis and hyperglycemia have now been reported in association with furosemide therapy, but are not yet established clearly as causally related. The extent of the hyperglycemia appears to be considerably less than that which occurs with the benzothiadiazines. The major problem with furosemide is excessive diuretic effect. This is the major adverse effect in the use of this agent.

In summary, then, furosemide is some three to five times as efficacious as the thiazides and causes less potassium loss. Because it is so rapidly effective, it has been used in the treatment of pulmonary edema and in cerebral edema. It is important to note that it has a steep dose response curve and that it continues to be effective even in the face of electrolyte derangement, hypovolemia, and azotemia.

**Ethacrynic Acid**

The structural formula for ethacrynic acid (Edecrin) is shown in figure 6. Note here the absence of the sulfamyl group, but again the halogenated cyclic structure. The free carboxyl group is thought to be a major determinant of its activity. This agent appears to work on the identical tubular mechanisms affected by furosemide. If one gives a maximally effective dose, of

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Fig. 4—Urinary response to equal milligram doses of furosemide and hydrochlorothiazide (Reproduced with permission from International Furosemide Symposium, fig. 27, 1963).

Fig. 5—Dose-response curves for hydrochlorothiazide and furosemide based on natriuretic effect (Reproduced with permission from International Furosemide Symposium, fig. 9, 1963).
either furosemide or ethacrynic acid, and then gives the other agent, no further response ensues. This would tend to indicate that the same mechanisms are affected by the two agents. Figure 7 shows the pattern of electrolyte excretion; a marked chloruresis, natriuresis, diuresis, and a minimal kaluresis. This is similar to the pattern shown for furosemide (fig. 4). When ethacrynic acid is given intravenously, an extremely prompt and massive response can be expected. Ethacrynic acid is available for parenteral use and is recommended in the treatment of pulmonary edema. A diuresis of 500 or 600 ml in one hour is not unusual. This is equivalent to using a phlebotomy or venous tourniquets to reduce the circulating blood volume. Figure 8 illustrates the response of one such patient. One and one-half liters of urine had been passed in one hour after 50 mg of intravenous ethacrynic acid, and about 3 liters by three hours.

The dose response curve is also shown in figure 7. There is an increasing response until one reaches a dose of 200 mg, and at that point maximal therapeutic effect has been achieved. So again, there is a very steep dose response relationship. One patient whom we treated in the metabolic ward is shown in figure 9. Note that with gradually increasing doses from 50 to 100 mg, there was essentially no response in weight. With an increase to 150 mg, there ensued a slow but steady diuresis until dry weight was obtained. This was a patient known, from our previous experience with her, to have highly resistant congestive heart failure.

Table 4 indicates the toxicity, which is probably identical to what was listed for furosemide. Rare rashes and thrombocytopenia have

**TABLE 3**
Toxic Effects of Furosemide

1. Rare hypersensitivity
2. Nausea, vomiting (dose related)
3. Hyperuricemia and gout
4. Pancreatitis
5. Hyperglycemia
6. Excessive effect
   Hypovolemia; hypochloremic alkalosis; hypokalemia; hyponatremia

**TABLE 4**
Toxic Effects of Ethacrynic Acid

1. Rare hypersensitivity
2. Nausea, vomiting, diarrhea (dose related)
3. Hyperuricemia and gout
4. Tinnitus, vertigo, deafness
5. Excessive effect
   Hypovolemia; hypochloremic alkalosis; hypokalemia; hyponatremia

**TABLE 5**
Toxic Effects of Triamterene

1. Rare hypersensitivity
2. Nausea, vomiting, diarrhea (dose related)
3. Azotemia
4. Hyperkalemia

FIG. 6—Ethacrynic acid (Edecrin), 2, 3-dichloro-4-(2-methylenebutyryl) phenoxycetic acid.

**FIG. 7**—Urinary response to graded doses of ethacrynic acid (Reproduced with permission of Merck, Sharp & Dohme Research Laboratories).
been reported; nausea, vomiting, and diarrhea appear to be dose-related. Hyperuricemia and gout will occur. Tinnitus, vertigo, and deafness have been reported with ethacrynic acid. It would appear to be a function of the acute change of the dynamics across the inner ear endolymph, since continued therapy with the agent is not associated with continuing or worsening of these symptoms, but rather they tend to disappear over a few days as soon as fluid balance appears to be more stable. This is probably not toxicity in the usual sense any more than excessive effect is toxicity, but is an extension of the pharmacologic properties of these rapidly and potently active diuretic agents. Excessive effect was considered earlier.

Ethacrynic acid, then, is also a potent, highly-effective diuretic. It continues to be active in the face of electrolyte derangements and azotemia. It is available for intravenous use and probably has a real place in the treatment of the patient with acute pulmonary edema in addition to our usual measures.

Triamterene and Amiloride

Turning now to agents that act by entirely different mechanisms, triamterene (Dyrenium), now available, and amipramizide or amiloride (Cholectril) (MK-870), not yet available, are shown in figure 10. The similarity in the structures is evident. There is a considerable difference in the potency as triamterene is given in doses of 100 to 200 mg and amiloride is given in doses of 5 to 30 mg. These are the agents which act to block the sodium-potassium exchange mechanism in the distal tubule. This is totally different from any of the activities of the other two agents described above. They are similar in effect to spironolactone, but spironolactone is a competitive inhibitor of aldosterone and is thus only effective in the
presence of aldosterone. These agents block this tubular reabsorptive mechanism regardless of whether aldosterone is present. In this way they tend to be more effective and do not require that the patient be in a state of induced hyperaldosteronism.

One can then predict the diuretic response. Figure 11 depicts a modest increase in sodium excretion and a decrease in potassium excretion in response to triamterene. Essentially a maximal effect results from a dose of about 100 mg of triamterene. These agents are modest in their natriuretic effect.

Something of the toxicity is noted in table 5. Again rare hypersensitivity and dose related nausea and vomiting are listed. Azotemia has been interesting in that slight, but significant increases in blood urea nitrogen have been recorded. They tend to stabilize and have not generally been a cause of significant concern. The problem with these agents is the development of hyperkalemia. When given either alone or in conjunction with thiazides, triamterene and amiloride may cause serious and even fatal hyperpotassemia. There is no way to predict in a given patient the exact response. Potassium levels must be checked in patients receiving such therapy.

In summary, these two agents, triamterene and amiloride have a modest natriuretic effect, about one-half to one-fourth that of the thiazides. They cause potassium retention, and most importantly, they are additive in effect to the other diuretics, thiazides, furosemide, and ethacrynic acid. Figure 12 illustrates this additive effect. This is the same resistant patient (fig. 9) treated on an out-patient basis receiving furosemide. Note that 40, 80, 160, and even 240 mg of furosemide per day was associated with no significant weight loss. At this point triamterene was added to this steady regimen, and the patient achieved a weight loss of approximately a pound per day over

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**Fig. 10—Structural formulae of triamterene (Dyrenium) and amiloride (Colectril).**

**Fig. 11—Dose-response for trimaterene (Dyrenium) depicting urinary sodium and potassium response.**
the next two weeks. These agents have not been shown to induce hyperglycemia or hyperuricemia and may have some special advantage in patients in whom these are problems.

Some of the typical effects of differing types of diuretic agents can be noted in the results of a study we have done.* Twelve patients with chronic congestive heart failure, hospitalized on our metabolic ward on constant sodium and fluid intake, were each given ethacrynic acid, triamterene and hydrochlorothiazide. Each patient received all three drugs, one on each of three successive days. The order of administration was so randomized that each drug was given with equal frequency on the first, second, and third days. The order of administration was so randomized that each drug was given with equal frequency on the first, second, and third days. 100 mg of each diuretic was given at 8 AM and again at noon. Carry-over effect was minimized since 20 hours separated the successive drugs.

Statistical analysis indicated no significant variation due to the order of drug administration or to the pattern of individual patient response. There were, however, statistically significant differences in the responses to the three diuretics.

Ethacrynic acid effected a significantly greater weight loss, natriuresis, chloruresis, and diuresis than did hydrochlorothiazide or triamterene and did so in both the first four hours and for the 24 hour period (fig. 13). Hydrochlorothiazide resulted in a somewhat greater diuresis, natriuresis, and chloruresis than did triamterene, but these differences were not statistically significant at the 5% level of probability.

On the other hand, triamterene resulted in significantly less kaliuresis than either ethacrynic acid or hydrochlorothiazide. The potassium excretion with the latter two was not significantly different.

This study, then, substantiates the greater potency (diuresis, salu-

* Proctor, J. D., and A. J. Wasserman, to be published.
resis) of ethacrynic acid and the potassium sparing effect of triamterene. In this study, furthermore, ethacrynic acid effected the most favorable sodium-to-potassium excretion ratio, viz for each milliequivalent of potassium lost, ethacrynic acid caused the greatest loss of sodium (fig. 14). Stated conversely, less potassium was lost for each milliequivalent of sodium excreted with ethacrynic acid than with either hydrochlorothiazide or triamterene.

Summary

There are now a number of different classes of diuretics with different pharmacologic effects. Several considerations dictate the choice of diuretic:

1. The responsiveness of the patient is of prime importance. If the patient is not known to be resistant to diuretic therapy, thiazides should be tried first.

2. The danger of alterations of volume and of electrolytes in the specific patient must be considered. Patients receiving digitalis will be subjected to much greater danger by the induction of hypokalemia than patients not receiving cardiac glycosides.

3. The pharmacologic effects of the specific diuretics must be understood for now the physician has available agents of differing potency, efficacy, and especially differing mechanisms of action.

Fig. 13—Mean responses of 12 subjects with chronic congestive heart failure to ethacrynic acid, hydrochlorothiazide, and triamterene. Each subject received each diuretic (see text).

Fig. 14—Urinary sodium:potassium ratios in response to each diuretic.

References

Iatrogenic Disorders

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The contemporary physician and his patient are riding the crest of the most dramatic expansion of medical capability in history. But the rapid proliferation of medical knowledge has not been entirely benign. Although our reverses have been minor in contrast to our advances, negative effects cannot be ignored. My discussion involves one aspect of this problem—the emergence of what I have called "Diseases of Medical Progress" (Moser, 1964).

Pertinent to the evolution of medical capability has been the improvement in quantity and quality of drugs. In the early days new drugs came in a trickle, and there was time for the physician to become familiar with their virtues and idiosyncrasies. Soon the trickle became a stream, and there was less time for study and reflection. The stream has now become a torrent; it is impossible for the physician to keep pace. His little black bag runneth over.

It has been said that drug-induced adverse effects are the price we have to pay for more effective medicaments (Zbinden, 1964). There can be no quarrel with this statement; it is the high price we are haggling about. The thalidomide disaster indicated how expensive it can be.

The deluge of new drugs has produced widespread discontent with empiricism in therapeutics. The modern practitioner demands drugs with proper credentials. This has precipitated a virtual renaissance in drug investigation, and thus we have come to learn more of the wonders and hazards of contemporary therapeutic agents.

The demands of the clinician to know more about drugs are being met by increasing capability in the laboratory. New insight and appreciation of the complexities of drug effects have come from several diverse avenues of investigation. The wedding of percutaneous biopsy and electron microscopy has resulted in dramatic revelations; the mysteries of intracellular morphology and physiology in the living organism have begun to yield. Often, we are able to observe the specific site of drug action within the cell.

In other areas techniques continue to be perfected for assay of blood and tissue levels of drugs, intermediate products and enzymes. The problems of adverse drug effects are many. Reduced to simplest elements, when Drug "A" is introduced into the body, ultimately it or its intermediate products will be carried in blood and body fluids to all cells of the organism. The effects of Drug "A" become clinically perceptible only when the function of certain organs is modified, either beneficially or detrimentally, to the point of producing perceptible changes, and it is by these phenomena that we learn to characterize the nature of Drug "A." As we focus attention upon the response of a specific organ (or organs) to this drug, we are inclined to forget that Drug "A" is also in contact with other tissues of the organism. Effects in
in whom accelerated demineralization occurs through corticosteroid anti-anabolic effect, is an example of exaggeration of degenerative disease caused by a drug. We start with one disease and our treatment for it produces another disease.

Let us modify the question again. What is known of the effects of drugs upon a previously diseased organ, with limited capability to metabolize or detoxify or otherwise cope with a drug given to treat another illness? I have mentioned the phenacetin controversy. The discussion here revolves around the status of analgesic compounds in the provocation of interstitial pyelonephritis in a normal kidney. But what effect do phenacetin, aspirin, or the combination have upon a sick kidney, already poorly disposed to resist assault from either micro-organism or nephrotoxic drug?

Consider the patient with subclinical hepatic disease, e.g., a mild cirrhosis, who is given chlorpromazine or phenylbutazone, drugs known to be occasionally toxic to the liver. One could cite multiple examples wherein an organ with marginal function may be further insulted by a drug administered, most innocently and with proper indication, to treat another ailing system.

Pharmacogenetics and Enzyme Induction

Perhaps the most fascinating corollary to these observations is the identification of a relationship between enzyme systems and drug effects. Vogel (1959) introduced the term "pharmacogenetics" into clinical medicine. This was defined as "the study of genetically determined variations that are revealed solely by the effects of drugs." The genetic variation results in the absence or insufficiency of certain enzyme systems. This mechanism has already been cited as one major explanation of the extraordinary human variability in response to conventional doses of conventional drugs (Evans, 1963).

The historical and classical example of a pharmacogenetic disease is the hemolytic anemia suffered by some members of certain ethnic groups, specifically, Mediterranean basin dwellers and Negroes (Berry, 1965; Beutler et al., 1955). Brisk hemolysis may follow exposure to many common therapeutic agents (among these are the 4-aminoquinolines, certain sulfonamides, acetylsalicylic acid, the nitrofurantoins, sulfones, paracamo-salicylic acid, phenacetin acetylid, probanthine and the water soluble analogues of vitamin K). Even the Fava bean apparently provokes hemolytic anemia on the same basis.

The cause is a genetically transmitted defect that results in deficiency of the intra-erythrocytic enzyme, glucose-6-phosphate dehydrogenase. Such patients are normal clinically; they have no morphologic or physiologic abnormality of their red cells, until one of the provocative drugs is given. Then brisk hemolysis occurs. Deficiency of glucose-6-PD has been cited as one cause of neonatal jaundice. It is somewhat of a problem in the chloroquine primaquine anti-malarial prophylaxis program in Southeast Asia (personal communication, Col. Marshal McCabe).

Other red cell enzyme deficiencies of greater subtlety have begun to emerge; these include aldolase, catalase, glutathione, glutathione reductase, pyruvate kinase, triosephosphatase and isomerases.

In addition, kernicterus of the newborn is related to immaturity of the neonatal liver. This organ is deficient in glucuronosyl transferase and, therefore, unable to conjugate bilirubin. Administration of sulfisoxazole (Gantrisin) or vitamin K analogues exaggerates this reaction. Novobiocin may provoke jaundice in the newborn and rarely in adults by direct inhibition of glucuronosyl transferase (Moser, 1967, in press).

Do these adults have a marginal
deficiency of this enzyme which becomes evident only when they are challenged with novobiocin? Is it congenital, or is it acquired as the result of a preceding episode of hepatic disease?

There are other equally fascinating pharmacogenetic diseases. Hemoglobin Zurich (Frick, Hitzig, and Betke, 1962) is an example. If a certain Swiss family had not been given sulfonamide drugs, it is quite likely that this abnormal hemoglobin disease would have continued to escape detection. A frank hemolytic anemia developed after administration of sulfadimethoxine and sulfamethoxypyridazine (Kynex) to family members. A new hemoglobin with electrophoretic mobility between A and S was identified; fingerprints of peptic digests revealed three unusual peptides.

Time permits only a brief glance at other equally fascinating pharmacogenetic disorders.

1) Hemoglobin H disease: patients with this illness have hemoglobin which is a tetramer of four beta chains. Their erythrocytes appear normal until they are given sulfoxazoxole; then a brisk hemolytic anemia may develop.

2) Patients may be divided into phenotypes on the basis of their ability in inactive isoniazid (Porter, 1964; Editorial, S. African Med. J., 1964). There is reason to suspect that isoniazid polynuropathy is more common in “slow inactivators” than “rapid inactivators.” Fortunately there is no difference in therapeutic responsiveness to isoniazid, and the development of resistance by the tubercle bacillus to isoniazid is similar in the two phenotypes.

3) About 1% to 2% of patients have a genetically determined deficiency of pseudocholinesterase (Hodgkin et al., 1965); this may be qualitative or quantitative. The malady will remain asymptomatic and undetected unless the patient is challenged with suxamethonium. Then the response is dramatic; a 2 to 3 min period of apnea will ensue. Pseudocholinesterase is required to metabolize suxamethonium.

4) It is suspected that increased susceptibility to dyskinesias subsequent to administration of phenothiazines such as chlorpromazine, may have a genetic basis.

And in view of the multitude of known enzyme systems, as well as those suspected but not as yet identified, one could predict that many reactions now classified as idiosyncratic or hypersensitive will soon be gathered into the fold of pharmacogenetic disorders or acquired enzyme insufficiencies.

A related phenomenon is drug-induced inhibition of the metabolic breakdown or release of albumin binding with escape of free drug. This is epitomized by the potentiation of coumarin drugs by several rather common agents, such as phenyramidol (Carter, 1965), acetyl salicylic acid, tetracycline, streptomycin, D-thyroxine, androstenolone, phenylbutazone (Eisen, 1964) and oxyphenbutazone (Fox, 1964).

Now there is a new dimension, quite antithetical to the concept of enzyme deficiencies unmasked or inhibition of metabolic breakdown caused by drugs. This is the phenomenon of “enzyme induction,” in which the administration of one drug accelerates the metabolic breakdown of another. (Burns, et al., 1965; Conney and Burns, 1963; Fouts, 1963). Clinical suspicion was aroused when it was discovered that some patients receiving coumarin drugs required increased doses to maintain therapeutic anticoagulant levels while taking barbiturates.

Residual Drug Effects

Residual drug effects remain another enigmatic area. For example, reserpine continues to exert its influence in certain patients for several weeks after it has been discontinued. It may cause unpredictable responses to general anesthetics. Reserpine may obscure the phenolamine (Regitine) test for pheochromocytoma for several weeks after it has been stopped. The persisting and even progressive retinal damage induced by residual chloroquine has been the subject of much commentary.

Elevated levels of protein bound iodine were found in the sera of women who had received iphe-noxic acid (Teridax, a cholecystographic medium) six to seven years previously. Babies born several years after their mothers had ingested iphe-noxic acid had extremely high levels of protein bound iodine (Goss and Dickhaus, 1965). These agents may lie dormant in fat depots for many years, apparently innocuous, but in curious contradiction to the usual tendency of an organism to rid itself of foreign substances. What other drugs are “stored” for prolonged periods? Do they exert adverse effects? Questions come easily; answers do not.

An equally fascinating new aspect of drug mechanisms is revealed in the recently recognized phenomenon of transferable drug resistance. This was first observed in Japan in 1959 during studies on Shigella which proved resistant to several anti-microbial agents. It is now recognized that Shigella and Salmonella are capable of genetic transmission of drug resistance (Smith, 1966). It has been suggested that the widespread use of antibacterial drugs in agricultural feeds has contributed to this problem. To my knowledge genetically transferred resistance factors have been identified only in gram-negative micro-organisms and acid-fast bacilli.

Now that we have seen something of the broad introductory area of drug-induced diseases, a logical question might be: What will be the ultimate effect of these new therapeutic endeavors? The answer must lie somewhere in the interface between philosophy and physiology.
The evolution of man is a continuing source of wonderment to students of physiology. Through the centuries of painful metamorphosis, each challenge thrown at man by his environment was met by a gradual genetic modulation that enabled him to survive. The species has arrived at the current state of advanced physiologic capability—admirably adapted to its environment. We can dig diamonds at 9,000 feet in 123° heat and 100% humidity; we can spend a lifetime mining tin at a 14,900-foot elevation, we can hike across the pole, and we can float weightless in space for 14 days.

But in the past few decades we have devised techniques unprecedented in the previous experience of the species to challenge the adaptability of the organism. We have designed molecules unique to human physiology and have intruded them into blood and tissue by techniques that are also unique in physiologic experience. Intravenous, intramuscular and subcutaneous injections, positive pressure inhalation, rectal administration, and agents that facilitate passage through intact skin all are unfamiliar modes of gaining access to the body. Add, for example, radiation by x-ray, beta ray, gamma ray and neutrons, plus oxygen under greatly increased barometric pressure, and one begins to appreciate the magnitude and genius of man's conspiracy to by-pass the conventional avenues for introducing new environmental factors to the physiology of man.

In the past we only had to cope with nature and environment. And they were confined to the gastrointestinal tract, lungs and occasionally the abraded skin to admit alien materials to the core of man.

The implications of these ingenious tactics of assault, these strange man-made chemicals and emanations upon the beleaguered human mechanism are fascinating to contemplate. One could speculate that this incredibly resilient physiologic machine of ours is sufficiently advanced in design to be able to cope with all transgressors. We have evolved defenses at all levels from the simplest reflex to the most complex immune reactions to meet the daily challenges of environment. And we have done very well in the matter of self preservation.

Yet it is quite evident that some of these unprecedented therapeutic intrusions will overtax the ability of the body to accommodate, and it will react with displeasure, if not violent rejection. Of course this is the heart of our thesis, drug-induced diseases.

Every new drug must be evaluated for efficacy and toxicity, and this is not an easy task. Only passage of time and acquisition of experience will determine the ultimate verdict. Firm pronouncements based on animal experimentation or fragmentary early clinical trials are premature and meaningless. Often it takes years before the full spectrum of efficacy or toxicity of a drug becomes evident. This poses an almost insoluble conundrum. If we are timid and withhold the drug, how will we ever gain the necessary clinical experience? If the agent is effective and safe, it would seem unfair to withhold it. If the drug is ineffective or toxic, it would seem equally unfair to use it on patients. All that one can propose is prudence, caution, and reservation of final judgment until objective studies are completed.

In an effort to dramatize the problem of drug toxicity, I have selected one group of drugs, the tetracyclines, to serve as a prototype to illustrate the continuing challenge that faces the medical profession in arriving at a comprehensive appreciation of the spectrum of toxic effects of drugs. One might select almost any popular drug to do the same thing. This could properly be called the evolution of the toxic profile of a drug.

Tetracyclines are valuable therapeutic allies. They qualify as antibiotics of choice in a host of in-
fectious diseases. So let it be established at the outset, there is no denying the efficacy of tetracyclines in clinical medicine.

Included in this group of drugs are chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline, tetracycline phosphate and rolitetracycline.

Chlortetracycline was introduced in 1947. Despite the wearisome flurry of superlatives that attends the introduction of every major new drug, chlortetracycline was found to be remarkably effective. By 1949, a reflective review of the literature on this drug stated "it is an important landmark in the field of antibiotics. Its extremely low toxicity and wide range of activity and absorbability from the gastrointestinal tract combine to make it a powerful therapeutic weapon" (Rose and Kneeland, 1949). A prodigious literature extolling its virtues soon accumulated.

Early adverse effects were minor. They could almost be characterized as annoyances, and they were confined to the gastrointestinal tract. Loss of appetite, nausea, vomiting, flatulence, dyspepsia and diarrhea occurred in about 10% of patients receiving significant doses (Pflug, 1963; Schindel, 1965; Bevelander, 1963). For several years the profession was quietly congratulating itself on having found a new variety of wonder drug with broad application and low toxicity. Even the appellation "broad spectrum antibiotic" had a solid ring, adding a dimension of comprehensive coverage and confidence.

In the early 1950's slight rumblings could be heard in this therapeutic paradise. Other adverse effects related to gastrointestinal tract, more severe than the early ones, began to creep into clinical cognizance.

Antibiotics, especially the tetracyclines, can disrupt the normal ecologic balance of the colon. Destruction of friendly commensals facilitates overgrowth of organisms resistant to the antibiotic. And, of course, if any of these hostile bacteria escape their enteric confines and gain access to blood or urinary tract, they can cause significant mischief.

This alteration of bacterial flora has been associated with stomatitis, glossitis, pharyngitis, and black hairy tongue, a cosmically grotesque, but pathologically benign condition. Also xerostomia, hoarseness, and vulvo-vaginitis were related to tetracycline treatment. In most of these situations, disruption of bacterial balance permitted the fungus Monilia Albicans to flourish in these unseemly sites (Pflug, 1963; Bonniot, 1964; Caruso, 1961; Clendenning, 1965).

A corollary phenomenon was the rare occurrence of bleeding in elderly patients with cirrhosis of the liver. It was postulated that the damaged liver was less efficient in producing its coagulation factors. Added to this was the belief that Vitamin K synthesis in the small bowel was inhibited by the alteration of flora incident to tetracycline administration. But now this mechanism is strongly disputed. A final step in this hypothetical pathogenesis was that the sick liver, already struggling to produce its coagulation factors, had its supply of Vitamin K cut off. Therefore, no Vitamin K, no coagulation factor—and we have bleeding. Unfortunately, there is little evidence to support this concept.

It was in 1958 that from the British Isles, Germany, and Scandinavia came word that an old scourge was revisiting us with a vengeance. This was the granddaddy of all gastrointestinal syndromes that tetracyclines and other antibiotics had caused: staphylococcal pseudOMEMBRANOUS-enterocolitis (Bonniot, 1964; Caruso, 1961; Clendenning, 1965; Altemeier, Hummel, and Hill, 1963; Nemeth, Feher, and Szinay, 1963; Pockrandt, 1964; Silvertsen and Juel, 1958; Wegmann and Bucher, 1964). Once the friendly bacteria had been decimated by the antibiotic, the Staphylococcus, previously suppressed by normal bacterial inhabitants, had gained ascendancy and invaded the colon wall. This resulted in destruction of the superficial cellular layers, with necrosis and sloughing. The result was a denuded colon wall which wept vast amounts of fluid, and death was not an infrequent consequence.

This dread complication had been known before antibiotics, but there was a distinct impression that the incidence had risen significantly with the use of antibiotics, including the tetracyclines. It was a tragic paradox that in some instances the antibiotics had been given in a sincere but naive effort to prevent the development of a bacterial infection.

In the early 1960's, rare sporadic cases were recorded describing a variety of hypersensitivity reactions. These included sudden cardiovascular collapse due to anaphylaxis, (Bedford, 1951; Editorial, J.A.M. A., 1965; Fellner and Baer, 1965). Others included ecchymoses (Schonfeld, 1964), hemolytic anemia (Takahashi, 1963), and dermatologic reactions (Schindel, 1965).

A related and even more curious problem was the reactivation of systemic lupus erythematosus (Domz et al., 1959). Some observers even reported the precipitation of this disease de novo, following the administration of tetracyclines (Sulkowski and Hasevick, 1964). This must be an unusual occurrence, since I have seen no subsequent reports.

In early 1963, a paper appeared which described a new entity related to tetracyclines. It bore superficial resemblance to diabetes mellitus, since there was an excess of glucose in the urine and even albumin. But closer scrutiny revealed that amino-acids also were being excreted. Thus it conformed to the pattern that had only been observed previously in patients with the Fanconi syndrome (Cleveland et al., 1965; Castell and Sparks, 1965;
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It was an intriguing situation, especially when the cases were collated and it was discovered that all victims had ingested out-dated tetracycline. The mysterious malady regressed about one month after the drug had been withdrawn.

Warnings went out to physicians and pharmacists advising them to prescribe precise amounts of tetracycline and to admonish thrifty patients to clean out the medicine chest. The American tradition of family sharing of unused antibiotics was publicly denounced.

A paucity of subsequent reports seemed to indicate that the pharmaceutical industry had modified the procedure by deleting citrate to obviate the problem of tetracycline degradation. However, two recent cases were reported in which potassium depletion was a remarkable feature of a Fanconi Syndrome, again induced by out-dated tetracycline.

This incident called to mind some earlier work linking tetracycline toxicity and renal disease (*Editorial, Ann. Int. Med.*, 1963; Mavromatis, 1965; Pulliam and O'Leary, 1964; Robins, 1963; Shils, 1963; Solomon, Galloway, and Patterson, 1965; Wegienka and Weller, 1964; Zimmerman and Werther, 1964). These antibiotics tend to interfere with protein synthesis. In patients with poor kidney function, tetracyclines may exaggerate elevation of blood urea nitrogen. Rarely, an excessive sodium diuresis may cause hyponatremia. As the kidney disease becomes more severe and function declines, the tetracycline-induced problems are compounded proportionately. Severe retention of protein breakdown products, urea and phosphate, result in a metabolic acidosis, and this could cause loss of weight, uremic symptoms, including anorexia, nausea and vomiting. Tetracycline administration to the unfortunate patient with severe renal disease may result in exacerbation of clinical uremia; gastric ulceration and bleeding has been reported.

In 1963 a new dimension was added to the tetracycline story. It was discovered that these drugs had a strange affinity for teeth, bones and tumors (Benson, 1964; Cuttita, 1965; *Editorial, J. Am. Dental Assoc.*, 1964; *Editorial, Lancet*, 1965; *Editorial, Nutrition Rev.*, 1964; Frankel and Hawes, 1964; Hilton, 1962; Kutscher, et al., 1963; Kvaal, 1965; Madison, 1963; Stewart, 1964; Swallow, 1964; Taguchi, 1963; Vickers, 1964; Wallman and Hilton, 1962; Weyman, 1965; Witkop and Wolf, 1963). A group of 50 young children were receiving long-term chlorotetracycline or oxytetracycline for the control of pulmonary infection associated with cystic fibrosis. Staining of the teeth occurred in 80%. Those given tetracyclines in early infancy exhibited the most severe discolorations.

Apparently tetracycline has an affinity for the active growth sites of bones and teeth; it migrates to these areas soon after it is given, and there it remains. A definite inhibition of normal calcification occurs at these sites of tetracycline deposition.

In teeth this amounts to delayed growth and intrinsic staining of dental enamel; this may be the commonest cause of deciduous enamel discoloration in infants.

Perhaps equally distressing is the capability of tetracyclines to migrate through the maternal placenta to be deposited in the skeleton of the fetus (Tubaro, 1964). In premature infants this could cause inhibition of bone growth. On a happier note, it must be noted that this effect is reversible if the course of tetracyclines given to the mother is brief.

Other authors have suggested that tetracyclines administered to women in early pregnancy could result in congenital abnormalities in their offspring (Barkalaia, 1964; Manning, 1964; Cohlan, Bevelander, and Tiamsic, 1963). The data here was entirely inferential. This did call to mind a paper published in 1963, which described a strange phenomenon in which tetracyclines administered to six infants caused a rise in cerebro-spinal fluid pressure with bulging of the fontanelle. This process regressed promptly upon withdrawal of the drug (Offer, 1963). This is most assuredly a rare adverse effect. I have seen no subsequent reports of this phenomenon.

In another direction it has been observed that some individuals who are taking tetracyclines develop increased sensitivity to sunlight (Deveber, 1962; Kingsley, 1963; Sallow, 1961; Sogal, 1963; Storck, 1965; Tromovich and Jacobs, 1963). This apparently is more severe with demethylchlorotetracycline, but has occurred with others of the group. This may take a rather severe form on rare occasions with actual epidermolysis.

Later a report described a young lady who became myopic while taking tetracycline; it disappeared when she stopped the drug (Capparelli, 1964; Edwards, 1963). Later a few others made similar observations.

In 1964, Dr. Searcy and co-workers reported that tetracycline when given intravenously interfered with coagulation of blood (Searcy, Simms, and Foremar, 1964; Searcy et al., 1965). This was considered to be a direct effect against specific clotting factors. These patients did not have liver disease and there was no apparent disturbance of Vitamin K production.

In late 1963, the New England Journal of Medicine carried an article that described the deadly misfortunes of six young pregnant women who developed kidney infections. They were given tetracycline intravenously in larger than average doses by the intravenous route. All died within 5 to 13 days after the start of tetracycline treat-
I searched the literature; there was nothing. I considered this a neurotic manifestation, patted my patient on the head, and persisted in my naivete and ignorance. Finally symptoms became more severe; I stopped the drug; symptoms regressed. I started the drug again; symptoms recurred. At least I was convinced. The patient (who happened to be my wife) was also convinced that I was an idiot. And one week later the first article appeared on Serpasil-induced tremors. This is not an uncommon experience, and that is why it often takes 20 years.

Conclusion

"Diseases of Medical Progress" will be with us forevermore. They cannot be swept under the rug, either by clinician or drug producer. My own naivete in the world of commercial enterprise is revealed by my admission that I think a fine new drug will become known to the profession on the basis of its merit. I am embarrassed when this noble community is demeaned by mercantile dirigism, however subtle or artful, better suited to less vital products, such as soap or soda pop. The fact that over $750 million is spent each year for drug advertising is a staggering testimonial to the enormity of this effort. This is almost three times more money than is required to run all of the medical schools in this country for one year. I do not feel that drugs should be propagandized to the medical profession. The pressure of commercial competition is not conducive to objectivity in the presentations of drug detail men or in published advertisements. I feel these factors add to the confusion in the already difficult problems of evaluating the efficacy or adverse effects of new drugs.

The requirement for an impartial agency that can provide current, reliable and objective data about the characteristics of new drugs, and alert the physician to their toxic hazards is abundantly evident. This requirement has been met by the American Medical Association Council on Drugs, which created a national "Registry of Adverse Reactions." A comparatively new facility, it was the natural successor to the "Registry of Drug-Induced Blood Dyscrasias," a most successful pioneer study guided and nurtured by Dr. Maxwell M. Wintroub and Dr. Charles Huguley. The new, broader registry makes it possible for any physician to contribute his personal experience with adverse drug effects to a central pool. This information is recorded on a form designed for automatic data processing. The data are extracted and recorded in the memory banks of a computer system.

Volunteer teams of nationally recognized specialists study all information submitted to the Registry. Thus, the input from physicians throughout the country is evaluated and recorded. Hopefully, for the first time, we have the means to obtain realistic incidence data about adverse drug effects. The response from hospitals and private physicians has been disappointing, in quantity and quality but the program is young, and already the Journal of the American Medical Association has carried several brief pertinent articles describing recently discovered adverse drug effects and summarizing drug information derived from this new facility.

The Federal Drug Administration has inaugurated a similar program that complements the AMA Registry and expands the total data gathering capability. FDA concern in the matter is oriented somewhat differently from that of the AMA. Nevertheless, such activity in the nation's highest medical councils indicates the growing importance of adverse drug effects.

The AMA Registry represented a significant step toward meeting the challenge of new responsibility that accompanies increased capability. Our remarkable therapeutic arsenal...
is a tribute to the commercial drug industry and the devoted chemists and pharmacologists of our medical schools. But neither medical schools, AMA, FDA, nor the industry can solve the problem completely.

My plea has been, and is directed to the physician on the firing line, the doctor who prescribes the drug. It is farthest from my intention to suggest therapeutic timidity or homeopathy. Our predecessors in medicine had limited diagnostic and therapeutic resources. The complement of nostrums in their little black bag was austere, but these drugs were regarded as old familiar friends. Some were worthless, others dangerous; some were impure and unstandardized to the point of unpredictability. The few effective drugs were trusted allies whose strengths and weaknesses were well known. The practitioner of the past attempted to compensate for lack of material resources with meticulous attention to his patients, personal charm, kindness, and pervading equanimity.

His lonely hours of private hell, tormented by his inability to come to grips with most of the severe illnesses that he encountered, constitute a long, bleak chapter in medical history. The modern physician is afforded rare glimpses of this agony when faced with malignancy or degenerative disease or neurologic illness. Modern pharmacology has brought this unhappy era to an end; we now enjoy the privilege of fine, powerful, well-standardized therapeutic weapons.

Now we must work to create an atmosphere of rational caution and critical evaluation, where each physician will pause before putting pen to prescription pad and ask himself, "Do I know enough about this drug to prescribe it? Does the possible benefit I hope to derive from this drug outweigh its potential hazard?" I do not preach therapeutic nihilism, but rather therapeutic rationalism.

Thank you.

References


FDA Reports of Adverse reactions, 5002–1236, 1966.


NORMAN, T. D., J. C. SCHULTZ, AND R. D. HOKE. Fatal liver disease fol-
IATROGENIC DISORDERS


The Treatment of Anxiety*

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Rational therapy requires accurate diagnosis. When we apply this precept to anxiety a fundamental question arises. Is anxiety an illness in terms of the now be-rated medical model which holds that an illness has a cause, a natural history, and hopefully a cure? Or is anxiety a basic aspect of the human condition, an innate pattern of response which becomes pathological when stress, induced by physiologic and social forces, is magnified out of proportion to the original stimulus? If the latter is true, then stress and social interactions are the causative factors, the anxiety only a reaction. Logically then, the condition of anxiety can be modified by alleviating stress or changing the social environment. Although there is no definitive answer to this major question concerning the nature of anxiety, we would like to present briefly some of the present knowledge about it.

In 1921, Freud stated: “We call it [anxiety] an affective state, although we are also ignorant of what an affect is.” He discussed three components of anxiety: (1) the specific feeling of displeasure, (2) acts of discharge (autonomic and endocrine functions), and (3) perceptions of these acts. Although more knowledge of biochemical and neurophysiologic mechanisms has accumulated since Freud made this observation little more is known about anxiety. Engel (1962) proposed that anxiety is the earlier of two basic biological patterns of which depression-withdrawal is second. He says that anxiety “includes a variety of active modes of coping with stress which are designated the flight-fight patterns to indicate corresponding behavioral aspects (Cannon, 1939). These involve not only the biochemical and physiological preparations for flight or fight but also internal changes anticipating bodily injury.” The psychophysiology of anxiety is neuroendocrinological, including activity of the limbic system and the hypothalamus, which leads to activation of the pituitary-adrenal cortical system and facilitates a wide range of metabolic processes involved in the long-term responses to injury (Engel, 1953; Ingle, 1952; Selye; 1960).

Grinker (1956) characterized the clinical manifestations of anxiety quantitatively. Mild anxiety is consonant with alertness or vigilance; it may be automatic, and the patient has little psychical or physical awareness of his anxiety. Greater quantities are manifested as episodes of recognized apprehension with physical symptoms. Thirdly, free anxiety, which may be episodic or continuous, is obviously neurotic. As the anxiety becomes more severe, disorganization of function occurs.

These are the fundamental psychiatric concepts. For the sake of completeness we should include that Berger (1962) propounds a strictly organic point of view when he says that anxiety is a “disease of the brain.” In contrast, others see anxiety as a patterned re-

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spontaneous, neurotic symptoms are learned faulty patterns of behavior (Hall and Lindzey, 1957). Further, many theorists believe that anxiety is a constructive force, which not only acts as a danger signal to protect the organism, but also accounts for motivation and monitors behavior. In medicine, psychosomaticists hold that excessive or sustained anxiety produces disturbances of bodily functions or structures which in turn result in organic illness. Physicians find that anxiety is a contributing factor, a correlate, or a result of many disease states. They are concerned with treating patients with acute, distressing "anxiety" attacks and those with high levels of chronic anxiety who are difficult to work with because of their general nervousness, irritability, fright, and erratic behavior.

Incidence of Anxiety

Despite our difficulties in understanding the nature of anxiety, awareness of it is increasing in the Western world (Andresen, 1963; Finn and Husten, 1966; Rennie, 1948). Adams and Hope (1962) observe: "As a clinical syndrome, the anxiety state outranks all other problems in general medicine." Our studies (Schwab et al., 1966a, b, and c) with medical inpatients showed that 20% to 27% of them had severe anxiety. These data are in accord with Cattell and Scheier's statement (1961): "Epidemiological estimates vary...[but] a conservative consensus estimate would probably place 20% of the American population as needing treatment for disorders in which anxiety plays a prominent role."

Treatment

The effective treatment of anxious patients hinges on the combined benefits of psychotherapy and medications. The limitations of psychotherapy are well known, and the limitations of drug therapy have been aptly expressed by Goodman and Gilman (1965a): "obviously neither drugs nor other somatic treatment can give the insight to the patient that can be achieved by psychotherapy."

Psychotherapy

We like Appel's definition of psychotherapy as quoted by Rickels (1964): "helping people to handle their feelings, motivations, and behavior more appropriately." And we should remember that psychotherapy is one of the oldest medical skills. The essence of psychotherapy is communication, and achieving the therapeutic dialogue is dependent on the relationship between the patient and the physician.

By listening, the therapist tries to obtain understanding, not necessarily agreement but rather comprehension. Either sympathetic agreement or antagonistic disagreement may produce distortions and solidify the neurotic organization. Thus, the task of the therapist is, in Wahl's words (1962) "...to convert apprehension to comprehension."

From awareness of his problems comes clarification; the patient is better able to make more appropriate decisions about his life. Other fundamentals of psychotherapy are the educative and the manipulative, deriving from increased knowledge of self and environment.

Just as communication is the essence of psychotherapy, self esteem is the fulcrum on which success balances. Only with increased self esteem can the patient order his world and create healthful relationships with it.

Medication

Medication is the second component of treatment. When tranquilizers were first introduced, it was feared that they would render the patient too comfortable for psychotherapy. Obviously, this fear has not been realized. Available medications do not purge anxiety, but they can reduce it to manageable proportions, thereby improving personal relationships, and forestalling ego disorganization and psychosis.

Guidelines

To obtain maximal advantages in the use of drugs, the therapist must adhere to certain principles.

1. Little is known about their pharmacologic action. Most of these agents act as weak sedatives. The barbiturates, of course, are depressants of the reticular formation in the brain stem. The action of meprobamate is quite similar; although no specific site of action has been identified. Hendley et al. (1954) indicated, however, that it produces some thalamic synchronization, and others have observed slow wave activity in the basal ganglia and limbic system. It may interfere with centrally mediated autonomic responses. Indirectly, by affecting conduction in the limbic system, it appears to depress the reticular formation.

According to Goodman and Gilman (1965b), the effects of chlordiazepoxide (Librium) and the related compounds diazepam (Valium) and oxazepam (Serax) are more ubiquitous than those of meprobamate and the barbiturates. Chlordiazepoxide has a central action, possible peripheral actions, and a definite sedative effect intermediate in potency between meprobamate and chlorpromazine. Like barbiturates and meprobamate, in experimental animals it blocks both conditioned and unconditioned avoidance responses.

The phenothiazines (Thorazine, Mellaril, Stelazine) appear to produce changes at many levels: the EEG is characteristic of drowsiness; arousal is diminished; there are some effects upon the limbic system and the basal ganglia; and conditioned avoidance responses are blocked without affecting the unconditioned responses. Jarvik
eral disparate views concerning the sedative action of chlorpromazine and its effects on the recticular system." Various investigators contend that it depresses, that it has a biphasic action, or even that it is stimulating. Through its depressive action on the hypothalamus, it has strong adrenergic and weak cholinergic blocking effects on the autonomic nervous system, and it acts on the endocrine system to reduce urinary gonadotropins, suppress estrous cycles, interfere with growth, induce lactation, and decrease secretion of ACTH.

The dosage must be carefully individualized. For example, some patients respond to 1200 mg of meprobamate per day, whereas others receive little benefit unless that is doubled. This is even more true of the phenothiazines; some patients improve on 100 mg of chlorpromazine in 24 hours, whereas others require many times that amount.

They provide only symptomatic relief by damping reactions and quieting inner turbulence. Thus they are only adjuncts.

They are not remedies for psychosocial distress. Too often tranquilizers are prescribed for the treatment of sociocultural dilemmas; obviously when used for these purposes the results will be poor.

Negative effects occur. Some patients react poorly to one or all of the antianxiety agents. Paradoxical reactions, to say nothing of side effects, are reported for meprobamate, the benzodiazepine compounds (such as Librium), and the phenothiazines.

Knowledge of the patient's personality is essential. DiMascio and Klerman (1960) concur with the almost universal recognition that the personality of the subject and his psychophysiologic state are important modifiers of drug action. Many anxious patients cannot tolerate a slowed-down feeling; it results in clinical depression for some and a loss of required motor activity for others. Importantly, Rickels (1964) has described the effects of the barbiturates as producing more improvement in lower socioeconomic patients who have low drive levels, low ambition, highly compliant behavior, and a strong passive-dependent character makeup. In the more intelligent, less dependent, less compliant and socioeconomically higher patient, the barbiturates are less well tolerated, producing more sedation and less improvement.

7. The physician should restrict his use of the countless sedatives and tranquilizers available to only a few, so that he can become familiar with their indications, side effects, and contraindications. Sainz (1964) states: "The rate at which new psychopharmacologic agents appear and old ones disappear attests only to their relative ineffectiveness." We advocate that one should switch to a new drug only when it has been proved demonstrably superior. Among the phenothiazines, chlorpromazine is still the standard against which others are measured. And, meprobamate and chlordiazepoxide have been used for so many years with so many patients that their effects and side effects are well known.

Clinical States

In practice, patients are seen with various anxiety states, which can be conceptualized on two dimensions: the first is the continuum from conscious to unconscious awareness of causes and dynamics; and the second is severity, ranging from the stress reaction, which may be mild, to the extreme anxiety manifested by the schizophrenic patient who is undergoing ego disorganization.

1. The acute stress reaction is evidenced clinically by: agitation, restlessness, autonomic symptoms, insomnia, and visceral dysfunctions. Conscious elements are predominant; i.e., the patient is aware of his tension and is able to describe its causes and effects. The severity is commensurate with the degree of trouble the patient is encountering. The ordinary dilemmas of human existence, i.e., problems of work and family, are the most common causes.

Psychotherapy should be directed toward helping the patient resolve the environmental stress or removing him from it. Medications may be necessary, but in these instances they should be given for only a short time because their chronic use may produce just enough relief that the patient, instead of seeking resolution, remains helplessly and symptomatically caught in a stressful situation. Barbiturates, either sodium amytal or butabarbital (30 mg three or four times a day), are useful. Sometimes adequate sedation at bedtime suffices. Of course, barbiturates have drawbacks: sedation, addictive properties, and possible use for suicide. Meprobamate (400 to 800 mg three times a day) is obviously preferable when there is any risk of suicide.

2. Although acute anxiety attacks usually appear as discrete clinical syndromes, the patient is relatively unaware of the precipitating events and the dynamics. He displays overt apprehension and the symptoms of autonomic nervous system imbalance. He complains of severe dread, a fear that he is dying, or that he is afflicted by a terrifying condition. The physical symptoms include headache, an inability to concentrate, rapid heartbeat, shortness of breath, gastrointestinal distress, bizarre sensations, and generalized motor hyperactivity. Also, he may be hyperventilating, complaining of tingling of the extremities and sharp twitches of pain in the chest, and showing signs such as pallor, profuse sweating, and muscle spasms.

Clarification of the patient’s physical status usually terminates the acute attack, but seldom pre-
vants its recurrence. When these patients are first seen the physician should explore possible causes incisively. If the anxious condition becomes chronic, the patient focuses on his symptoms so completely that his awareness of other stresses diminishes and valuable information cannot be obtained. Because these patients are suffering and frightened, they accept direct questioning about the quality of their interpersonal relationships, stresses at home and work, sexual activities, basic fears regarding adequacy, etc. Psychotherapy is essential because the patient is unaware of the dynamics and usually of the precipitating events.

Intravenous sodium amytal (200 to 500 mg) quickly relieves the acute attack. Meprobamate (400 to 800 mg three times a day) or chlordiazepoxide (Librium) (10 to 25 mg three times a day) alleviates the anxious condition but does not protect the patient from recurrence. Therefore, we recommend both intensive psychotherapy and medications. Side effects of the antianxiety agents (meprobamate and chlordiazepoxide) include withdrawal reactions, paradoxical reactions, and allergic conditions.

(3) Chronic anxiety states are persistent, the causes obscure, and the manifestations multifarious. Engel (1962) says: “The somatic symptomatology and the physiologic changes associated with anxiety set in motion a vicious cycle—the patient begins to fear the onset of the next acute anxiety attack and his perception of somatic symptoms reinforces this signal of danger.” Repeated acute attacks thus lead to the chronic condition; the baseline level of anxiety between attacks is raised.

Chronic anxiety is evidenced by the patient’s worried, tense appearance which is accentuated as the day goes on and the stresses and strains of activity take their toll. Although the anxious patient has difficulty going to sleep, he feels better in the morning. In contrast, the depressed patient is generally more apathetic in the morning and brighter in the evening. Morbidly anxious patients are pre-occupied with their mental and physical status, speaking freely of their symptoms, and betraying their agitation by trembling and tension. Although they describe symptoms easily, they do not know what is happening to them. If unchecked, the condition becomes progressively more severe and panic states develop.

Psychiatric referral is recommended. Because the condition is both severe and chronic, medications are usually needed to help the patient work with a psychiatrist. If the patient displays muscle tension and agitation and if his ego strength is reasonably good, meprobamate is preferred. For the patient who appears more psychatically ill, obsessive, and has diffuse complaints, chlordiazepoxide (Librium) is usually more effective. For the even more clinically ill patient who will require medication over a period of months, phenothiazine compounds should be used. We start with 25 mg of chlorpromazine (Thorazine) or thioridazine (Mellaril) four times a day, check for hypotensive reactions, and then increase the dosage by 50 to 100 mg every few days until the patient notices some relief or side effects appear. The most common side effects are dyskinesias, particularly parkinsonism and akathisia. Dystonia is seen only occasionally. In recent years the reports of jaundice and agranulocytosis have diminished greatly. Hyperpigmentation and photosensitivity as well as pigmentation of the cornea and lens have been reported (Redlich and Freedman, 1966). Recently Hollister (1966) noted that some patients taking chlorpromazine for many years were found at post-mortem examination to have coronary artery changes, but this has not yet been confirmed.

(4) Anxiety is also evidenced clinically by neurotic behavior and attitudes, and a host of characterologic defenses, particularly by patients who have little awareness of their anxiety. Interpersonal relationships suffer. These manifestations of anxiety appear so intangible that the physician is reluctant to refer the patient for psychiatric consultation until more obvious difficulties appear. The neurotic behavior includes emotional lability, erratic and inconsistent attitudes, and impaired communication—especially between patient and physician. This may be so great that the physician and his patient are unable to agree about the severity of the illness or the necessity for particular types of treatment.

We found that highly anxious medical patients hold distorted views of the severity of their illnesses, maintain negative feelings (even flagrant dislike) for hospitalization, and distrust their physicians. They display manifold characterologic defenses: irritability, suspicion, lack of cooperation, and passive-aggressive activities (Schwab et al., 1966a).

When anxiety is expressed through these defenses, the severity is variable; the defenses become an integral part of the character structure so that the person lives with the reputation of being troublesome. But more severe anxiety states develop when he is stressed by medical illness or one of life’s catastrophes.

In these patients medications have little value; the defenses bind the anxiety, and the patients consider their personality symptoms to be ego-syntonic. Psychotherapy also has limited effectiveness until the patient’s interpersonal difficulties multiply.

(5) Overwhelming anxiety is a conspicuous symptom of schizophrenic reactions, particularly the acute undifferentiated type. These patients show many of the classic signs of schizophrenia: they are
vague, their thinking is autistic and highly personalized, ambivalence and indecisiveness are obvious, their affect is one of fright and suspicion, and of course they may be hallucinatory or delusional. They are not aware of the sources of their anxiety, or their description is so incoherent that they cannot communicate with others. In the milder forms, misdiagnosis is common. For example, Lynn (1964) found that of 133 patients referred for psychiatric consultations to the Indiana University Medical Center, 34 schizophrenic patients had been either misdiagnosed or inadequately treated.

The schizophrenic patients with less severe disorders respond well to psychotherapy that emphasizes specificity, concreteness, and current realities. Phenothiazines are the only medications which are really beneficial. Ambulatory schizophrenic patients require 200 to 500 mg of chlorpromazine (Thorazine) per day for many months. When the medication is discontinued it should be reduced gradually over a period of months.

(6) Newer concepts of mental illness now recognize admixtures of anxiety and depression. Once they were rigidly differentiated as entities, but now we know a patient may appear at any point on the continuum ranging from so-called "pure" anxiety, through complex reactions which manifest both anxious and depressive elements concurrently, to the more classical, obvious, retarded depressive state.

Many of these patients respond to the newer antidepressant medications, particularly those which exert some phenothiazine-like action. Amitriptyline (Elavil) (10 to 25 mg three or four times a day) or nortriptyline hydrochloride (Aventyl) (20 to 100 mg daily) are recommended. Several British investigators (Sargant, 1962; Sargant and Dally, 1962) have reported on the successful use of MAO inhibitors for the treatment of patients showing anxiety as a prominent feature of their illness; however, we have had no experience with them in the treatment of these patients. These various antidepressants should not be used in combination and can be used in tandem only if there is a 7 to 14 day drug-free interval between them.

It is impossible to generalize about psychotherapy for these patients. Some are benefited; many are not. Each case must be individualized.

Conclusions About Drug Therapy

Evaluating the tranquilizing agents is complicated for a number of reasons; the literature is filled with inconsistencies.

First, the end result is often a non-specific, "feeling better," which defies quantification.

Second, selected patient samples are used for much of the research. In this respect, Rickels (1964) found that conscious and unconscious attitudes toward physicians differ greatly in lower social class patients visiting a medical clinic, as compared with middle social class patients visiting a psychiatric clinic. Moreover, the physician, usually a member of the middle or upper social class, is better able to understand and treat patients with similar backgrounds and aspirations than patients from the lower social classes. Yet, this latter group is frequently in even greater need of help.

Third, drug response varies with the motivation of the subject (DiMascio and Klerman, 1960). Financial remuneration, counterphobic defenses, and wishes to establish contact with psychiatric personnel motivate subjects who take part in drug studies.

Finally, most clinical trials are conducted for only four to six weeks. We have found that many anxious patients will improve on any medication during the first few weeks. Yet many reports of the efficacy of these medications are derived from such brief studies.

Notwithstanding these difficulties, when properly used, the psychopharmacologic agents have benefited many patients. And, just as importantly, the use of our relatively crude compounds of the 1960's lends hope that we are just on the threshold of a biochemical and psychopharmacologic era in which our knowledge of the physiology of the brain will become exact, the mechanics underlying mental illness will be revealed, and definitive drugs for treatment will be found.

References


TREATMENT OF ANXIETY

The Hogarth Press, 1921, p. 132.
The Physician as Humanist*

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It is appropriate that this lecture should be given in a building which is devoted to the broader aspects of living and which is located on the campus of an institution which treats bodily ills. This institution began as part of a liberal arts college. This tradition in the state of Virginia started with Mr. Jefferson when the University was established at Charlottesville. He decreed that one of the first chairs should be in medicine, not as preparation for a professional career, but as a discipline which should be understood by all educated men. The faculty at this institution has recognized this principle, and this lectureship was endowed by a member of the faculty—a rather unusual occurrence. The medical college is continuing its interest in this field through the ecumenical program which is just getting started and which is broadly based in the health sciences as a whole.

Historical Role of the Physician

We live in a time of great change in the world. The industrial revolution, only 200 years old, was made possible by the harnessing of the sources of natural power, particularly the fossil fuels—coal, oil and gas. At the rate we are being so profligate with these fuels, we can anticipate that the supply may be exhausted in a hundred years, if not less. We are beginning to turn to nuclear power, being so profligate with these fuels, but now being used for peace.

Even this source is not inexhaustible, and in the long run we must look toward the harnessing of the sun. These changes in the physical world around us have resulted largely from the growth of science. We in medicine are proud of the fact that the sciences as we know them today began in the faculties of medicine in the medieval universities through the efforts of physicians to improve the care of patients under their charge. Roughly 90% of all the trained scientists who have ever received graduate degrees in history are alive today, and many of them are still working. This development has resulted in an explosion of scientific knowledge, most of which we use for the good of man.

Along with this change in the physical world has been an evolution in society. Man, so far as we know, has been on this earth somewhere in the general range of a million years. He has been organized into civilizations for some reason, and it is likely that more than half of the children ever born died before they reached their fifth year. Illness was cared for by the family with the help of the shaman, witch doctor, medicine man, or physician. The first physicians, so far as we know, were probably specialized priests, because priests were the first educated men. They made observations on natural phenomena about them, and learned to predict the occurrence of natural phenomena about them, and learned to predict the occurrence of eclipses and other celestial phenomena. We see the evidence of their accurate observations in such monuments as Stonehenge, in the temples of the Aztecs and Mayas, and in pyramids and other buildings in Egypt and the Far East. Because of their ability to predict celestial phenomena, particularly the coming of disturbing things like eclipses, the priests were surrounded by an aura of magic and miracles. As the priests moved more into the study of illnesses, I am sure they continued to encourage the feeling of people that...
they were able to perform miracles. Even today many physicians are not averse to having their patients feel that they are, indeed, miracle workers.

As the physician evolved from the priest, he turned his observations from natural phenomena to human disease. The information observed was recorded, passed on to others, and often incorporated into religious laws. The Old Testament indicates the Hebrews accurately observed that whenever groups of people came together in an army, outbreaks of dysentery followed quickly. They noted the cats’ habit of burying their excreta, applied this principle, and found that epidemics could be controlled. Each soldier was required to provide himself with a wooden paddle and deposit his excreta outside the confines of the camp. We now know, scientifically, that the control is due to the secretion by soil organisms of antibiotics which kill the pathogenic bacteria causing dysentery. The Hebrews also observed that, when people ate pork, muscle pains frequently followed; hence, they proscribed the consumption of pork by their religious followers. We know today that the cause of these symptoms is trichinosis, an infestation by a small, round, parasitic worm which lives predominantly in hogs. We see in many religious ceremonies, such as the communion service, the washing of hands by the priest. This act is a recognition that the contamination of food by hands soiled with excreta can pass on infections to others.

The physician in the past had few effective drugs. All he could do was give comfort to families and wait for the natural history of the disease to run its course. The few ‘drugs’ he had to work with were chiefly natural products from plants. The poppy probably has been the most helpful plant with its product, opium, relieving pain or controlling increased gastrointestinal motility. Ipecac will alleviate amebic dysentery, cinchona bark will control the chills and fever of malaria, and the products from the deadly nightshade or oleander will relieve intestinal cramps. The ladies extended these latter observations on the effect of deadly nightshade by chewing the leaves so that the belladonna would dilate their pupils and thus make them beautiful.

In any event, the physician and the priest have always dealt with people—with the human being—and, hence, have always been humanists. Their concern is with the interests, motivation, and reactions of people. We recognize that each individual is distinctly different from another. The individual variability of all living things is a basic biologic phenomenon. Members of families, as a group of individuals, react with each other and react to the normal stresses of living. Families live in a community, which has a personality, just as people do. The community’s personality is determined largely by the cultural background of those who inhabit it. All of these factors affect the illness of the patient and are felt beyond him biologically, socially, and economically on the family.

Medical Profession

Professions have a responsibility to society to render service. Society, in turn, gives privileges to a profession. The practice of a profession is restricted to its members, and in return the profession as a whole is required to maintain its standards and to develop a code of ethics. We recognize that to practice medicine is to enter a highly confidential interpersonal relationship and, hence, requires professional and personal integrity of the highest order. This idea has been expressed in various ways, probably the best known of which is the Hippocratic oath. But similar statements brought up to date for this century have been put forth, as in the Declaration of Helsinki.

The medical profession is to serve the patient and society. In the Christian religion, Christ taught that we should help the sick and not cast them out as had been the custom in many primitive societies. Luke, the physician, was one of the early followers of Christ. He taught these humane practices which are also put into effect in many other religions. Previously, when people became aged and infirm or developed what was recognized as an epidemic disease, they were put out of the tribe, just as animals cast the weak out of the herd because they attract predators.

In the past, the sick have been cared for chiefly in the home by the family and the physician. The priest, however, has always visited the sick. During the crusades the religious orders—particularly the Knights Hospitallers—on their return from the Far East often came back with leprosy, so that they were required to stay outside the cities. This practice led to the development of the principle of quarantine. Because they were Knights Hospitallers, their habitation came to be known as a hospital, and we have kept this term to this day. The original hospital was an isolation unit to quarantine epidemics and to protect society, rather than a place to treat the sick. Later this idea was extended by the church which took the responsibility for providing a place for medical care. The original nurses, as you know, were called sisters since they were sisters in the church. This thread of the support of many hospitals by religious orders continues to this day.

We have seen the parallel threads of medicine and religion continued in the spread of our religious beliefs through missionaries who have learned that one of the most effective ways to get the attention and faith of primitive peoples is to establish hospitals and to render medical service. This pattern we have seen exemplified most strikingly in this century by Albert Schweitzer, who was a great hu-
manist interested not only in religion but in philosophy, music, and medicine, though he carried his philosophy for reverence of life to an extreme.

In any event, we have seen changes coming in society which affect these trends. We have seen increasing mobility in families, so that one family in five does not live in the same house it lived in five years previously and another one in five does not live in the same city it formerly lived in. This trend poses an increasing problem in medicine when the physician attempts to develop a close and continuing relationship with a family. In addition, the family itself is changing. In the past we saw several generations living in the same household, with the grandmother helping to mind the children, raise them, and care for their illnesses. Now families are essentially one generation families, and the parents and grandparents are living in separate households.

New Trends in Medicine

We have seen a great increase in the complexity of the instruments and types of machines with which we treat sick people. We have seen a growing centralization of medical care in institutions as our culture has become urbanized. This trend poses a real danger in the loss of the personal touch in the care of the patient.

We have seen changes in the character of illness. The infectious diseases which killed the majority of people as short a time as thirty years ago are now largely under control. The chief causes of death are no longer influenza, pneumonia, tuberculosis, and the enteric infections—tuberculosis fever and dysentery—but are now chronic illnesses—heart disease, stroke, and cancer. We have seen an increase in life span, which is greater now in women than in men. We have learned through preventive measures, the development of drugs and the application of new techniques of therapy, to interrupt the natural history of disease. Science has had a major role in causing these changes.

In the past, the professions were theology, law, teaching, and medicine. The education of the professions has been in the hands of the professions, at least since the Middle Ages. As I have indicated, the faculties of medicine in the medieval universities were the places where observations on sick patients led to studies in physical sciences. You are familiar with the portraits of the physician in his velvet robe and hat, holding up a Florence flask of cloudy urine. He began to perform simple chemical determinations, and out of these experiments grew the sciences of physics and chemistry as we know them today. In biology, the whole science of genetics, which is probably the most interesting and exciting scientific problem facing the world today, was started with this thread of medicine and religion. The accurate observations of Mendel, a monk, were made on flowers which he grew in the monastery garden; and the principles he developed have been applied to the breeding of many other types of living things. We are seeing social and behavioral fields just beginning to evolve as sciences in their own right, comparable to the physical and biological sciences. An explosive growth of knowledge has occurred largely as a result of research. From our point of view, the most important scientific principle we have recognized is that of biologic variability—the fact that no individuals in a group are identical. No two of you look alike, behave alike; and if we measured any physiological parameters on you, the data would scatter. If we plot the data, whether height, weight, blood pressure, blood sodium content, urinary chloride excretion or anything else, we come out with a smooth bell-shaped probability curve. We recognize also that the physiological measurements of an individual are variable from day to day. To develop scientific criteria in an essentially variable system, one must study large groups of individuals in order to smooth out the individual variations. The data on one individual, when applied to conclusions drawn from studies on a group, meet no scientific criteria that are acceptable. This is simply another way of saying that the practice of medicine as it applies to the individual patient is not a science, has never been a science, and can never be a science.

The practice of medicine is an art. The educational background of the physician and his training must take this fact into account. What the physician does in practice is to apply scientific and technical knowledge to the solution of an individual problem. Other professional people do the same thing. The architect, for example, talks to you about your sense of values, how you want to lead your life, what your cultural interests are, and then he designs an individual solution for your family, which is your home. This process is an exact parallel to what the physician does when he is faced with a diagnostic or therapeutic problem. The important thing is that, unless one takes into account the several factors that motivate people and drive them, one cannot be sure that the recommendations for care will be accepted by the patient and his family. Many times the failure to accept the recommendations of physicians is due to religious, philosophic, or economic factors outside the realm of science. For example, we need only call attention to child spacing when the mother has advanced renal disease and problems involving life and death are concerned. How do we carry these ideas over into the education of the professional man?

Historically, all professional men received a classical liberal arts education. Today we feel that in medi-
cine there should be parallel instruction in the sciences and in the humanities. Whoever commits himself to a life in the medical profession has committed himself to a never-ending process of self-education, which should be in both disciplines. The priest has always had a classical education, but more and more he is becoming involved in the behavioral and social sciences which are proving to be necessary for the practice of his profession.

In any event, those of us in medicine should see that we all work together for the education of the physician. All health scientists and workers will be better prepared to give patient care if they are trained together to work better together in the community. We recognize that the sciences on which medicine is based are not distinct disciplines but a continuum and that our designations are artificial when we call one science chemistry, one biology, and another physics. Take the simple problem of Mendel and his colored sweet peas, which is concerned with the study of genetic inheritance and the transmission of characteristics. We know now that this transmission is accomplished by a single chemical substance—DNA. But, if one studies DNA from the chemical point of view of the number of atoms and their arrangement, he may be called a biochemist since he uses biochemical tools. If a person studies this compound from the size of the molecule, its sedimentation gradient, its X-ray defraction pattern or uses some other physical technique, he is called a biophysicist. But if he studies its effect on living things, he would be called a molecular biologist. In effect, each person is studying the same chemical compound; but, the sciences are artificially separated according to the research tools applied to the solution of this scientific problem. Hence, in medicine, our education should be from as broad a multi-disciplinary point of view as we can devise, both in the basic and clinical sciences. If we extend this concept beyond the student years, we recognize that the physician in practice can begin to call on other people who have different backgrounds, such as the priest, who also have an interest in the motivation and reactions of people from a quite different point of view than the physician. Hence, the priest can be used as a professional colleague in the care of certain patient problems.

Current Problems

The major problems that face the world today, in my opinion, are not scientific, but ethical and moral. The basic scientific information on which we could arrive at workable solutions to these problems is largely known. We need to refine and extend our knowledge; but we have already learned that, even though we accumulate additional scientific knowledge, the acceptance by people of solutions to their problems on the basis of their beliefs and sense of values has not come about. Let us take one of the very practical problems which faces us today—the balancing of the food supply with the growth in the population. It does not seem likely that, even with the application of scientific principles we know, we can keep up with the increase in the food supply at the same rate as the population. We can turn to the sea as a source of protein; we can increase the use of chemical fertilizers on the land; we can increase the use of pesticides to improve crop yields. When we do the latter, it is not without danger; for when we use pesticides, we are upsetting natural ecology.

We have also learned how to control the rate of population growth. You know about “the pill” and the various intrauterine devices to control conception. The acceptance of these methods by people is determined not by scientific principles, but by philosophic, ethical, moral, and religious values. People in all parts of the world have known for centuries how to cause abortions. We are faced with the problem—and you see it in the newspapers daily—where the legislatures will not face revision of archaic laws devised many years ago before safe, scientific methods of abortion were worked out. What is the ethical problem if there are known genetic factors which will lead to handicapped children or if there has been exposure to rubella virus in early pregnancy? Is it proper that this pregnancy should be aborted?

We look at the population problem in India, where cattle roam the streets, cannot be killed for religious reasons, and eat food which could be used for human consumption. Yet, when any suggestion is made by government that the number of cattle be reduced, riots and political turmoil follow. We have a problem all over the world with rats. Rats eat as much food as human beings do, and we can control the rat population using one of several techniques. We do not face this problem, which is not a scientific one but rather one of inertia.

We are beginning now through scientific means to learn how to manipulate genes. We have recognized that viruses and drugs can alter the development of organs at certain stages of pregnancy. With this beginning, one can see coming down the road not too many years hence the ability by other techniques to make definite changes in genes as one might desire. Already, we can interfere with the natural history of the transmission of characteristics. We see artificial insemination, started in cattle breeding, now applied to human beings. It is perfectly possible now for a woman in a childless marriage to select the characteristics she wishes her child to have. We have seen more recently the ability to transplant an ovum from one human
being to another. This accomplishment raises the possibility of a sterile, non-ovulating woman picking another to furnish the ovum which can be fertilized by her own spouse, be implanted in her fallopian tube, and result in a pregnancy. We recognize that application of these techniques may stop the genetic transmission of diseases which are usually fatal. Hemophilia is a perfect example in which we know the recessive gene is transmitted only through the mother. What are the moral and ethical implications of these things which we now technically can do?

We are getting more and more into the problems of organ transplantation. What is the proper ethic for use of this technique? We have seen the refusal of certain religious sects with fundamentalist beliefs to permit transfusion of children or of themselves when they need this life-saving procedure. Should we take society's power through the courts to require transfusion when it is against religious belief? What types of people should we select for the implantation of artificial hearts and for the use of artificial kidneys or dialysis machines, particularly when we know there is an irreversible biologic process? What is our responsibility as physicians to prolong life if we know there is a hopeless illness? Is the withholding of drugs or procedures which could prolong life for a while ethically and morally the same as giving a drug which would hasten inevitable death—euthanasia? This problem has been debated, of course; but we have no clear code of ethics on which to base our actions.

We are becoming more and more concerned with problems of human experimentation, since we are learning that we cannot always extrapolate from lower species to the human being. This problem is going to become more important if legislation similar to that passed in the last Congress is extended. The restrictions on the use of animals for experimentation of all types, if continued, will require us to go more and more directly to the human being. We have to recognize, also, that in many types of disease processes we have no model which we have been able to reproduce in lower animals. In these instances, we must do our primary experimentation on the human being.

We have learned to interrupt the natural history of disease. We have learned to control the vectors which transmit infectious diseases and the reservoirs which harbor them. We have seen the philosophy of the reverence for life extended in Schweitzer's hospital so that you could not swat a mosquito even if you saw it land on you and be about to bite. You could not kill the rats that were eating the food in the storehouse. How do we interpret moral values in the light of the world in which we live? We have seen the development of mood-altering drugs and of penicillin, which is probably the most important single drug that has been developed. The mood-altering drugs have the greatest implications for moral, ethical and philosophic considerations, however. When we can control behavior, as we know we can with mood-altering drugs, what could be done with inclusion of these agents in food as additives? You are familiar with the novels that have been written on this general theme.

What about accidents, which are the third largest cause of death and most frequent in the most productive years of life, between the ages of ten and thirty? Accidents occur in individuals whom we call accident prone, and these accidents appear to be examples of reactive behavior. In any event, we need to consider what is society's responsibility and that of the physician in using the tools he has now at hand in these types of problems which he thinks may be soluble. We are contaminating our environment, as is written in the papers almost daily. What is our responsibility to prevent man from harming himself?

Educational Programs

How can we put these points into educational programs for the future? The ultimate objective is the improvement of patient care. We believe that solutions may come in the study of the whole man, not just of his biological interactions, but of his functioning as a unit of society in his family and particularly in his community.

It is there that the stresses of living cause him to react and produce symptoms which we cannot medically explain. These symptoms arise not only from the pace and pressures of living but from the frustrations of his job and from the normal stresses that occur within families. We think the educational process should stress continuing self-education of the physician from the beginning of his professional career. We recognize that the thread of human biology can start with other species but must go on to the human being. We believe that much more stress should be placed on behavior as a basic biologic phenomenon which is essentially variable. This study can start with group and individual behavior in animals and then extend into observations on man. We can then study the added impact of disease processes through all the years of the medical curriculum. To help in this program, we plan at Hershey a Department of Behavioral Science as a basic medical science which will teach through all the years and serve as a base for all the clinical disciplines.

We think there should be the parallel thread of the humanities through all the years of the curriculum. We have already appointed a man to our chair in religion, and we believe that the study of comparative religion is an important background for any professional man in the health sciences. Religious beliefs encompass the
personal, intimate, and emotional reactions of people to beliefs which they hold. As we have indicated, we feel that they affect the acceptance by patients and families of the physician's recommendations for care. We plan to incorporate teaching in the history of science to get the background on which the profession of medicine now rests, extrapolating into the future what we can see coming over the horizon. We think there should be another chair in philosophy and ethics. Unless the physician has come at peace with himself in a philosophy that is satisfactory to him, he cannot be the best physician to his patients. We believe that the interpretation of the changes in moral values that we see in the world, particularly in the community, is the responsibility of this field. We have called this area the Department of Humanities.

We feel the role of the family must be studied further. We must consider not just the care of illness after it has developed but the prevention of disease and the delaying of complications that we know are coming from the genetic background of the families. We must maintain health at its highest level and see that people have some joy in living. The family must be related to the community so that the resources available in the community can be used to achieve the best results in patient care. Accordingly, we are establishing a Department of Family and Community Medicine to teach throughout all the years of the medical curriculum.

All of these programs are designed to come together at a focal point—the patient in the family setting. Here we hope the physician will learn to bring colleagues in—the priest, the educator and others. The approach should be from the multidisciplinary point of view, exactly as we started with the scientific aspects of education, but in a broader sense. If we can capture the religious zeal that we have had in the past in the educational process, we can improve the care of the sick. We should remember the dignity of the individual and emphasize the individual both as a student and as a patient. We feel these ideas can be designed into the physical facilities in which the educational process takes place. With the student, it is the medical sciences building and the hospital where patient care takes place. We have planned the hospital with all single rooms for patients, where dignity can be maintained most easily.

We see changes in the patterns of support, with third parties coming in to help care for the cost of illness. But, in this trend is the danger that more and more an attempt will be made to substitute an institution for an individual in what is in essence an interpersonal relationship—that between the patient and his physician. We are posed here with another philosophic and ethical problem. How much do we use machine techniques in data handling? What is the effect of this technique on the patient when he knows that his data have to be made available to a third party who is going to pay the bills for his illness?

Conclusion

These problems are all soluble. If we give thought to them, both in the educational process and in the application to patient care with the dedication of all those working in the health professions, we will increase our service to people.
A drug (single chemical entity) is known by several names. First, the chemical name describes its structure by standard chemical nomenclature. Second, the research code number is assigned to the drug during pharmacodynamic studies in animals, and often during early clinical investigation. Third, it receives a generic name which is often a contraction of the chemical name, but which describes the drug and the class of drugs to which it belongs, e.g., barbital, phenobarbital, pentobarbital, etc. The U.S. Adopted Name Council (USAN), composed of representatives from the American Medical Association, U.S. Pharmacopeia (USP), National Formulary (NF), and Food and Drug Administration (FDA) recommends generic names for all new drugs. Since 1962, the FDA must approve all generic names. Before, 1962, the generic names were often not descriptive of the drug, and were confusing and difficult to use (Wilson, 1960). Fourth, the drug receives a trademarked name (brand name), designated by a superscript ® at the end of the name, signifying that this name has been registered with the U.S. Patent Office. Only the registrant may use the trademarked name for the particular drug; thus his product is distinguished from those of competitors.

Many older drugs that are public domain, or on which the patent has expired, are often best known by the generic name, e.g., phenobarbital. If a prescriber wishes to prescribe the phenobarbital produced by Winthrop Laboratories, he uses the trade name Luminal. Tetracycline HCl is the generic name for a specific antibiotic, which may be purchased or prescribed by that name. It is also known by certain trade names, e.g., Tetracyn (J. B. Roerig & Co.), Achromycin (Lederle Laboratories), Kesso-Tetra (McKesson Laboratories). Even if a company holds an unexpired patent on a drug, it may be the only manufacturer of that product, so the use of the generic name or the trademarked name becomes immaterial, e.g., Darvon (propoxyphene HCl, Eli Lilly & Co.) and there can be no controversy over equivalency. On the other hand, if many companies manufacture the same drug, in similar dosage form, the question arises as to whether all these products are equivalent with respect to physiological and pharmacological potency.

Equivalency of Generic Products

This is important because in many instances the prescriber has a choice of designating a product by its generic name or by a trademarked name. If the generic name is used, the pharmacist is permitted to dispense that drug manufactured by any company. In this method of prescribing the assumption is that all products of a specific generic name are equivalent. With our present knowledge, however, there is doubt whether products bearing the same generic name are equally efficacious, e.g., sulfisoxazole (F-D-C Reports, Jan. 2, 1967). It may be that the patient
GENERIC EQUIVALENCY CONTROVERSY

will get less than the desired dose, because the product does not meet labeled claim, or that the drug cannot be absorbed for some reason, e.g., the tablet fails to disintegrate or dissolve. If generic products are not equivalent, then prescribing, either voluntary or by directive, becomes a question of good professional practice. Forcing a prescriber to prescribe any drug in which he does not have confidence or with which he has no experience, is a potentially dangerous practice.

The problem of drug designation is further complicated in that any manufacturer can obtain a trademark for his products, and since all drugs now have generic names, both terms lose their power to differentiate between the quality of drugs. There is a new term coming into use, "branded-generics," which nicely bridges the gap between generic and trademarked drugs. Trademarks are now being obtained for both old and new generic drugs. Comparing statistics between these two groups of drugs becomes a meaningless game of numbers.

In addition, the trademark is on the drug, and not on the final product (dosage form). Yet, the patient is not given micro-packets of powder or liquid to take; he receives a combination of ingredients, including the drug(s), which makes an acceptable physical entity that can be conveniently handled, taken, or administered.

Discrepancies in Drug Costs

The cost of medication is interwoven into this controversy. The products sold under generic names are often less expensive than the trademarked products, e.g., 5 mg dextroamphetamine sulfate tablets may be purchased for as little as $1.25 for a bottle of 1,000 tablets, or purchased as Dextradrine (Smith, Kline & French Laboratories) for $22.60 (Drug Topics Red Book 1967). This phenomenon of price differentials occurs in other fields also.

The cost of medication is confounded by the pricing structure of many pharmaceutical manufacturers. They sell their trademarked products to government agencies and hospitals at much lower prices than to the community pharmacist. It was reported that Upjohn Co. sold prednisone tablets (5 mg) to the Government at $4.94 per 1000 (F-D-C Rept., July 29, 1967), whereas the price to community pharmacists was $20.94 (Drug Topics Red Book 1967). It was also reported that Ciba would give a bottle of 1,000 tablets free with the purchase of two bottles of 1,000 tablets of Esidrex (hydrochlorothiazide) and Esidrex K (hydrochlorothiazide and potassium chloride). This offer was made to public and private hospitals, dispensing physicians, but not to pharmacists (Weekly Pharmacy Rept., Jan. 2, 1967). Price cannot be equated to quality. If it is, one may ask if the manufacturers are making products of two different qualities, an expensive one of higher quality and a less expensive one of lower quality. Recently, E. R. Squibb & Sons announced the new price for its Sumycin (tetracycline). The product now will sell for $4.25 per 100 capsules (F-D-C Rept., August 14, 1967). This makes Squibb's prices more competitive with generic products.

Many of the arguments given against the concept of generic equivalency arose before the 1962 Kefauver hearings. These hearings resulted in the Drug Amendments of 1962 to the Federal Food, Drug and Cosmetic Act. These amendments gave new regulatory powers to the FDA, and as a result many of the problems associated with generic drugs due to poor manufacturing practices are being reduced or eliminated. For example, the number of drug recalls have been increasing every year (F-D-C Rept., Dec. 5, 1966), indicating that the poorer quality products are being forced off the market.

There are those who would like to see products prescribed by generic name only, and those who oppose this concept. The former group assumes generic and product equivalency; the latter group does not agree that products are equivalent. Unfortunately, proponents of both sides of the question of generic equivalency have indulged in the luxury of stating half truths.

Let us take a close look at the major arguments presented by the opposing sides in the generic equivalency controversy.

For Generic Equivalency

1. All generic products are equivalent, because they must meet USP or NF standards. If they are equivalent, then one can buy the least expensive product.

Reply: These compendia set standards for purity and identification of drugs and pharmaceutical adjuvants and for the range of drug content in various dosage forms. The compendia do not guarantee therapeutic efficacy or give formulas and directions for manufacture of dosage forms sold. Some of the tests have limited value, e.g., the tablet disintegration test may not be a reliable index of drug availability from the tablet. In some cases, the assay may be misleading, e.g., assay for total iodine in Thyroid USP (Brune et al., 1962; Gatz, Ginsburg, and Salenger, 1962; MacGregor, 1961; Williams, Meister, and Florsheim, 1963). Yet the standards prescribed by these compendia generally reflect present day manufacturing practices, because the committees which establish the standards include industrial scientists.

2. The Defense Personnel Support Center buys only generic products. If these products are used in the Bethesda hospitals and given to our Presidents, generals, and Congressmen, etc., why are they not good enough for everybody?
Reply: The Defense Department buys its drugs under generic names based on competitive bidding. Since all drugs have generic names, and anyone can make generic drug products not covered by unexpired patents, the bidding is open to all. The Defense Department inspects the manufacturing facilities before accepting any bid. After the product is made, representatives from the department again come to the manufacturer to observe all the final tests performed on the product. By this procedure the Defense Department presumably receives a product that meets all its specifications. Not even a large hospital, let alone individual pharmacists, can make these inspections. The manufacturer of trademarked products competes under this system and when successful, sells his trademarked product under its generic name.

As the FDA increases the number of inspectors and is able to enforce its regulations more widely, drug products should be of higher quality, because more manufacturers will be operating under good manufacturing practices and with sufficient quality control.

Against Generic Equivalency

1. The large manufacturers of trademarked products are engaged in research to improve existing drugs and to discover new drugs. The prices of their drug products must be higher to support this research. The small manufacturers of generic products do not engage in research, and have never discovered a new drug.

Reply: The companies who undertake research, do not do it for altruistic reasons. They do it to gain competitive advantages and to make money. This is not to be condemned, but do not ask for public support for it. Many other industries do research and support research, e.g., chemical, electrical, petroleum, etc., but they do not ask for public sympathy. The pharmaceutical industry's research efforts do not justify the large price differentials that often exist many years after the product has been introduced, even if the successful products must pay for the failures.

Companies that discover a new, unique, and useful medicinal can obtain a patent which runs for 17 years after the date of issue (about three years after application). During this time they have a monopoly on this drug, and there is no competition, generic or otherwise. In this manner they can protect their investment and make a profit.

2. The large manufacturers of trademarked products have better quality control and can spend more time and money in the pursuit of excellence. Their products are purer and there is less likelihood of contamination.

Reply: This should be true, but they are not immune to mistakes and accidental contamination. This difference is slowly being reduced by increasing FDA inspections, and hopefully, this difference will continue to diminish. Mr. Hansen, program operations director of the Bureau of Regulatory Compliance FDA, stated that there were less than 70 recalls per year before 1962; there were 110 in 1964, 340 in 1965, and 449 in 1966. Of the 449 violations in 1966, 351 (78%) were due to violations of the good manufacturing practice regulations (F-D-C Rept., Dec. 5, 1966).

Purity and control of contamination is a problem that has plagued all manufacturers. Contamination due to diethylstilbesterol (Weber et al., 1963), estrogen (Hertz, 1958), selenium (Keller, 1960), penicillin, Salmonella, metal particles in ophthalmic ointments, etc., have occurred in products of both large and small manufacturers. They are more likely to occur due to poor manufacturing practices. In 1953, a study of vitamin preparations in Canada showed that subpotent products were produced more often under conditions of inadequate quality control than those manufactured under adequate control (Campbell, 1953).

3. The trademark is the identification of the manufacturer, and says he assumes responsibility for the product.

Reply: True! Many manufacturers are concerned about their "good name," and, therefore, may exercise better quality control. All manufacturers are responsible for their products whether they have a trademark or not. A trademark, however, is not synonymous with quality; anyone can obtain trademarks for his products.

4. Physicians, dentists, etc., prescribe by trademark because they are familiar with the company and its products and know the therapeutic results to expect from these products.

Reply: True! But, do they really know the company? How much of the prescriber's information comes from the company representative, and how complete is that information? Ciba was accused of not reporting toxicity data on Elipten (amine-glutethimide) (FDA Rept., 1966). Frosst made an inadvertent mistake in its reformulation of Dicomerol (bishydroxycoumarin) (Loinski, 1960). Cannot the physician just as well become acquainted with certain companies that manufacture nonproprietary pharmaceuticals?

5. Some formula ingredients in a dosage form make generic prescribing hazardous for patients with certain diseases that require restricted caloric or sodium intake. When the physician prescribes by trademark, he knows what the patient will be getting.

Reply: How does the physician know what the ingredients other than the drug are? This information is not always readily available to the prescriber. The manufacturers do not list tablet formula ingredients and their amounts. One gram of sugar produces about four calories and no tablet would contain this much sugar as a diluent.
The prescriber must write to the company to ascertain the ingredients.

It is possible that a large manufacturer may be more concerned as to the ultimate user of his product, and therefore make adjustments in his formulation, e.g., omit calorie producing materials or sources of sodium ion. He would state this in the package inserts, etc.

6. When a generic product is prescribed, the same product is not always dispensed. This can lead to varying therapeutic results. A trademark or designation of the manufacturer insures that the same product is always dispensed.

Reply: The same product should always be dispensed unless it is no longer available. The source of the generic product should be noted on the prescription order by the pharmacist, to insure that the same product is dispensed when the prescription order is refilled.

When a patient is on long term drug therapy, e.g., insulin, penicillin, anticoagulants, thyroid, etc., a constant drug blood level in the therapeutic range is necessary to prevent relapse. A reliable product which will give the same absorption pattern is necessary. Changing brands may result in different levels of the drug in the blood. The second brand may be satisfactory for a patient just starting on the therapy regimen, but may not be satisfactory for refilling of a prescription order. Dosage adjustment is easiest when the patient is just starting therapy. The prescriber learns what to expect from each product regardless of the name.

7. The pharmacist has greater liability when filling prescriptions for products prescribed generically.

Reply: True, but what does this have to do with the proper treatment of patients?

If a trademarked product is prescribed, or the manufacturer of the product is stated on the prescription order, then the pharmacist has no choice as to what to dispense, and he is only liable under the implied warranty doctrine. If a generic product is requested and the manufacturer not designated, then the pharmacist has a choice. If he uses care and exercises his knowledge and experience to choose a reliable product from a source in which he has confidence, then he cannot be considered negligent, but he is not always dispensed. This can lead to varying therapeutic results. A manufacturer insures that the same product is always dispensed.

8. Products sold under non-proprietary names do not maintain their potency as well as proprietary products.

Reply: This is one of the quickest tests that can be performed on a product by the FDA or a state agency. Judging from the results reported in the Medical Letter (Aug. 19, 1960), potency is rarely outside the set limits. On the other hand, taking the data collected by the analyst of the city of Birmingham, England, it appears that the potency of many English products does not meet official requirements (Bagnall and Stock, 1955). There is not sufficient published data available at this time to determine if this statement is true.

9. The large manufacturer has more staff, facilities, information, and manufacturing "know how" than the small company. Therefore the large manufacturer is better able to produce a more stable, uniform, and efficacious product.

Reply: The large manufacturers do not have a monopoly on information and the small manufacturer can hire knowledgeable and experienced personnel. The good manufacturing practice regulations and their interpretation are available to all. A great deal of stability data and incompatibility information has been published. Unfortunately, however, the availability of this information does not guarantee its application. The FDA has this knowledge too, and uses it in judging new drug applications, and in their plant inspections.

The argument does not end here. It has been demonstrated many times that there are numerous factors in the formulation and manufacture of dosage forms that may affect the efficacy of the product. Levy and Nelson (1961) and Delgado and Cosgrove (1963) review this problem in detail. These authors discuss the effect of variables such as drug particle size, sterility of ophthalmic preparations, rubber and polymer closures on multidose vials, ingredients of ointment and suppository bases, salts and esters of the parent drug molecules, and the ingredients added to the drug to permit manufacture of the dosage form such as solvent, sufactant, and fillers.

A commonly used filler for tablets and capsules, dicalcium phosphate, was found to depress blood concentration of tetracycline (Böger, 1959). Drug particle size may affect absorption of both oral and parenteral product (Levy, 1963a), e.g., sulfa drugs, griseofulvin, and insulin. Increasing the solubility of the tablet base increased the absorption of spironolactone (Levy, 1962). "Soft" tablets of phenylindanedione produced drug blood levels similar to that produced by loose powder in capsules, whereas "hard" tablets gave delayed and poor absorption (Schulert and Weiner, 1954). The salt form of PAS and the presence or absence of an enteric coating influenced the PAS blood level (Frostad, 1961). The salt form, molecular modification, and the formulation of aspirin tablets affected the salicylate blood level (Leonards, 1963; Levy and Gagliardi, 1963; Levy and Sahli, 1962). An in vitro test to determine the dissolution rate of a drug has explained why certain drug products, such as predni-
produced drugs for a very limited time. This is not an exception immediately (no sustained effect) to almost no absorption (Shenoy, Chapman, and Campbell, 1959).

Stability of a product is important not only because the potency of the product must be maintained, but also because the decomposition products may produce untoward reactions, e.g., tetracycline (Frimpter et al., 1963; Editorial, J. Am. Med. Assoc., 1963).

Isolated clinical cases have been reported in which a generic product gave poorer results than a trademarked product, e.g., prednisone (Keller, 1960), cortisone (Rosenheim and Ross, 1958, Boch, 1959; Bayliss, 1959), tolbutamide (Carter, 1963; Caminetsky, 1963), and phenylbutazone (Searl and Pernarowski, 1967). Even if ineffectiveness has not been shown, it may still be there.

We have learned much about the formulation and manufacture of dosage forms, often only after the product has been marketed. Over-sights, even by large manufacturers, have come to light in this manner. The large manufacturer has the personnel and the facilities that would seem to make him more able to do thorough investigations before marketing a product, but he has not always done so.

The large companies also have produced drugs for a very limited market as a public service, because the drug is needed. This is not an argument against generic equivalency.

Conclusion

The truth about generic equivalency has not yet been determined. The arguments in the generic equivalency controversy are confounded by names, proprietary (trademark, brand name) as opposed to non-proprietary (generic, branded-generic), yet quality of the products is not necessarily related to any name. The efficacy and not the name of the product is important. The crucial question to ask is whether the product is clinically or therapeutically effective, giving reliable and uniform results.

Drugs called by their generic names are here to stay and more than likely their use will increase, especially as state and federal governments pay more of the medication bills. Kentucky and Louisiana already have issued lists of generic equivalents to trademarked products.

Meanwhile, the prescriber and the pharmacist still must ponder the question of therapeutic equivalency of drug products. What product is to be requested on a prescription order and what product is to be dispensed if the drug is prescribed by its generic name. More information is needed to answer this question. Clinical trials testing the hypothesis of generic equivalency are required. A national clearing house for information on the efficacy of drug products may be necessary. A national organization such as the American Pharmaceutical Association, American Medical Association, or the FDA, or an organization composed of representatives of interested groups could collect and disseminate the information to physicians, dentists, pharmacists, etc.

The U.S. Pharmacopeia and National Formulary monographs should include formulas and manufacturing directions for the various drug products. The specifications should be based on clinically demonstrated efficacy. The monographs could also include information on known factors that may impair the effectiveness of the product. Formula and process variations would be permitted only if the same therapeutic results can be demonstrated clinically.

The knowledge that the Defense Department has concerning its drug purchases and the use of these products in its facilities could be made available. Manufacturers, both large and small, could make available clinical and physicochemical data on their products, such as assay, drug content variation per unit dose, tablet dissolution rates, drug levels in blood or urine, and stability. It is important that the FDA or the proper state agency be informed of any suspected drug products so that substandard products may be removed from the market as rapidly as possible.

Finally, it is necessary that more people become aware of the true magnitude of the problem of generic equivalency. Because of the present lack of knowledge of which drug products are therapeutically equivalent, the prescriber and pharmacist must rely on their experience as to which products and companies are reliable. They must also continually search their journals for information on the therapeutic equivalency of products. Perhaps the pharmacist should compile information on generic and therapeutically equivalent drug products, which companies consistently make poor products, using sources as Weekly Pharmacy Reports (The Green Sheet), F-D-C Reports (The Pink Sheet), FDA Papers (U.S. Government Printing Office), and The Medical Letter on Drugs and Therapeutics. These compilations would then be available for the prescriber.

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References


F-D-C Reports. 28(49), Dec. 5, 1966.

F-D-C Reports. 29(1), Jan. 2, 1967.

F-D-C Reports. 29(31), July 31, 1967.

F-D-C Reports. 29(33), Aug. 14, 1967.


Keller, W. Short communication concerning the difference in effectiveness of prednisone tablets [in German]. Die Pharmazie 15: 56, 1960.


*Medical Letter on Drugs and Therapeutics. 2(17), 65, Aug. 19, 1960.


Wilson, C. O. Statement to Subcommittee on Anti-Trust and Monopoly of the Senate Committee on the Judiciary, May 10, 1960.

* Refers to only the first of a series of articles reporting results of assays on various commonly prescribed drugs.
The goal governing dosage schedules for the chemotherapy of gastrointestinal cancer has been, in general, to induce significant drug toxicity in order to insure maximum therapeutic effect. The pursuit of maximum therapeutic effect led logically to the development of “Life Islands” which permit the isolated, relatively germ-free care of patients treated with intensive chemotherapy. However, intensive chemotherapy may have deleterious effects on patients other than that of increased susceptibility to infection. It is, therefore, important to be aware of the alternative approaches implied in a recent analysis of data obtained from the Eastern Clinical Drug Evaluation Program (CDEP). In this cooperative study, Bross et al. (1966a, b, c) have shown that patients manifesting drug toxicity do not necessarily show a greater frequency of tumor regression than do patients without toxicity.

In the CDEP program a total of 956 patients were treated with 5-fluorouracil (5-FU), dimethylurethamine (AB-132), mitomycin C, chlorambucil, and 6-mercaptopurine (6-MP) in a 60-day study of objective response. There was no increase in tumor response with high toxicity scores. In fact, the patients with the greatest toxicity showed a somewhat lower tumor response. These data (Ausman, 1965; 1966; Bross, 1965; Bross et al., 1966a, b, c) suggest that overt toxicity may not always be necessary to obtain an oncolytic effect. This is further supported by a recent study of the Eastern Solid Tumor Group which compared 5-FU, fluorodeoxyuridine (FUDR), and methotrexate (MTX) at dose levels producing comparable toxicity in a group of patients with colon-rectal and breast cancer (Hall, in press; Schneiderman and Krant, 1966). With increased toxicity a plateau was reached beyond which no significant further regression of tumor could be obtained, and survival, despite tumor response, was shortened in comparison to those patients showing tumor response but minimal drug toxicity (fig. 1).

These observations as well as those of Ansfield (1964) and others (Cudmore and Groesbeck, 1964; Groesbeck and Cudmore, 1963) are supported by animal data (Louis, 1965) and suggest that it is not necessary to take patients to toxic drug levels to achieve a significant remission. Such data should reinforce our awareness of the possible deleterious effects of drug action on survival and remind us that the gain afforded by tumor regression can be lost in the morbidity and mortality induced by drugs.

The Eastern CDEP data suggest that 5-FU and mitomycin C can produce significant therapeutic effects without severe toxicity (Ausman, 1965; 1966; Bross, 1965; Bross et al., 1966a, b, c). Therefore, it is important to avoid severe...
diarrhea, stomatitis, and marrow depressions with white counts below 3,000/mm$^3$ or platelet counts below 75,000/mm$^3$. When used this way, 5-FU becomes of more general clinical usefulness in gastrointestinal cancer.

A renewed interest in alkylating agents has resulted from observations indicating objective tumor regression (>50% shrinkage) in colon-rectal cancer with AB-132 (8 of 33), gastric cancer with AB-132 and chlorambucil (6 of 26), and pancreatic cancer with AB-132 and chlorambucil (6 of 8) in a study by the Eastern CDEP (Ausman, 1965; 1966; Bross, 1965; Bross et al., 1966a, b, c).

Chlorambucil showed no activity in 15 patients with rectal cancer, while 5 of 12 responded to AB-132. Chlorambucil was given by mouth and appeared to be most effective in the upper gastrointestinal tract. Unfortunately, this study as performed by the Eastern CDEP was non-comparative and limited to only two months of observation in ambulatory patients. More critical studies of these agents need to be done. In the meantime, the ease with which chlorambucil can be given makes it worthy of serious consideration as a useful agent in gastric and pancreatic cancer, although its superiority to other alkylating agents has not been clearly shown. Similarly, AB-132 or another parenteral alkylating agent can be used in colon-rectal cancer.

Chemotherapy Combined with Surgical Treatment

Laboratory evidence has supported the usefulness of adjuvant prophylactic chemotherapy at the time of surgery in the absence of known disease. However, the clinical applications of this evidence have shown puzzling results. There is no improvement in recurrence rates in men with colon-rectal cancer who received high-dose thio-TEPA (0.8 mg/kg) at the time of surgery, although women show a significantly increased survival time (U.C.L.A. Statistical Unit, 1965). In this study a high dose, with its increased mortality and morbidity, was felt necessary. Fluorodeoxyuridine (FUDR) used as an adjuvant by the Veterans Administration study shows no significant difference in recurrence rate at 30 months (personal communication, M. W. Wolcott, 1965). These studies await simultaneous controls but evidence supports the possibility

Fig. 1—Colon and rectum cancer. Eastern group double blind, 3 drug study (all drugs combined). Data and graph courtesy of M. A. Schneiderman, M. J. Krant, and T. C. Hall of the Eastern Solid Tumor Group. A major portion of this data was presented in Cancer Chemotherapy Rept. 50: 107–112, 1966.
that repeated 5-FU administration increases the survival of patients with occult tumor left behind.

Recently, Mackman and Curreri (1967) reported the results of a "second-look procedure" evaluating patients who had curative resections for colon cancer but who showed positive mesenteric node or serosal involvement at the time of "curative" resection. Post-operatively, these patients were given 5-fluorouracil for four or more courses prior to their "second-look," one year post operatively. Twenty patients were examined, 17 of which had no tumor at the end of this one-year period. An additional 11 patients who had direct extension to adjacent organs or structures, who were treated with only palliative resection, were examined following four to 10 courses of 5-fluorouracil. Seven of these patients were free of tumor, and three had tumor which was removed for possible "cure."

This experience has recently been supported by a report by Rousselot et al. (1967, in press) who have reported on the survival of patients over a five-year period following the effectiveness of both intraluminal 5-fluorouracil administration and systemic intravenous 5-fluorouracil in the post-operative period. This was a comparative study between nitrogen mustard and 5-fluorouracil. Adjuvant nitrogen mustard had no effect on statistics regarding recurrence rate. However, for 5-fluorouracil in those patients who had nodes (stage 3) significant improvement appeared. At five years the survival rates were 65% for the 5-fluorouracil treated versus 32% in a nationwide control series and 26% in the St. Vincent's Hospital control series. There was no apparent improvement in survival rates in stage 1 and 2 colon cancer cases (negative nodes) as compared to those seen on the basis of the nationwide averages and this reflects the over all effectiveness of surgery in early colon cancer.

These studies despite the lack of concomitant controls point out the possible usefulness of an adjuvant drug in the treatment of colon carcinoma particularly when known tumor is left behind.

The value of massive intermittent chemotherapy in the absence of clinical disease as applied to acute leukemia is a proven one (Hananian, Holland, and Sheehhe, 1965), but proof of an analogous situation in colon-rectal cancer is only suggestive and requires further data. A study of this kind for gastric and bowel cancer using repeated courses of cytoxan or mitomycin C is being conducted in Europe (Karrer, 1964a and b), and the results should be of great interest when they become available.

Wood et al. (1961) and others (Clifton and Agostino, 1963; Koike, 1964) found a decrease in the viability of circulating tumor cells following the administration of fibrinolysins or anticoagulants. The adjuvant anti-tumor action of anticoagulants has not been explored at the clinical level, but there are controversial retrospective epidemiological data that suggest that cancer patients who received anticoagulants for post-surgical phlebitis or coronary disease may have shown an increase in tumor-free survival time (Michaels, 1964). Based on this evidence, a study using heparin or fibrinolysin in the postoperative period deserves serious consideration.

Regional perfusion has limited value except in very special cases (e.g., primary or metastatic disease to liver) and may not offer more palliation than is produced by systemic drug administration. However, the aggressive approach of repeated intra-arterial administration of cytoxan and 5-FU by Bierman's group (Mesler, Winer, and Bierman, 1965) deserves closer attention as does the work of Sullivan et al. (1965) on prolonged intra-arterial infusions.

The frequency of cancer cell seeding in abdominal wounds has led to the development of animal screening methods to develop effective agents for wound irrigation that would kill tumor cells. The clinical use of monoxychlorosene (Chlorpactin XCB) and mechlorethamine (HN4) and Thiotepa (TSPA) followed on these observations. Despite the demonstrated optimal activity of Na Hypochlorite and HN4 as tumoricidal agents in an animal tumor implantation screen, long-term follow-up of head and neck cancer patients receiving post-operative wound irrigation with these agents has shown accelerated tumor take in the irradiated area when compared to wound washing with normal saline (Mukhtar et al., 1963). More recent five-year survival data fully supports these observations. These studies indicate that so called "topical chemotherapy" or "cytocidal wound irrigation," should be absolutely contraindicated in the treatment of gastrointestinal cancer until long term follow-up indicates the efficacy of newer agents.

Radiotherapy Adjuvant Chemotherapy

Radiotherapy in combination with chemotherapy for synergistic or additive effect has a valid rationale, based on data of responsive animal tumors, when combined with AB-132 (Regelson and Pierucci, 1964), 5-FU (Heidelberger and Ansfeld, 1963; Baclesse, Dusplan, and Romer, 1964), or mitomycin C (Baclesse et al., 1964). Results from past clinical studies of this type are difficult to analyze owing to the absence of concomitant controls. In addition, such large doses of both drugs and radiation were used that the therapeutic gain possible through a more judicious selection of dosage levels may have been lost. One cannot expect patients with advanced cancer to show increased survival time when treated with combinations of radiation or drugs that would result in severe debilitation from either agent alone. Despite these difficulties there are reports of increased survival for patients with cancer of
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the pancreas or stomach treated with 5-FU in conjunction with radiation (Moertel et al., 1965). The current Veterans Administration long-term continued study which uses combinations of FUDR with radiation may give a more definitive answer, but systemic or local effects on host resistance could nullify the anti-tumor effect.

New Approaches to Chemotherapy

Of particular interest are drug combinations which may act synergistically or additively by interfering with alternative metabolic pathways to eliminate the resistant tumor population. Most of the studies reported so far are preliminary and have not unequivocally demonstrated the virtues of combination chemotherapy in gastrointestinal cancer over the action of single agents. A report of regression in a pancreatic and epidermoid cancer with the combination of 6-thioguanine with duazomycin A is encouraging and is based on sound rationale (Lefkowitz et al., 1965).

Animal data in the area of collateral sensitivity has not been systematically applied to human tumors. The results of one collateral sensitivity study that could be applied immediately demonstrated that a 5-FU resistant tumor in rodents showed increased response to alkylating agents (Rutman, 1964). To my knowledge this observation, which calls for the use of an alkylating agent after failure to respond to 5-FU, has not been tested clinically. Similarly, there are laboratory observations that uracil mustard makes transplanted Sarcoma-180 tumor cells in mice more sensitive to the anti-tumor action of 6-thioguanine (Booth, Creasey, and Sartorelli, 1964). Reports of synergistic inhibition of S-180 by mitomycin C and 6-thioguanine or 5-FU (Sartorelli and Booth, 1964) are also clinically interesting, since the clinical pharmacology of these agents is well known.

A study is warranted on the use of methotrexate in 5-FU resistant patients based on the hypothesis that the resistant tumor may be dependent on a de novo pathway of thymidylate synthesis (Welch, 1963). However, Weiss and Jackson (1961) gave patients with gastrointestinal tract cancer MTX (5 mg orally per day) following 5-FU and found no evident therapeutic gain. More recently evidence has accrued that MTX can increase the level of thymidylate synthetase in human leukemia (Roberts, 1966). Thus pretreatment with MTX may deleteriously effect the response of tumor cells to 5-FU.

Suitable for more immediate study is the verification of suggested evidence in man that glucose enhances 5-FU therapeutic effect (Gotto, Belkhode, and Touster, 1964; Kessel, 1966; Lemon et al., 1963). Inosine (Gotto et al., 1964) or adenosine (Kessel, 1966) also results in increased tumor-cell uptake of 5-FU. These observations may have clinical bearing and should be tested in comparative studies.

The importance of varied dosage regimens is seen in the observations that the prolonged intravenous administration of 5-FU is less toxic than rapid drug administration. However, any therapeutic gains from prolonged infusion may be offset by the convenience of rapid intravenous injection and greater control of dosage. Moertel et al. (1964) have found no improvement in therapeutic results with 5-FU in prolonged intravenous administration as opposed to the single rapid daily loading program. Similar anti-tumor results, but with considerable decrease in toxicity, have now been observed clinically by Ansfield (1964) using 12 mg/kg/day for four days as compared to the earlier program of 15 mg/kg/day for four days, and the lower dose should clearly be the one of choice. Furthermore, the selection of patients for treatment with 5-FU should exclude severely debilitated patients, since such patients show a
decreased drug tolerance. This is supported by data in the nutritionally deprived rat (Wolberg and Curreri, 1960). In using 5-FU, it is well to remember that reports of a high order of regression such as that of Vaitkevicius et al. (1961), objective regression in 20 of 55 patients with adenocarcinoma of the large bowel, are tempered by the observation that regression was clinically worthwhile in a small proportion and even that occurred at the expense of severe toxicity in many patients. However, as discussed earlier, the evidence that responses can be seen in the absence of discomforting clinical toxicity or serious hematopoietic depression indicates that 5-FU might be given to advanced cancer patients for shorter periods and at lower dosage to avoid toxicity. In such a study Young et al. (1960) obtained responses in 10% to 15% of patients with bowel cancer with total dosage ranging from 30 to 150 mg/kg. Similar results have been obtained by Ansfield (1964) and others (Cudmore and Groesbeck, 1964).

The topical administration of 5-FU in a 10% ointment base has resulted in the disappearance of metastatic cutaneous adenocarcinoma of the bowel without damage to normal skin (Klein et al. 1965). This observation, while limited in its application, is pertinent to a consideration of using local 5-FU for palliation of recurrent or residual tumor. Up to 10% of 5-FU is absorbed by the gastrointestinal lining of the tumor segment (Cole, 1963). Patients have tolerated up to 8 mg/kg/day P.O. for up to six weeks with gastrointestinal side effects occurring, on an average, in 18 days and hematologic toxicity in 21 days (Ellison, 1962). Although anti-tumor effects have been seen (Cole, 1963; Ellison, 1962; Kennedy and Theologides, 1961; Khung, 1965), the virtues of local intraluminal instillation of 5-FU into tumor-involved segments of bowel in prophylactic or adjuvant studies have not been adequately explored.

There are other agents becoming available, and reports of new drugs are awaited with interest. For example, antibiotics which behave similarly to actinomycin D, such as chromomycin A₂, olivomycin, and mithramycin, which combine with DNA to impede RNA synthesis (Ward, Reich, and Goldberg, 1965) may show promise (Mayevsky, 1964; Akopliants, 1962). Studies of ethidium and daunomycin which have effects in common on purine metabolism (Ward et al., 1965) may prove useful. 6-Azauridine has been reported to produce objective improvement in one of three gastric and pancreatic carcinoma patients for periods of four to five months (Welch et al., 1960).

There are fairly extensive Japanese literature regarding the clinical efficacy of a variety of porphyrin derivatives (Fukuyama, Tsuji, and Nakagawara, 1963; Matsubara et al., 1963; Tazaki, 1962; Tazaki and Furue, 1961). Hematoporphyrin mercury was reported to inhibit nucleic acid metabolism in stomach and intestine with an increased uptake of the drug in tumor as compared with normal tissue. This compound was said to produce objective and subjective improvement in several patients with gastrointestinal cancer (Fukuyama et al., 1963; Tazaki, 1962; Tazaki and Furue, 1961). Similar effectiveness was reported for a cobalt protoporphyrin preparation (Fukuyama et al., 1963; Matsubara et al., 1963). It is hoped that an evaluation of these reports will not take as long as those studies involving mitomycin C.

In early clinical trials the toxicity which eventually blunts the initial enthusiasm of extended trial is frequently minimized. It was this type of experience with mitomycin C that delayed its entry into clinical practice. Much of the Japanese work with mitomycin C has been associated with its administration as an adjuvant at the time of surgery (Frank and Osterberg, 1960; Osada, 1963; Shiba, 1963). A three-year survival rate of 66% in comparison with a control of 30% was found by Osada et al. (1963) in patients with gastric cancer who had undergone palliative surgical resection. Skepticism is in order, since one can also find reports indicating increased survival time in patients treated after gastrectomy with mechlorethamine, nitromin, sarkomycin, or carzinophilin (Ishiyama, 1965), Pa and TSPA (Osada, 1963). Hoerr (1965) has found an 11% five-year survival rate in palliative surgical resection for gastric cancer even in the absence of chemotherapy. Similar results have been obtained in untreated bile duct tumors (Lippman, McDonald, and Longmire, 1959). Therefore, isolated case reports of long term responses must be analyzed carefully, as they may be related to the selection of a group of long-term survivors that are present in any given gastrointestinal tumor population.

Varied approaches to dosage and timing of drug administration are important in any program of drug evaluation. This was dramatically demonstrated when the "old" drug, methotrexate, was used in a new way which led to the cure of chorocarcinoma (Li, Hertz, and Spencer, 1956). Modified methotrexate regimens increased survival of children with acute leukemia (Selawry and James, 1965; Acute Leukemia Group B, 1965) and are producing responses in bronchogenic carcinoma (Ross and Selawry, 1965) and bowel cancer (Condit, Shnider, and Owens, 1962). The twice-a-week administration of methotrexate (0.25 mg/kg or 0.6 mg/kg) for gastrointestinal cancer is under study by the Eastern Solid Tumor Group, and the results are awaited with interest.

As suggested by this review, much remains to be done in the chemotherapeutic approach to gastrointestinal cancer. The conservative use of 5-FU and alkylating agents have a place provided that severe toxicity is avoided. The sur-
gical adjuvant use of 5-FU has a rational basis and its application to patients with nodal involvement or disease left behind is warranted. It is hoped that studies will continue that can lead to comparative information pertinent to evidence of objective regression of disease and the practical reality of increased survival.

Summary

5-Fluorouracil (5-FU) is the best agent for the treatment of all gastrointestinal cancers but should be used with restraint, since severe toxicity does not guarantee increased response or survival time. Experimental work suggests that glucose enhances cellular uptake of 5-FU. Alkylating agents are definitely useful and occasionally produce long-term responses. Mitomycin C shows activity but is not available. There are reports of responses to methotrexate, vinca alkaloids, and mithramycin, but their place in the management of gastrointestinal cancer is not established. The usefulness of alkylating agents or 5-FU as adjuvants to surgery is not clear, but evidence is accumulating which supports the adjuvant use of 5-FU when disease is left behind. There is laboratory evidence that anticoagulation can prevent tumor recurrence, and this should be studied further. The best combination chemotherapy has not been determined. Regional chemotherapy offers a logical approach, but comparative data with systemic treatment are lacking, although techniques for protracted infusion, particularly of primary and secondary hepatic tumors, may justify its increased use. Wound washing with available contact tumoricidal agents is contraindicated, as it may increase local recurrence.

References


HALL, T. C. The Comparative Effectiveness of Three Antimetabolites in the Treatment of Human Cancer, in press.


JOHNSON, R. Personal communication, 1965.


KARRER, VON K. Zur Kombinierten Cytostatischen und Operativen Behandlung des Carcinoms. 3. Mit-


REGELSON, W., AND O. PIERUCCI. The effect of radiation on splenomegaly

125
induced by the Friend leukemia virus and its modification by ethyl-
N-bis (2, 2-dimethyl-ethylamidinophosphorocarbamate (AB-132),

ROBERTS, D. Dihydrofolate reductase activity and enzyme “induction”
7: 60, 1966.

ROSS, C. A., and O. S. SELAWRY. Comparison of three dose schedules

ROUSSELOT, C. M., D. R. COLE, C. E. GROSSI, A. J. CONTE, E. M. GONZALES,
and B. S. PASTERNACK. A 5 year progress report on the effect-
tiveness of intra luminal chemotherapy. St. Vincent’s Hospital,

RUTMAN, R. J. Experimental chemotherapy studies. V. The collateral
sensitivity to alkylating agents of several antimetabolite-resistant

SARTORELLI, A. C., and B. A. Booth.
The synergistic inhibition of sarcoma 180 by combinations of mito-
mycin C with either 6-thioguanine or 5-fluorouracil. *Proc. Am. Assoc.

SELAWRY, O. S., and D. JAMES. Ther-
apetic index of methotrexate as related to dose schedule and route
of administration in children with acute lymphocytic leukemia.


SHIBA, S. Postoperative administration of mitomycin in the treatment of
carcinoma of the stomach. *Nippon Kagaku Yocho Gakkai Zasshi* 11:

SULLIVAN, R. D., and W. Z. ZUREK. Chemotherapy for liver cancer by
1965.

TAZAKI, Y. Present status of cancer chemotherapy in Japan. *Acta Can-

TAZAKI, Y., and H. FURUE. Clinical experiences with a new anticancer
compound hematoporphyrin mer-
cury complex, disodium salt. *Cancer Chemotherapy Rept.* 13: 41–45,
1961.

U.C.L.A. STATISTICAL UNIT. 17th Re-
port on Colo-Rectal Clinical Trails, Adjuvant Cancer Chemotherapy
Studies. Los Angeles: University of California Los Angeles (90024),
July 1, 1957 through June 25, 1965.

VARTKEVICIUS, V. K., M. J. BRENNAN,
V. L. BECKET, J. E. KELLY, and
R. W. TALLEY. Clinical evaluation
of cancer chemotherapy with 5-
fluorouracil. *Cancer* 14: 313–152,
1961.

WARD, D. C., E. REICH, and I. H.
GOLDBERG. Base specificity in the
interaction of polynucleotides with
antibiotic drugs. *Science* 149: 1259–
1263, 1965.

WELCH, A. D., R. E. HANDSCHU-
MACHER, S. C. FINCH, J. J. JAFFEE,
S. S. CARDOSO, and P. CALABRESI.
A synopsis of recent investigations
of 6-azauridine (NSG-32074). *Cancer
Chemotherapy Rept.* 9: 39–46,
1960.

WELCH, A. D. Summary of informal
discussions on the role of pyrimi-
dine antagonists following paper by
Drs. Heidelberger and Ansfield.

WEISS, A. J., and L. JACKSON. The
effect of 5-fluorouracil upon carci-
nomas of the gastrointestinal tract
and related organs. *Am. J. Gastro-

WOLBERG, W. H., and A. R. CUR-
REI. Toxicity studies of 5-fluorou-
racil used as an adjunct to surgery.
*Cancer Chemotherapy Rept.* 6: 16,
1960.

WOLCOTT, M. W. V. A. Adjunct
Study Program. Personal communica-
tion, 1965.

WOOD, J. S., JR., E. D. HOLYOKE, and
J. H. YARDLEY. Mechanisms of
metastasis production by blood
borne cancer cells. Proc. 4th Cana-
adian Cancer Res. Conf. New
167-223.

YOUNG, C. W., R. R. ELLISON, R. D.
SULLIVAN, S. N. LEVICK, R. KAUF-
MAN, E. MILLER, I. WOLDOW, G.
ESCHER, M. C. LI, D. A. KARNOFF
SKY, and J. H. BURCHENAL. The
clinical evaluation of 5-fluorouracil
and 5-fluoro-2-deoxyuridine in solid
*Cancer Chemotherapy Rept.* 6:
The increase in foreign travel has produced an admirable interest in international health. Drs. Kean and Tucker’s preface states that “This book has been written for the international traveler, with best wishes for his continuing good health.” It contains information useful to the physician not only as a traveler, but also as a practitioner who must answer the queries of his medically sophisticated patients. The section on the universal “Diarrhea of Travelers,” otherwise known as “turista, Aztec two-step, Casablanca crud, the Lower Burmas, the G.I.’s, and to demonstrate its universality, San Franciscitis”, is a summary of a series of investigations by Dr. Kean who is professor of clinical medicine (tropical medicine) at Cornell University Medical College. His recommendation of diphenoxylate hydrochloride (Lomotil) as a control measure was justified recently in this reviewer’s experience. About one-quarter of the book’s contents justifiably pertain to the prevention and treatment of the communicable disease, but other health aspects of travel such as motion sickness and allergies receive attention in one or the other of the volume’s three sections entitled “Preparations for Staying Well Abroad,” “Traveling or Living Abroad,” and “And Now You Are Home...”

The final 34 pages of the book consist of three appendices which, apart from the first two pages which list 17 references, could have been omitted. One reference not noted is the Consumers Union publication, Health Guide for Travelers, a 41-page pocket-sized 50¢ pamphlet which contains an adequate amount of information for the layman. A further reduction in size, and presumably therefore in price, could have been achieved by eliminating items such as “Packing,” “Tipping,” “Soft Pricing,” “Allowances, Duty-free Gifts, Restricted Articles,” “The Advantages of a Travel Agent,” and “Passports and Visas” in Chapter IX which purports to be “A Few General Hints for Your Consideration.” Appendix II, “Visa Fee Schedule,” which states that “Information of this nature is subject to change...persons...should check the passport and visa requirements with the consular official” then spends 18 pages supplying this information. Appendix III deals with “Frostbite,” a somewhat unusual concomitant of modern travel which hardly warrants a discourse of 14 pages. All in all, however, the authors have improved upon previous publications in this genre and have written a valuable text for international travelers and their medical counselors. Note: Since this review was written a companion volume has been published specifically for physicians—Traveler’s Medical Guide for Physicians. B. H. Kean and Harold A. Tucker. Springfield, Illinois: Charles C Thomas, 1966, $12.50.

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Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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