SOCIETY, DRUG RESEARCH AND FUTURE TRENDS*

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Times change and social goals undergo metamorphosis. Things and social objectives of my generation which were considered good and desirable are now being seriously questioned by many of the young generation. All politicians were, for example, advocates of motherhood, apple pie, and the flag in my youth. Now the Zero Population Growth group condemns motherhood, the medical profession frowns on apple pie, and many of the student militants take pleasure in insulting our flag.

In my own area of research we were brainwashed to a point in our youth that we considered it socially desirable to seek to relieve pain and suffering, to cure a sick child, to extend human lives, to restore the mentally ill to society. If these goals are now wrong—I guess it would be nearly impossible to prove them absolutely right or wrong—I am probably too old and set in my ways to think otherwise probably for the rest of my life. If you are still willing to accept my concept of what is socially desirable and look to my type of personal goals, I would like to share with you some of my thoughts.

I would like to talk to you first a bit about benefits of curative drugs. Many of you must recall the dread and fear that constantly beset your parents as they were raising their children—the very real fear, the growing fear which arose whenever a child took sick. It is impossible for you to realize the nature of this animal fear and dread which came gushing forth whenever you saw your child lying feverish in bed. Bottles of camphorated oil, mustard plasters, and cold towels were of little benefit against pneumococcus, tuberculosis, diphtheria, polio, staphalococcus infections, or measles. These diseases are, however, no longer the menaces to the young they were, thanks to the development of antibiotics and vaccines.

In another area the tremendous economic impact of drug research becomes even more evident. Until the mid-fifties the number of mental patients being admitted to our hospitals was growing rapidly in a near exponential fashion. In terms of public hospital beds occupied, these cases, nearly all chronic, had grown to roughly fifty per cent of the patients in hospitals. If this trend had continued, our medical system would have, by this date, been under an impossible added load. Fortunately, the development of the much-abused tranquilizers and mood drugs has drastically reduced these projected high economic costs by helping return many of the chronic cases to society. Even today we are, however, still spending four billion dollars a year in mental health services. There is yet much to be done.

Thus from standpoints of both humanity and economics, drug research has in the past, it would appear, more than justified the efforts which have been dedicated to it. It has led to happier lives for most of us and it has reduced, for the living, the economic costs of remaining healthy and effective. It would appear that this activity which has been so successful in the last third of a century would continue to be a desirable type of activity in the future.

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I would now like to discuss with you some of the broad research trends that I have observed during my active life. When I was in high school during the early thirties, druggists' shelves were crowded, as I recall, with nearly as many items as there are today. Among the drugs available then, however, we today recognize only a few with any significant medical value—for example, aspirin, procaine, ephedrine, insulin, morphine, digitalis, and quinine. These and a handful of others represented all that science and medicine was able to discover from prehistory to that time. Today, less than forty years after, we have hundreds of potent, medically useful drug chemicals, largely of synthetic origin. Most of these were discovered during the late forties, the fifties, and the early sixties.

It is of some sociological interest to note that this avalanche of findings have slowed to a trickle during the late decade. Indeed, there have been more drugs taken off the market during the last few years than have been introduced. This has been due, I believe, to the shift in attention during this period from the therapeutic benefits to the toxic effects of drugs.

All substances, particularly drugs, when used in excess or in an improper manner are toxic. Even common *food* substances can kill you—whether by quickly swallowing a tablespoon full of table salt or slowly by just eating to much over a long period. Drugs are especially dangerous if they are misused because they are *designed* to be biologically active and have potent pharmacological action.

In the quantitative sense I am firmly convinced that even drugs which are procured and used following legally acceptable channels are largely misused. Most drugs taken today do more harm than good. Most drugs prescribed by physicians, I am inclined to believe, also do more harm than good. It has been shown for example, that somewhere between ten to eighteen per cent of hospital admissions today are a result of reactions from prescribed drugs.

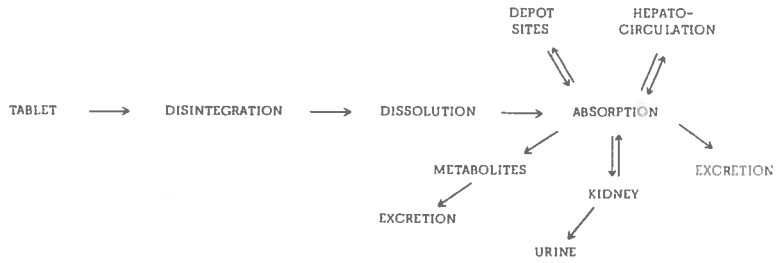
There is a great deal of concern of late about ecology and pollution. In truth, although air pollution and water pollution are of concern, probably the most intensely polluted area is man's own body. Some people who complain about air pollution, blithely pour smoke, tar, and carcinogens into their body; other poison themselves with alcohol, destroying their livers, whole body systems are contaminated with both illegal and legal drugs. Pot smokers, glue sniffers and drugs-of-abuse users apparently find satisfaction in corrupting their own biochemical systems, often leading to suicides. I have suggested that even with legal drugs which are used under a physician's direction there always exists a real danger of significant toxic effects. This problem arises in part from the way that drugs are administered at the present time.

So far I have commented on the benefits of drug research. I have, however, also pointed out the toxicity of all drugs. I have also said that the search for new drug chemicals seems to be yielding less as our concern for toxicity arises. Which way should pharmaceutical research be directed for the future?

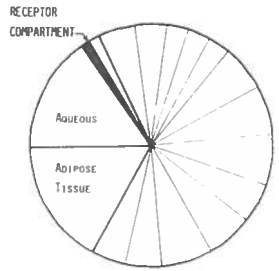
If one looks at the amazing progress made by the chemists in uncovering new drug chemical substances during the past fifty years, the relative inability of pharmacists in developing new dosage forms, new ways of delivering drugs to the patient, becomes very apparent. Pills, compressed tablets, elixirs, intravenous injections, lotions, ointments, plasters, solutions, gelatin capsules, and powders were all in use a hundred years ago. During the past three decades we have seen some depot and prolonged action dosage forms developed of both intermuscular and oral types, but little else new in pharmaceutics.

It is apparent to me that the modes of drug administration must necessarily undergo rapid and radical changes in the ensuring period. For the patient to receive potent chemical agents as tablets, for example, which are swallowed and are permitted to disintegrate and dissolve in largely uncontrolled fashion within the GI track hardly represents the precision drug delivery system which can maximize the therapeutic benefits of the medication and minimize side effects (see Figure 1). It is obvious that there must be certain levels of drug concentration at particular sites within the patient which must be reached and not exceeded to obtain the best results. These target levels would be expected to have certain temporal patterns—in certain instances the pattern may be a single square wave, in others, for example,cyclical waves depending on the circadian demands of the patient.

Biopharmaceutical scientists have, in the past two decades, shown the tremendous variability in blood and tissue levels associated with most of the currently used modes of



drug administration (see Figure 2). Variations in bioavailability, variations in the rates of absorption, variations in the rates of metabolism, variations in the rates of excretion, and variations in the rates of transports all affect the elicited concentrations and the concentration-time profiles at the target sites (see Figure 3). It is thus obvious that there are tremendous margins for improvement possible in drug administration such as to decrease toxicity and improve therapeutic responses. We should understand the requirements and develop approaches which will meet them.



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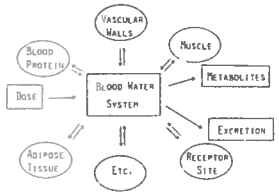

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Some of you who have been concerned more closely with pharmaceutical manufacture and also with the economics of drug distribution may say that sophisticated approaches as may be needed to obtain such improvements will be too expensive and uneconomical. The public and the medical profession, it has been said, will not pay for such levels of sophistication. I say that they will and they must. The overwhelming majority of medical treatment is based on use of drugs—hospital costs these days are approaching a hundred dollars per patient day. If the therapeutic benefits can be materially improved, and incidences of side effects significantly reduced, the dosage from costs at the present of a few pennies a day can, with ready justification, be raised to a few dollars a day.

I charge the pharmaceutical profession and the pharmaceutical scientists with the responsibility of coming up with the necessary solutions. The ultimate drug delivery system will provide delivery of medicaments at identified sites of action according to the exact need of the patient. In some cases the delivery rate may be preprogrammed—in others it may be necessary to obtain the optimal level by means of a sensor which can observe the chemical and/or the physiological state of the patient and control the delivery rate.

In this day and age when we can inscribe a complete circuit on a pinhead or put a man on the moon, I cannot see that we lack the necessary technology to do a much better job than we are doing today. We must accept the challenge.

Dr. Takeru Higuchi, Regents Professor of Chemistry and Pharmacy, University of Kansas School of Pharmacy, is shown receiving the 1971 Rho Chi Award from Vice-President Raymond E. Hopponen at the San Francisco meeting of the Society.