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WORKSHOP ON ANTIEPILEPTIC DRUG DEVELOPMENT

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Contents

vii

Appendix VI.

INNOVATION IN ANTIEPILEPTIC DRUG THERAPY

A Study Prepared for the
Commission for the Control of Epilepsy and Its Consequences

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Contents

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29

SUMMARY

There are currently two major constraints on the clinical investigation of new drugs: (a) the IND/NDA procedure set up under the Food, Drug, and Cosmetic Act and its regulations, and (b) constraints on human experimentation, monitored by institutional review committees.

The law and its regulations, having been passed in response to tragedies arising from drug toxicity, are heavily skewed towards the avoidance of risk and have no mandate to enhance the benefits obtainable with drugs. This has resulted in predictably conservative regulatory postures aimed at minimizing risk rather than in maximizing benefit to the patient.

Institutional review committees, although socially desirable, add several layers of bureaucracy to the existing constraints on human research, and restrict research further.

Both these effects are reaching back to impinge on earlier and more sensitive areas of the drug development process, and can be expected to constrain innovation more tightly in the future.

Considering all therapeutic areas, there has been an extensive shift abroad of early drug research by the U.S. pharmaceutical industry since 1970. *International Comparison of Marketed Antiepileptic Drugs.*—An examination of all new antiepileptic drugs introduced into either the U.S. or Britain from 1960 through 1976 (a total of 11 drugs) showed that all drugs except one were introduced later in the U.S. than in Britain, sometimes by many years. Furthermore, although all the drugs marketed in the U.S. are marketed in Britain (and—with one exception—much earlier in Britain) almost half the drugs that were marketed for epilepsy in Britain have not yet been marketed in the U.S. *Antiepileptic drugs under clinical investigation in the U.S.*—An examination was made of New Chemical Entity (NCE) drug candidates for epilepsy studied from 1963 through 1975 in the U.S. (restricted to compounds owned by the companies themselves, i.e., excluding those licensed from other companies). Out of a total of 1,029 NCE IND's studied clinically in all therapeutic areas by 46 U.S. and foreign companies, representing virtually the entire research-based pharmaceutical industry operating in the U.S., only eight new drug candidates, from five companies, were studied for epilepsy over the entire period. Seven of these were filed in the U.S. as IND's, but none reached the stage of NDA submission and all had been closed (and no more were active) by the time of this survey (September 1975). Thus, the recent level of research activity in the U.S. into new antiepileptic drugs is (apart from licensed compounds which were not included in this study) nearly zero.

The *current problems* in the development of better antiepileptic therapies include:

(1) The high cost of developing any new drug in relation to the expected small size of the market for new antiepileptics.

(2) Societal (and hence regulatory) demands for drugs that are completely safe, regardless of any efficacy they may possess (even if very large) for small but needy sections of the patient population.

(3) Future prospects of continuing stringency in these and related developments.

Some possible solutions to these problems:

(1) Public recognition is required of the plight of patients with severe disease for whom no adequate therapy currently exists (or will ever appear) on the basis of today's trends.

(2) Patients should have easier access to antiepileptic drugs that are already marketed in advanced countries abroad and about which considerable information is already available.

(3) There should be public awareness of the need to trade off toxicity for efficacy if drugs are needed for increasingly refractory disease in smaller segments of the population.

(4) There should be governmental subsidy or sponsorship of commercially nonattractive drugs for epilepsy, with examination of some of the existing models of government sponsorship that already exist, to determine the most fruitful arrangements for cooperative projects between government and pharmaceutical industry.

The most essential of all these solutions is public education and recognition of the fact that the diseased patient is a consumer with rights to new therapy and with rights to make risk/benefit decisions in conjunction with his physician.

30

INTRODUCTION

Progress in therapeutics requires the discovery of new knowledge and the application of that knowledge to clinical practice. Implicit in this process is the need for performing clinical research.

Clinical research in general, and drug research in particular, come under the control of a variety of laws and regulations, which in some areas determine how the research can proceed. For this reason, it is necessary to review the regulation of therapeutic research; this is done in Section I of this paper.

Section II examines first some general facts about clinical drug research in the U.S. since 1962, then compares the marketing of new antiepileptic drugs in the U.S. and Britain since 1960. Finally, it proceeds to examine a crucial earlier stage, namely the rate at which new antiepileptic drug candidates are being investigated clinically in the U.S., by both U.S. and foreign pharmaceutical firms.

Section III identifies some of the main current problems in the development of new antiepileptic drugs, and suggests ways of overcoming these problems.

31

SECTION I

THERAPEUTIC DRUG RESEARCH AND ITS REGULATION

(A) *Current Laws and Regulations.*—The most important regulation of pharmaceutical innovation and development stems from the Food, Drug and Cosmetic Act of 1938, the Kefauver/Harris Amendments of 1962, and the relevant regulations enforced under these Acts by the Food and Drug Administration (FDA).

The 1938 Act was a "safety" law, enacted in response to the Elixir Sulfanilamide tragedy. This law required tests of safety before a new drug could be marketed. This was the origin of the New Drug Application (NDA), which has to be approved by FDA before the marketing of the drug can begin.

With the Kefauver/Harris Amendments of 1962 (passed in the wake of the thalidomide tragedy that occurred in Europe) two substantial additions were made to the law:

(1) the addition of a "proof of efficacy" requirement before the NDA could be approved;

(2) regulation of the clinical investigation (pre-NDA) phase of drug development, including specification of the preclinical (animal) toxicology testing requirements. This regulation of the clinical and preclinical phases was achieved by creating, in 1963, the Investigational New Drug (IND) procedure, which is essentially a permit to begin clinical testing of a new drug. Under the IND, the FDA regulates both the clinical investigation phase itself, and the animal tests required before human (clinical) testing can begin.

Although the efficacy requirement is sometimes regarded (and indeed in law arose) separately from the safety requirement, questions of efficacy are, in practice, inseparable from those of safety. This is because therapeutic decisions inevitably involve a risk/benefit trade-off, explicit or implicit in the mind of the regulator, the prescriber and ultimately the patient. The efficacy of a drug has always to be judged against its safety or hazards, and vice versa, in any decision-making situation—either regulatory or clinical.

While the existing law has led to putting risk/benefit decision-making in the hands of regulators, these regulatory decisions do not necessarily result in the same conclusions as those that would be made by patients and their physicians in specific therapeutic situations. Such differences between regulatory and therapeutic decision-making (which can be very important) arise because the law is skewed toward risk avoidance and involves the population as a whole, while therapeutic decisions are concerned with optimizing treatment for individual patients.

In fact, the FDA is not obliged, or even empowered by Congress, to promote the improvement of health in drug-related matters; it is primarily required to prevent harm from drugs. This is probably the single greatest defect in the present law and regulations. (The same imbalance is seen in the omission of a "benefit" mandate even from the new Medical Device Amendments, which were enacted as recently as May, 1976). It is understandable that risk-avoidance has been the theme of much drug legislation, because both the 1938 and the 1962 Drug Acts were passed in wake of tragedies. Nevertheless, risk-avoidance is one of the main causes of the problems that have arisen in the development of new therapies, because the two goals are incompatible. Given this fact, it is not surprising to find that concerns are now arising about the inhibition of innovation by regulation.

Indeed, the question is not "whether" regulation inhibits innovation, but simply "by how much". As Dr. J. Richard Crout, Director of FDA's Bureau of Drugs, succinctly stated the problem in December 1975 [1]:

> *". . . The issue isn't whether . . . regulation cuts down on innovation. Indeed it does. It must. There's hardly any way that regulation can stimulate innovation. Those are cross purposes. The issue is whether the regulation accomplishes some higher purpose and does so with minimum inhibition of research. That's hard. I won't say it's easy. That is hard. But that's what the argument is about, to some extent why research has moved overseas, and that's a problem. . . ."*

In addition to the Food, Drug & Cosmetic Act, its subsequent amendments and numerous implementing regulations, which deal specifically with the process of drug and device development, there are other controls that, while not aimed directly at drugs and devices, nevertheless impinge heavily on the process of therapeutic innovation. The most important of these other controls is control of human experimentation.

Over the past decade, and particularly in the past five years, several developments have occurred which have made all types of human investigation in the U.S. more difficult. At the institutional level, formal Institutional Review Committees (IRC's) are required at any institution that receives federal funds, and these committees in practice monitor all human experimentation at the institution*, whether fed-

*At the author's institution, for example, the procedure required to obtain informed consent for a patient to participate in any study has changed, in the space of five years, from informally-obtained verbal consent with a notation in the patient's chart, to written informed consent from the patient in the presence of one or two signed auditor-witnesses. The Investigational Review Committee, which must include a lawyer, a clergyman, and lay members, takes several months to examine the study protocol and to approve the consent forms. In a recent example of the author's, a trivial investigational procedure required four months to be cleared, the main requirement of the committee being that the consent form be changed to University letterhead stationery. Final permission for the study was received 12 days before the grant, under which the study would have been carried out, expired. The effect on cancer research has been even more pronounced. Our

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32

erally funded or not. These new requirements certainly improve the appearance of safety and curb the grossest examples of abuse that were possible under the old system. However, in the author's opinion, the increase in review requirements does not add greatly to the protection of the subject against hazard from most drug studies performed by reputable physicians and firms. Drug studies, particularly at the early research stages, are among the safest types of human investigation procedures,[2] and the subject's ultimate protection still remains, as with any study, the integrity and concern of both the subject's personal physician and the investigator. Nevertheless, the additional bureaucratic layer imposed by Institutional Review Committees adds materially to the regulatory barriers that must be surmounted in order to perform research at all, and is inevitably driving up the costs of research and lessening the chance that a given project will be performed at all.

Another example of constraints on human research is the current trend against the use of prisoners as research subjects. Recently, the use of prisoners in federal institutions was banned, and state and local institutions are following suit. This will remove a segment of the facilities that were once available to U.S. clinical research, thus further raising both costs and barriers.

The above two sources of controls, namely specific regulation of drug research, and rising constraints on human experimentation, are the most important controls presently affecting drug development and innovation. (There are numerous other, less direct sources of regulation such as the Occupational Safety and Health Act (OSHA), which are beyond the scope of the paper and will not be considered here.)

As summarized by FDA's Dr. Crout:[3]

"The major constraint on pharmaceutical innovation in the U.S. today is probably the IND regulations coupled with the institutional review committee requirement."

As the President's Biomedical Research Panel reported in April 1976:

"There is a clear impasse arising between society's desire for new and better drugs and the barriers society is erecting to their development and introduction. These barriers, based on a valid desire to improve the standards of safety and efficacy and to insure ethical control in clinical evaluation, increase developmental costs. There is a real danger of bringing the development process and access to clinical resources to a halt.

Many feel that the American public is being denied new drugs currently available because of excessive FDA requirements."

(B) *The Technical Mechanisms by which Drug Innovation and Development are Regulated—Historical Progression and Avenues of Regulation.*—As shown above, regulation of the development process began at the later phases of the drug development process (the NDA, 1938) and has subsequently progressed back to impinge on the earliest aspects of the development process and on the later post-marketing phase. Since 1962 it has focused on the clinical investigation phase (via the IND) and, through the IND's requirements concerning preclinical toxicology evidence, it has also controlled the preclinical (animal toxicology) phase of drug development. Recently, attention has been focused on the control of drug prescribing for non-approved uses and on Phase IV investigation—both aspects of postmarketing regulation.

The nature and extent of regulation has continued to expand since 1962, and the following changes or new regulations are currently either being discussed or actually implemented.

1. The further supervision of the clinical phase by means of FDA's proposed "developing NDA" concept. In this, there will be hold-and-review steps at the end of Phases I and II of the IND process (in addition to the built-in hold at the NDA submission stage at the end of Phase III as at present). This is designed to speed the overall process for drugs identified as "important" by FDA*; the exact impact this will have is debatable: it is conceivable that the overall (IND + NDA) time could be either shortened or lengthened; however, it does raise for the first time extensive direct FDA participation in the design of clinical trial protocols *throughout* the clinical development process. This is a new concept, and a new addition to the regulatory control process. It is a particularly powerful addition because in addition to the implications just discussed, it introduces close regulation, reinforced by "hold" steps, at the earlier phases of the clinical study process, which are much more vulnerable to external influences on innovation than are the later phases.

2. As a result of recent irregularities (either sloppiness, withholding or falsification of data) in industrial preclinical toxicology studies aired in 1976 at Senate Health Subcommittee hearings, the FDA is now moving to regulate the details of *animal* studies performed by the pharmaceutical industry, particularly animal toxicology studies. At present the mechanism of control envisaged is the implementation of "good laboratory practice" (GLP) regulations, similar to the good manufacturing practice (GMP) regulations that have been required for some time for the manufacturers of pharmaceuticals. The impact of these newly promulgated regulations on the innovative process cannot yet be fully predicted, although one manufacturer's estimate is that it will increase costs at this very early stage by 25 percent. The full impact of this new control will not be measurable until many years after its implementation.

3. Increased policing of *clinical* investigators has now been instituted by FDA as a result of a GAO report that showed lack of adherence by investigators to clinical investigation protocols.

4. In connection with both (2) and (3) above, FDA's budget was increased, in 1976 alone, by $16.4 million to allow for a team of 600 field inspectors to ensure that animal testing and clinical investigations conform more closely to the regulations. Some of the proposed regula-

oncology research division (a member of the Eastern Cooperative Oncology Group) found that approval of the already-established national cooperative protocols by the local IRC was taking so long that the national studies were nearly completed (and the protocol expired) before the local group received approval to begin the study.

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33

tions for controlling clinical investigators include more than 10 grounds on which a clinical investigator can be disqualified by a field inspector.

5. The Health Research Group, a consumer organization, has petitioned the FDA commissioner to prohibit any human testing of a new IND until all long-term animal toxicology has been completed. This would obviously require very extensive restructuring of the early discovery and development process in the U.S., from the parallel mode that exists at present (short-term human and long-term animal studies proceeding simultaneously) to a series mode, in which no human studies would begin until the completion of all animal toxicology, including two-year lifetime tests in rodents. Some industry research directors have predicted that such a restructuring would make drug discovery as it is currently known in the U.S. almost impossible to perform, and would almost complete the existing strong trends towards shift abroad of early drug development by the U.S. pharmaceutical industry.

6. At a seminar on "The Future of Drug Regulation in the Next 20 Years," held in May 1976, the following discussion was reported between FDA lawyer, William Vodra, and Allan Fox, counsel to the Senate Health Subcommittee:[4]

> *"Fox and Vodra disagreed re the* better-than *concept for drug approvals. Fox predicted that in the future, drugs which offer no improvement over already-marketed products in the same therapeutic class would not be approved. Vodra said that while drugs which have a 'significantly lower benefit-to-risk ratio' than existing drugs would not be approved, he did not foresee that 'new drugs would have to be better-than' current ones.*
>
> [. . . . .]
>
> *Fox projected that the identification of a substantial patient population could become a future requirement prior to approval of a drug. He said:* 'Usage *could join safety and efficacy as a consideration for approval.' He also indicated that direct govt. control of drug research is a possibility. 'Testing of drugs could be at the federal level.' Vodra disagreed, maintaining that while FDA will 'have control of all drug research (in terms of regulation), it will not supervise research.'"*

7. In March, 1977 at a symposium on expediting the IND-NDA process, Dr. Marion Finkel of FDA made the following points:

(a) FDA has begun to refuse NDA approval for new drugs that are "losers"—i.e., drugs that are no more effective, and less safe, than existing drugs; and (b) FDA will not approve NDA's for certain new drugs if only some of their important predicted uses have been evaluated.[5] It appears, therefore, that FDA is already implementing both the relative efficacy concept and the usage concept discussed in (6) above. The implications of this for new antiepileptic drugs are as follows. First, drugs that in the past might subsequently have been found to benefit small portions of the population with severe disease will, in future, be dropped at an early stage of development if they are found in the general epileptic population to be no more effective and less safe than existing drugs. Thus, an important serendipitous pathway of discovery is being closed at a point long before the activity of the drug in subpopulations can be tested. Second, a drug that has been proved to be effective in one type of epilepsy could have its NDA refused if FDA believed that it should first be evaluated for other types of epilepsy (or all types of epilepsy) as well. This policy of "guilt by prediction", if implemented for antiepileptic drugs, will have a chilling effect on antiepileptic drug research programs. One phamaceutical company executive has already said that if FDA required tests of a new drug in all types of epilepsy before NDA approval was granted, his company would abandon its antiepileptic research program.

In summary then, the regulation of pharmaceutical innovation which began in 1938 with simple controls over the access of a drug to the market, has moved (particularly rapidly in recent years) in two directions: towards the earliest and most easily affected phases of the discovery process; and towards control over drug utilization. The potential impact of these controls on the discovery of new antiepileptic drugs is obvious, and, as will be apparent from Section II of this study, it is difficult to escape the conclusion that a negative impact has already occurred.

(c) *The Science-Regulation Interface.*—So far, we have described in general terms where regulation impacts on the process of innovation. We will now consider the crucial mechanisms by which scientific matters are dealt with in the regulatory context. This is the most difficult problem conceptually. It concerns questions such as "how much is enough?" (i.e., How much evidence will satisfy the law's particular demand for safety or efficacy?) This area is discussed at length in Chapters III and IV of Reference 6.

(d) *The Technical Mechanisms by which Innovation is Regulated in Practice.*—The procedure for technical implementation of the regulations can be summarized as follows:

(i) The IND requirement determines how much animal work (especially toxicological study) is required before any drug can be given to man, and whether the initial study protocols are satisfactory.

(ii) Good Laboratory Practice regulations will determine in considerable detail how the long-term animal studies must be performed.

(iii) The Institutional Review Committee will determine whether the human study protocols are satisfactory and whether the consent forms are adequate. Since the IND review has already theoretically determined whether the first study protocol is adequate, review responsibilities are being duplicated.

(iv) The IND procedure will regulate how the human studies are to be performed in order to obtain data on efficacy and toxicity that will satisfy the law's requirements. This will become a particularly powerful point of regulation, both in the control over clinical investigation and as the "developing NDA" concept is formally incorporated into the IND; when the latter occurs, there will be strong regulation of the complete development process from the point of animal toxicology to the point of marketing.

(v) FDA's 600 new field inspectors, possessing extensive disciplinary powers, will inspect both laboratories and clinical investigators to ensure stricter compliance with the regulatory requirements for both animal and human investigations.

(vi) After NDA submission, decisions will be made during FDA's review on whether the evidence satisfies the law's requirements for safety and efficacy, as interpreted by FDA.

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34

New studies may be asked for. (The current mean NDA review time, which includes the time required for any new studies, is 21 months, compared with the 6 months specified in the law.) Under the developing NDA concept, however, it is presumed that any loose ends will have been identified during the IND phase and will not have been left to be discovered at the NDA phase, so that the NDA phase could decrease in duration.

(vii) After approval for the market, Phase IV studies (monitored release or postmarketing surveillance) may be required as a condition of NDA approval. The manufacturer must then design and carry out these studies.

(viii) Advertising and promotion of the drug are regulated to conform closely to the indications and wording of the package insert.

(ix) If certain postmarketing requirements of at least two bills that were considered by Congress in 1976 come to be implemented (S2697, Federal Drug and Devices Act [Kennedy/Javits], and HR11617, Drug Safety Amendments of 1976 [Rogers/Maguire]), limitations could be imposed on the distribution of the drug and the conditions for which it can be prescribed. (At present, there is a medico-legal threat to a physician who prescribes a drug for conditions outside the package insert: stiffer sanctions will be incorporated into the law if the provisions described in the above bills are enacted.) FDA also is asking for stronger powers to regulate drug utilization.

One of the effects of tight controls that restrict the use of drugs to "approved" indications is that the serendipitous discovery of new uses for existing drugs (which is an important way in which therapeutic advances have been made in the past in many fields, including epilepsy) will be seriously inhibited.

35

SECTION II

A. SHIFT OF EARLY U.S. CLINICAL DRUG RESEARCH ABROAD

In the course of a survey of all new drug candidates investigated since the 1962 Drug Amendments by the U.S.-owned pharmaceutical industry (36 research-based companies with a total of 854 drugs), we found a shift of *early* drug studies (defined as the country of location of the first human study of the drug) from the U.S. to overseas countries.

Taking all companies, from 1963 through 1969 the percentage of NCE's studied abroad was 10% or less, but from 1969 through 1974 (the last year for which complete data are available) this rose to over 30%. The shift was more marked among the larger companies. For example, among the eight largest companies (which accounted for just over half of all NCE's taken into man), the fraction of drugs that were studied first abroad was 50% in 1973 and 43% in 1974.

B. COMPARISON OF THE INTRODUCTION OF NEW ANTIEPILEPTIC DRUGS INTO THE U.S. AND BRITAIN, 1960-1976

From 1960 through 1976 a total of 11 anticonvulsant drugs were approved for marketing in the U.S. or Britain. The drugs, and their introduction dates, are listed in Table 1, and the differences that existed between the countries at any given time during this period are illustrated in Figure 1.

Five of the drugs were marketed exclusively in Britain, and six were marketed in both countries. None were marketed exclusively in the U.S. Of the six drugs introduced in both countries, one (methsuximide) was available first in the U.S., but this drug is quite similar to ethosuximide, which was already available in both countries. The other five mutually-available drugs all became available (or approved for epilepsy) earlier in Britain than in the U.S., in some cases by many years.

Exclusively Available Drugs—There are five antiepileptic drugs currently exclusively available in Britain: pheneturide, sulthiame, chlormethiazole, nitrazepam and valproate.

Thus, from 1960 to date, all except one of the 11 drugs introduced for epilepsy in the U.S. or Britain have been introduced first in Britain (by margins up to 11 years, based on date of approval for antiepileptic usage); and half of the drugs are not yet available in the U.S. Those drugs unavailable include important, major antiepileptic drugs such as sodium valproate. They also include drugs that, while not of great importance to large numbers of epileptics, are known to be uniquely effective in some patients: nitrazepam and sulthiame.

Table 1.—Antiepileptic drugs approved for marketing (1960-1976)

Ingredient	Year	
	Britain	U.S.
Ethosuximide	1960	1960
Aminoglutethimide	(?)	1960*
Pheneturide	1961	—
Sulthiame	1961	—
Chlormethiazole	1963	—
Methsuximide	1963	1957
Diazepam	1963	1963 (1968)
Carbamazepine	1963	1968 (1974)
Nitrazepam	1965	—
Sodium Valproate	1974	—
Clonazepam	1974	1975

Note: These data are the best available to us as of March 1977. Date shown in each main column is the year of marketing in that country. The year of approval for epilepsy, where this is known to be different from the date of marketing, is shown in parentheses. Since approval dates for subsequent indications are not yet fully known for Britain, it is possible that the size of the British leads is in some cases overestimated.

* Epilepsy indication withdrawn for toxicity reasons.

36

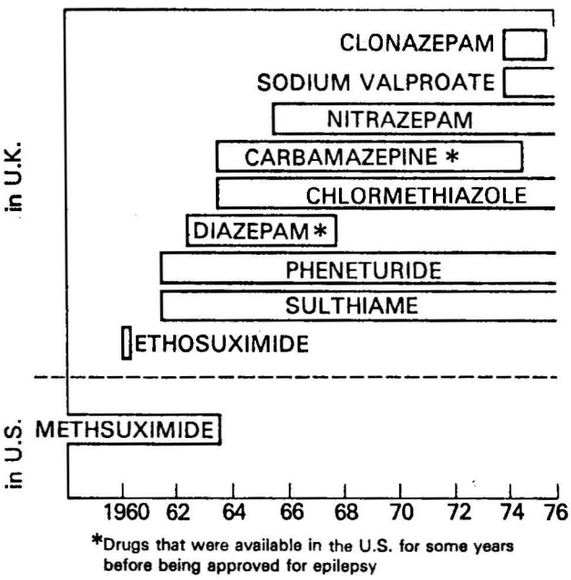

Figure 1. Graphical display of exclusive availability or approval of antiepileptic drugs in the U.S. and U.K., using data from Table 1. The year is represented on the abscissa, and a dashed horizontal line bisects the field. Those drugs that were exclusively available in the U.K. are plotted above this line, while those in the U.S. (of which there was one) are plotted below it. The horizontal bar representing each drug extends from the time it became exclusively available (or was approved for use in epilepsy) until its exclusive availability ceased—which was usually because the drug was marketed (or approved for epilepsy) in the other country. A vertical line drawn at any point in time allows one to see at a glance the differences between the range of drugs available in each country at that time. As the graph shows, there was a large preponderance of drugs exclusively available in the U.K.

C. CLINICAL INVESTIGATIONAL ACTIVITY ON ANTIEPILEPTIC DRUGS IN THE U.S.

The following data are derived from a survey of all 1,029 original investigational drugs (New Chemical Entities) taken into man worldwide by the U.S.-owned pharmaceutical industry, plus all drugs investigated clinically in the U.S. by foreign-owned pharmaceutical companies, from January 1, 1963 (the year in which the IND requirement was instituted) through September 1975. (Note that this does *not* include drugs licensed from other companies, nor drugs that were first tested in man prior to 1963.)

U.S.-Owned Pharmaceutical Industry—Responses were obtained from 36 companies representing virtually all original compounds.

A total of four drugs were tested clinically for epilepsy by three companies, clinical trials being initiated between 1964 and 1970. Three were first tested in the U.S., while the fourth was tested abroad and an IND was not filed. Of the three with IND filings, none reached the stage of NDA submission, and all the IND's were closed an average of five years after the studies began.

Foreign-Owned Companies—Responses were obtained from 10 out of the 11 foreign-owned companies performing research, representing nearly all original compounds.

IND's were filed on four compounds by two companies in 1964. None of these reached the stage of NDA submission, and all IND's were closed by 1968.

Thus, the entire result of all original NCE research on epilepsy by both domestic and foreign-owned companies was therefore that, by September 1975, no new original IND's had been submitted in the U.S. since 1965; no original NCE produced by the U.S. or foreign pharmaceutical industry had reached NDA submission; and none were still active. The only clinical investigation taking place at that time in the U.S. on new antiepileptics would have been compounds licensed from other companies, or compounds first taken into man prior to 1963, both of which were excluded from this survey.

We do know of one IND for an antiepileptic drug candidate that has been submitted since September 1975 by a foreign-owned company after the date of the present survey. However, this is an extremely small number of original compounds for a 12-year period; the level of clinical research activity on newly-originated antiepileptics, at least from this survey, appears to be almost zero.

37

SECTION III

CURRENT PROBLEMS AND POSSIBLE SOLUTIONS IN THE DEVELOPMENT OF BETTER ANTIEPILEPTIC THERAPIES

This discussion considers problems other than strictly scientific or medical ones.

1. *Size of the Market.*—Antiepileptic therapy has reached the stage where drugs now exist for at least moderate control of a large proportion of epileptic patients, particularly if the drugs are used in combinations and if doses are increased to the point where side-effects appear. While existing drugs are not fully satisfactory, only a relatively small fraction of the total epileptic population is completely uncontrolled or has side-effects that are intolerable. The result of this is that a new antiepileptic drug, even one that offered unique advantages (either improved efficacy or reduced side-effects) to some fraction of the epileptic population would have a relatively small market.

2. *Cost of Developing New Drugs in Relation to the Expected Market Size.*—For the variety of reasons discussed earlier, including both increased scientific standards and the regulation of human experimentation in general and drug research in particular, the cost of developing new medications and bringing them to the U.S. market is now relatively high. Estimates of the cost of developing successful drugs show an approximate ten-fold increase in the last 15 years, and current estimates of the cost of introducing a single new chemical entity to the U.S. market range from 10 to 24 million dollars.* At the same time, the effective patent life (i.e., the time from approval of an NDA until the expiration of the composition patent) is shorter than its nominal 17 years by at least the mean time for initiating and completing development (the preclinical period plus the sum of the IND and NDA phases, which rose to over five years in 1974). In 1975 the mean effective patent life of those new chemical entities introduced to the U.S. market was ten years.

The cost of developing new drugs, combined with the shortening of patent protection will likely lead companies to regard the epilepsy market as financially unattractive. Exceptions will be those drugs that have proved to be commercial successes abroad and which may be licensed and developed for the U.S. market at a lower cost and with much lower risk than required to develop one from scratch. However, the marginal market for new antiepileptic drugs is probably small, and these drugs therefore have limited commercial attractiveness to a company that is deciding how to allocate its total research budget. This is a problem that applies to all diseases where the number of patients involved is relatively small. (On the other hand, the chronicity of therapy for epilepsy tends to offset, to some extent, the small size of the market.)

* After this workshop a study was completed that estimated the total cost of developing a new chemical entity to the point of marketing in the U.S. to be 54 million dollars. (Hansen, R.: The pharmaceutical development process: Estimates of current development costs and time and the regulatory changes. Center for Research in Government Policy and Business, University of Rochester, Working Paper #GPB 77-10, 1977.)

3. *Societal (and Hence Regulatory) Demands for Drugs That Are Completely Safe.*—Increasingly, safety is being used to denote, in the mind of legislators and the public, absence of risk. Therefore, both pharmaceutical companies and the regulatory agencies are becoming increasingly unwilling to be involved with a product that has any unusual toxicity, regardless of the amount or type of efficacy that the drug may have.

In the case of a drug which may be beneficial to only a small segment of the population (e.g., those epileptics marginally controlled on current therapy) then, *a fortiori*, that drug will have less chance of being studied and, if studied, of gaining approval.

This problem is well illustrated by an example from another field, namely azaribine (Triazure), a drug approved, and soon afterwards withdrawn, for the treatment of extremely severe psoriasis and psoriatic arthropathy. FDA approved Triazure in 1975, after many years of discussion among advisory committees about the known toxicity of the drug (approximately 4% incidence of thrombosis). In one year after marketing, the drug was used in 500 to 1000 patients (a very small market) at the end of which time it became apparent that although the incidence of thrombosis was as predicted, the character was more severe, being predominantly arterial rather than (as previously believed) venous. The drug was therefore withdrawn. Despite this, many patients who were fully aware of the risks of arterial thrombosis wished to continue taking the drug because they are unable to function without it. A Congressional hearing was held (The Subcommittee on Intergovernmental Relations) in which the FDA was criticized for approving the drug with a Phase IV (post-marketing) surveillance requirement on the grounds that, if the safety of the drug was sufficiently in doubt as to require Phase IV surveillance, then the FDA Commissioner might have broken the law in approving the drug as "safe" for the market. In the expert testimony that accompanied the hearing, it was apparent that some of the dissenting members of FDA advisory committees, i.e., those who had recommended against approval of the drug, considered that the number of patients who would benefit from the drug was "too small" to justify approval of the drug for the market, *regardless of its efficacy*. No psoriatic patient was invited to testify at these hearings. It is apparent that with the current trends and pressures on FDA, the minority of patients with extremely severe disease of any type can expect little comfort from the actions of legislators and regulators in an environment that is heavily biased toward "protection" and the approximation of absolute safety.

("Protection," in this context does not include protection from the consequences of severe disease; severely diseased patients, and patients for whom no satisfactory therapy currently exists, have essentially no voice in the current debates about therapy currently going on in the nation.)

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38

SOME POSSIBLE SOLUTIONS TO THESE PROBLEMS

In the current debates over drug development, which are largely political rather than scientific, the real consumer (the sick patient) is not being adequately represented by self-styled professional "consumerists" nor effectively by anyone else. Indeed, the activities of the consumerists now hinder the development of new therapies.

1. *The most important single step is to bring to the attention of the public the plight of patients with disease for whom no adequate therapy currently exists and who, on the basis of today's trends in society's thinking and regulation, will never get adequate therapy for their disease.* Since most of the people who were formerly regarded as advocates for such patients (researchers, physicians, etc.) are increasingly disregarded and even discredited by legislators, regulators and consumerist groups, an effective approach would be for the patients themselves, through their private disease-oriented foundations, to highlight this fundamental problem.

It will be necessary for the disease-oriented foundations to establish themselves as the consumers who deserve a hearing. This will be difficult in view of the momentum presently possessed by the handful of vocal and influential consumerist lobbyists who now totally overshadow the patients; but since the case is so obviously in the patients' favor, the disease-oriented foundations should prevail in a direct confrontation.

An example of the type of conflict that may be expected can be seen in the present debate between FDA and the NIH's National Cancer Institute (NCI) over the regulation of IND's for new cancer drugs. FDA wishes to regulate more tightly the research being done by NCI, while NCI counters with the argument that it is acting in the cancer patient's best interest. FDA is supported by Mr. Nader's Health Research Group, which believes that NCI and cancer researchers have too much latitude. On the other hand, NCI is strongly supported by the American Cancer Society, which wishes to remove the supervision of cancer drug research from FDA and transfer it to NCI. This is a classic example of the difference in goals between professional anti-industry, anti-drug lobbyists and a patient-oriented group. Epilepsy associations should follow this debate very closely.

2. *Patients should have easier access to antiepileptic drugs that are already marketed in advanced countries abroad and about which there is considerable information already.* As shown in the previous section, the history of the marketing of antiepileptic drugs in the U.S. over the past 15 years is that these drugs are generally available abroad for years before they are finally approved in the U.S. Patients should at least be able to try out, for their own particular disease conditions and under medical supervision, drugs not yet available here.

There is an important distinction to be made between the amount of information required for general marketing of a compound, and the amount needed to evaluate a drug in an individual patient. A patient refractory to all marketed therapies, for example, should be able to evaluate personally all the drugs available for his condition in case one of them is found to be particularly effective. This can be done with minimal exposure of the patient to each drug, provided the patient's physician is familiar with the general problems inherent in new drugs whose overall efficacy and toxicity have not been established.

Epilepsy is a particularly suitable disease for this approach. The main point at issue is whether the drug is effective, with acceptable toxicity *for that particular patient;* the best judge of this is the fully-informed patient himself, aided by his physician.

The current system of drug investigation and approval in the U.S. makes it very difficult for a patient to obtain a new drug other than on an IND (unless he is affluent enough to purchase drugs abroad). Moreover, the main function of the IND investigation is to gain evidence for the company's NDA, and *not* to help an individual patient. Therefore the system is working *against* the patient unless he happens to fit the predetermined criteria for admission to an IND study. (In any case, in a controlled study [such as most IND studies are], he will be assigned—usually randomly and blindly—to the treatment, which will include a placebo or other control drug, so that he has no guarantee of receiving the drug he seeks.)

Furthermore, the IND procedure imposes substantial burdens on the IND's sponsor (usually a pharmaceutical company) that make the patients receiving the drug very much at the discretion and sufferance of the company. For example, questions of the free supply of the drug, reporting requirements, and the overall suitability of the patient for the proposed NDA, are all problems that arise in the IND phase and affect the supply of drugs for therapeutic purposes.

Thus, individual patients who genuinely need (or ever need to try) a new drug have no guaranteed access to it in this country. They are entirely dependent on the sponsoring company, whose primary aim must be to satisfy its NDA requirements. If no company or other sponsor has yet filed an IND application, or if a sponsoring company is unwilling to allow the drug to be used outside its own program, then the patient's problem is even more difficult. Short of the patient or his physician filing a private IND application (which can require submitting complete chemical, pharmaceutical and animal data) there is no practical way for a patient to obtain such a drug legally in the U.S. Even then, possession of a private IND exemption does nothing to ensure physically obtaining that drug from an unwilling sponsor.

This is a sorry state of affairs. Indeed, it is contrary to the Declaration of Helsinki adopted by the eighteenth World Medical Assembly in 1964 which, under the heading "Clinical Research Combined with Professional Care," states, "In the treatment of the sick person, the doctor must be free to use a new therapeutic measure if, in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering."

Clearly, there is an obvious need to ensure that the procedures for governing the investigational use of new drugs in the U.S. do not hinder the therapeutic use of those drugs for patients who need them.

We propose the creation of a distinction between the therapeutic and the investigational use of yet-unmarketed drugs. In addition, we advocate earlier but restricted release of certain drugs for therapeutic purposes. Clearly, safeguards have to be set up so that the use of a drug for therapeutic purposes does not preclude the acquisition of the scientifically acceptable information necessary for the NDA. It would therefore be desirable to keep therapeutic

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39

use within the framework of the IND process. This would need considerable modification of our approach to the IND procedure, including the question of whether a drug's sponsor should have absolute control over how it is to be used in this phase. In the proper scientific framework, the therapeutic use of investigational drugs could do much to improve the utilization of very new drugs. It would, furthermore, remove some of the conflict between the practicing physician, who wishes to prescribe the best therapy for individual patients, and the regulatory agency, which wishes to deal with drugs on a community-wide basis.

3. *There should be education of the public, legislators, and regulators about the therapeutic facts of life; namely, that if we desire drugs that are effective for more resistant disease in smaller segments of the population, toxicity will have to be accepted.* One way of minimizing such toxicity is to control utilization of the drug in such a fashion that it is restricted to those patients who really need it and who understand the dangers involved and give full informed consent so that they understand the risk/benefit trade-off. The problem is that the tighter are the utilization controls, the harder it becomes for patients to obtain the drug, and the less economically attractive it becomes for a company to continue to sponsor the drug at all; this leads us into profound questions such as restructuring of the nature of therapeutic drug research.

4. *One solution is that there should be government sponsorship or subsidy of these so-called "orphan" or commercially nonattractive drugs.* If commercial sponsors cannot be found, application for IND's by the government could be considered, particularly in the case of those drugs available abroad and also promising drugs possessed but not actively under study by domestic companies.

This is part of the overall problem of funding research dealing with "commercially unattractive areas".[7] Government support has been considered in the U.S.,[3] and was favorably considered by a working party of the Chemicals Economic Development Committee of the British National Economic Development Office, which is the national forum for economic consultation between government, management and unions.[8]

There are several examples of such governmental participation in drug discovery and/or development in the U.S. These should be studied further. The most relevant ones are:

1. The U.S. Army's tropical disease program.
2. The National Cancer Institute's antitumor drug program.
3. The antiepileptic drug development program of the NINCDS.
4. The combined program of contraceptive R & D, set up under the Family Planning Services and Population Research Act of 1970 (mainly in NIH).

Some aspects of the National Cancer Institute's program are of interest here.

Dr. Gordon Zubrod, while director of the Division of Cancer Treatment at the NCI, said in Congressional testimony that one of the main differences between government-supported research and private industry is that the NCI's mission . . .

"tends to be much broader than that of private industry. The pharmaceutical house must limit drug development to those areas that are of direct interest to the company, while the focus of the NCI program is upon the patient. We are charged with following every lead for active drugs, even though these may be of benefit to relatively small numbers of patients, and we do this with leads developing not only in the United States, but across the whole world. Therefore a number of anti-tumor drugs have been developed in which industry would not have been interested."[9]

It should be noted that even the NCI, with hundreds of drugs at the IND stage, has never brought a drug to market or even filed an NDA. After carrying out much of the preclinical or clinical workup of certain drugs, the NCI offers them for licensing to the pharmaceutical industry. Despite such assistance, the commercial promise of a drug is often not attractive enough to tempt prospective manufacturers.[10] This should warn us that drug research and development that is not commercially attractive to the pharmaceutical industry may ultimately become unattractive to government-sponsored research institutions as well, if arrangements cannot be made to ensure that promising drugs eventually reach the market.

Examples do exist of the distinction between therapeutic and investigational uses of new drugs. In the U.S., the National Cancer Institute has used the IND procedure extensively for therapeutic drug use. Zubrod testified as follows:

"In regard to anti-tumor drugs, I would call attention to one major problem, namely, the long time lag that exists between the point at which the professionals become convinced by the data generated under an IND, that a new drug is truly helpful to cancer patients, and the approval of the NDA.[11]

. . . [Some reasons for this are given.] . . .

The impact of this lag has not been of serious import in the cancer field because our widespread research network allows us to supply drugs to a fairly large number of patients . . . .[12]

Until an NDA is granted, the NCI must be responsible for seeing that every patient who needs a drug will get it. If we are the sole distributors of a drug, it is unjustifiable to withhold the drug from patients who need it." [13]

However, in reference to the drug adriamycin, "one of the most active antitumor drugs under present study [and one for which U.S. IND studies confirm British experience], Zubrod notes that it "is being used throughout our research network, but the drug reaches only a small fraction of those patients who could benefit from it." [14] Adriamycin was already marketed in Britain at the time of Zubrod's remarks, and was finally approved in the U.S. in 1974, after approval in 31 other countries.

The NCI is a unique case in the U.S.: a large government program, implemented at 200 institutions throughout the country, is being used to bypass the obstacles set up by the law's IND procedures in order to help individual patients obtain promptly the fruits of modern research; however, by its director's own testimony, even these substantial efforts are inadequate. Comparable procedures do not exist for making investigational drugs therapeutically available to patients in other disease areas.

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40

documented—for example, abroad—and more positive action on approving new uses for already marketed drugs.

Some help may be obtained by exploring the experience of other countries. Recognition of a distinction between therapeutic and investigational use of new drugs, which is not widely appreciated, represents a fundamental difference between the American and British approaches to the regulation of new drugs. In the British Medicines Act of 1968, there is a distinction recognized between investigational and therapeutic use of new drugs. The Act *excludes from its scope* the treatment of individual patients by physicians. Section 9 of the Act, referring to its general provisions and exemptions, states that "the restrictions . . . do not apply to anything done by a doctor or dentist which (a) relates to a medicinal product . . . [prepared or imported] . . . for administration to a particular patient of his. . . ." [15]

Section 31 of the Act requires licensing and certification for the investigational use of drugs, but Paragraph 5 of that Section exempts from this requirement, in language similar to Section 9, a physician acting on his own behalf to administer any drug to his own patients.

A distinction similar to the British one seems also to be recognized in the Swedish system of drug regulation.

CONCLUSIONS

Of all the solutions proposed above, probably the most fundamental one is the first, namely that the patients and their representatives should make known to Congress and the public in general the current plight of patients for whom no adequate therapy is available, and the diminishing chances of rectifying this situation if current trends continue. This negative trend is happening despite the fact that (thanks to past and present government investment in basic biomedical research) we are in an era of unprecedented growth in our knowledge about fundamental mechanisms of disease and potential avenues of therapy.

There needs to be a greater public awareness of the realities of therapeutics and drug research and the constraints upon these. It should be realized that drugs that are on the average not particularly impressive may nevertheless be very effective in some individual patients. It should also be realized that the concept of a "safe" drug is a hope and not a scientific reality; it is a notion of politics, not of science. Finally, there needs to be understanding of the factors described in this paper that make drug research increasingly unattractive and render it unlikely that the present unfavorable trends will spontaneously correct themselves.

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41