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BASIC RESEARCH IN DRUG DEVELOPMENT IN INDIA — POSSIBILITIES AND PROBLEMS

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Introduction

The pharmaceutical industry can be truly considered to be the one industry wherein there is maximum impact of science. Its survival and growth depend upon maintaining and improving its performance which in turn is achieved only partly by optimisation of or improvements to existing processes, design of better galenical forms or the discovery of new indications for old drugs. Basic research which only can lead to new drugs is a more important requirement and is a **sine qua non** for the very existence of this industry. This is still a rather rare phenomenon in India with only very few private industries and government institutions being engaged in this pursuit.

Basic research in drug development is a challenging and complex task entailing the interaction of several scientific disciplines and calls for much investment in men and materials. We have been engaged in this task for the last fifteen years and would like to set out in this paper our experience. We would specially like to focus our attention on some of the problems which are of particular relevance to Indian conditions.

The Process of Drug Development

In this connection, it is important to have a brief description of the process of drug development as it is practised today. The process may be considered to start with the organic chemist synthesizing a compound or making an extract of a natural source. A team of biologists belonging to various disciplines like pharmacology, endocrinology, parasitology, microbiology, etc. would then examine it for activity in one or more selected parameters or subject it to broad screening, the tests being conducted in vitro and/or in laboratory animals. Once a substance is found to have interesting activity and acceptable acute toxicity, it passes through four well-defined stages. Noted below are the principal activities involved in these four stages. It is interesting to mention that one estimate considers that there may be as many as 80 different activities in the whole process ![1]

Development of a Drug

Active substance

Stage 1

Extended biological characterization

Range-finding and 4-weeks toxicity in a rodent and a non-rodent species

Animal pharmacokinetics (mainly using radiolabelled substance)

Pharmaceutical development, stability studies

Clinical orientation
Drug Controller's permission to initiate trials.

Stage 2

Clinical investigation

Phase I — tolerability

Phase II — dose searching, efficacy

Further biological work

Human kinetics, bioavailability (using cold methods), metabolism

Chronic (generally 6 months) toxicity in 2 animal species

Preclinical and clinical reports

Drug Controller's permission for Phase III

Stage 3

Clinical investigation — Phase III

Expanded trials, double blind studies

Biological work (continued)

Toxicological work (continued), Reproductive studies

Human kinetics

Chemical development for production of active substances

Finalisation of formulation

Submission of data for registration

Stage 4

Drug Controller's Approval

Clinical investigation — Phase IV

Monitored release trials

Manufacturing permission

Price approval

INTRODUCTION

It must be emphasized that activities in the laboratory continue long after the drug has been released for public use, since the characterization of a drug is a continuing process.

Areas of Research

Drug development activities in industry are initiated by the formulation of projects. The first problem that arises in this connection is naturally concerned with areas and indications that should interest the sponsoring institution. The most important features that need to be considered are :[2]

medical needs
financial considerations
market research
company's policy
research ideas.

In a developing tropical country like India, even though the primary need is for research in antiprotozoal, anthelmintic and antitubercular drugs and for fertility-control agents, it is fallacious to think that efforts in other areas like cardiovascular diseases or CNS disorders are not important. It is easy to mistake the absence of adequate statistics on morbidity or mortality rates for absence of the diseases themselves. For example, already existing data show that there are at least five million untreated chronic psychotics and another five million with severe degrees of mental abnormality in the country[3]. These figures are necessarily very much on the low side since no proper survey has ever been carried out. Again we have the world's highest population of epileptics, about ten million febrile and afebrile cases, who need treatment[4]. So is the case with diabetes. Unlike bacterial infections, CVS or CNS disorders call for a greater array of drugs for adequate treatment.

In this context it is interesting to note[5] that an eminent visiting doctor recently observed that "we (Indians) do not suffer from external tensions as much as the Germans do, but internally, we are tense. People in the industrialised countries are not more tense than others. In Samoa, the three most common causes of death are hypertension, bleeding ulcer and diabetes. All the three result from tension.

But to an outsider, Samoa appears to be a peaceful and underdeveloped region. But that is not really so. Samoans are in the grip of change"[5].

A recent survey[6] of a semiurban, mostly illiterate, lower and lower-middle class community near Madras has revealed that nearly 32% of those aged over 50 suffered from mental disorders, with at least 10% of them needing psychiatric consultation and outpatient care and another 2% treatment in hospital.

It is thus certain that drug research in areas other than tropical diseases is not unwarranted. If additionally we bear in mind the fact that drugs developed here may attract an international market, it is obvious that basic research for drug development in these areas also is justified.

A second point that needs some elaboration is the importance of financial considerations in formulating research projects. Pharmaceutical industry, like any other branch of industry, must be run on profitable lines for its survival and expansion. It can meet its social obligation of providing medicines for the sick and employment for the able-bodied, only if it prospers. Viewed in this light, profit is not a dirty word, but a social responsibility of the drug industry. It undoubtedly has to shoulder the burden of doing research in some areas where the incidence of disease is low but the toll high. However, it can do so only if it is engaged in research in a sufficient number of areas that would provide a good return on the investment. "Like it or not, somebody has to pay for research projects. In the pharmaceutical industry, market analysts will have a voice in the choice of such programmes. That means that the number of patients with a given disease will be a persuasive argument to risk research capital".[7]

Thus, the interplay of market research, medical needs, financial considerations and company policy determines the nature of research programmes and projects that characterise basic research in drug development. Additionally, there will be always a portion of the total effort that will be devoted to testing out novel research ideas.

Lead discovery and optimization

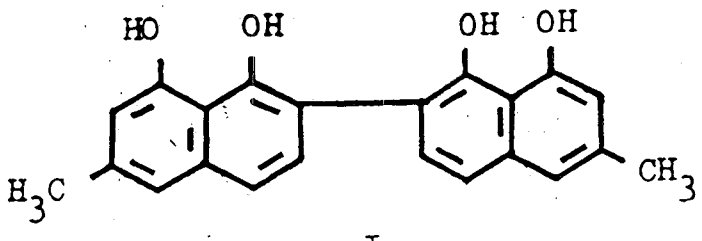
The initiation of research projects is often in the laboratory of the chemist who faces the problem of providing the active substance for the biologist. His efforts are initially to discover and optimise a lead. Some of his time is also spent in testing out more fundamental or long-range ideas. Lead discovery can be inspired by folklore medicine. We have various indigenous systems of medicine in the country from which ideas can be drawn. A rational biochemical concept can be a rewarding approach. B-blockers, gastric secretion inhibitors, antiparkinson drugs and sulphasynergists are all valuable products which have their origin primarily based on biochemical concepts. By far the largest number of drugs of today have resulted from random screening of a large number of compounds. In the late fifties and middle sixties aptly called the 'Golden Age' of drug development, this approach has paid rich dividends; however in recent years its success rate has fallen considerably. Lastly must be mentioned the continuing role of serendipity in the laboratory as well as during clinical trials.

Once a lead is discovered, its optimisation follows a relatively well-defined path which involves molecular manipulation. This has been, unlike recently, an empirical science that depended heavily upon the chemist's intuition and perception. Serious and sustained efforts are now

being made to substitute these by Quantitative Structure Activity Relationship studies[8] which, notwithstanding their immense potential, are yet to demonstrate their usefulness.

A couple of examples of lead discovery and optimisation from our work are given below :

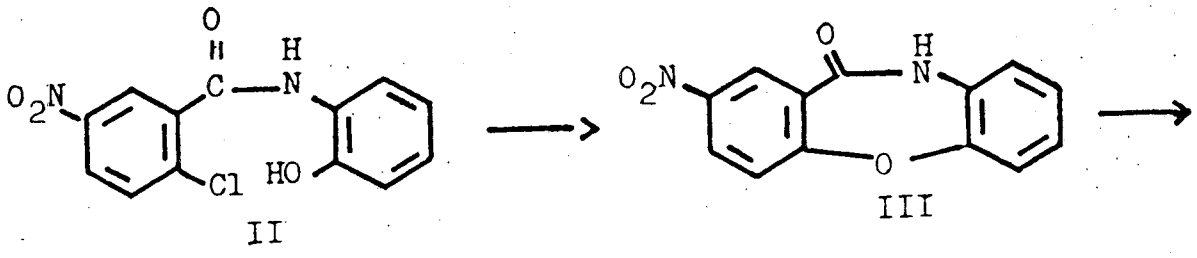
In Thailand the fruits of Diospyros mollis have been reputed to have curative activity in hookworm infestation in man. Chemical examination resulted in the isolation of diospyrol (I), which was found to have the activity in our experimental animal model[9]. The challenging task of synthesizing it was successfully accomplished[10]; but its cost and more importantly its relative instability to normal storage conditions ruled out the possibility of developing it further.



I

Extensive efforts were deployed to synthesize simpler or stabler analogues, but none of them had the desired antihookworm activity.

The second example concerns the antidepressant, Sintamil, and illustrates the many facets of the chemist's contribution to drug development. The high reactivity of chlorine atom in derivatives of 2-chloro-5-nitrobenzoic acid was utilized in a simple and facile synthesis of the dibenzoxazepinone III from the amide II[11]. III was manipulated to provide a variety of structures with diverse CNS activities[12]. Thus for example, aminoalkylation of the amide nitrogen led to compounds with potential antidepressant activity, out of which IV, carrying a dimethylaminopropyl side chain (present in imipramine, one of the drugs of choice for this indication)



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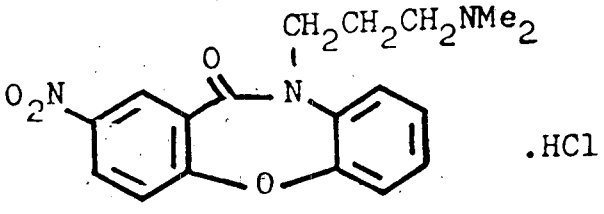


.HCl

IV

Sintamil

exhibited the maximum activity in laboratory experiments[12]. This was finally developed into a safe and effective antidepressant, Sintamil[13].

Biological models

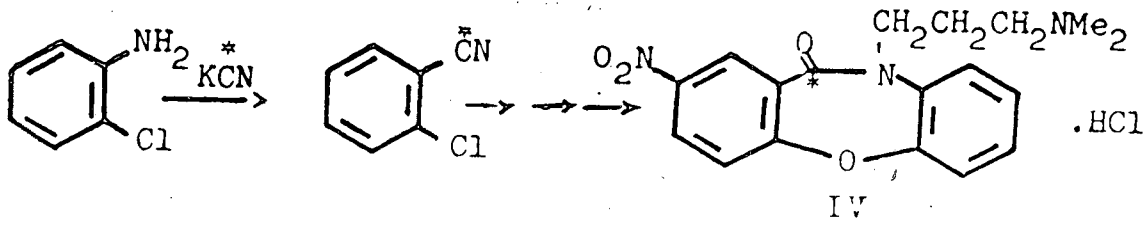
Some of the problems in biology are methodological in nature. In principle, these are encountered in drug development all over the world, but affect us specially with respect to the areas in which we in India would like to exercise our efforts. A couple of examples from our experience would be pertinent and illustrative.

Hookworm infestation is widely prevalent in the country to the extent of about 25%. It is debilitating since these worms suck the blood from the intestinal walls. The resultant anaemia leads to considerable morbidity. The worm Necator americanus could not be adapted earlier to a suitable experimental animal and the closest model was the dog carrying a related hookworm, Ancylostoma caninum. This model suffered from at least two serious disadvantages : the dog being a larger animal required large amounts of the compounds to be tested; but more seriously laboratory results did not correlate well with human findings. We have been successful in adapting Necator americanus to neonatal golden hamsters and setting up a relevant and valid test system[14 15].

The second example is concerned with epilepsy. One problem which concerns investigators engaged In research on experimental epilepsy is the animal surrogate for clinically encountered forms of epilepsy. Epilepsy is a chronic disease affecting 1 in 200 people in the West and 1 in 60 in India, approximately 10 million. In order to test new and novel antiepileptic drugs, we have induced a chronic epileptic state in monkeys by surgically injecting minute amounts of $Al(OH)_3$ into discrete brain areas. These animals develop seizures, similar to those in human subjects, which if uncontrolled by antiepileptic drugs, persist for the simian life span. Such epileptic monkeys give us valuable data regarding the efficacy, tolerability and safety of potential anticonvulsant drugs which can be extrapolated to the human situation. Our animal models are also designed to encompass other facets such as petit mal and focal and psychomotor epilepsy[16 17].

Methodological problems like these occur in all phases of drug development. In drug metabolism for example, it is becoming more and more imperative to know the availability as well as the fate of the drug in the human, directly if possible or by extrapolation of data from laboratory animal experiments. Such studies employ radio-labelled compounds or utilize very sensitive techniques for measuring pico to microgram quantities of intact drugs.

During our studies on the antidepressant Sintamil, we synthesized the molecule with ^{14}C at the starred position (IV) by the route shown[13] and studied its metabolism[18]. It is important to note here that several ^{14}C labelled precursors, eg, KCN, KSCN, CH_3I, CH_3CO_2H, $NaHCO_3$,



IV

etc. are available from Bhabha Atomic Research Centre, which has also facilities for marking compounds with ^{3}H (tritium). Later, we developed 'cold methodology', to measure levels of intact and desmethyl Sintamil active substance, using gas chromatographic techniques.[19]

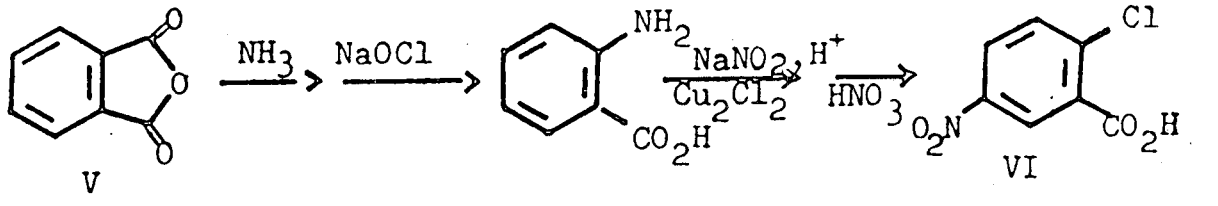
Manpower for basic research in drug development

We noted earlier that the several stages of drug development necessitate a multidisciplinary approach, which in turn calls for a team of specialists. Such a team ideally consists of organic chemists well-versed in synthetic or natural products chemistry, biologists belonging to a wide spectrum—pharmacology, endocrinology, parasitology, microbiology and toxicology, biochemists, pharmacists, clinical investigators, etc. The country has a good number of organic chemists with Ph.D. and further posdoctoral experience abroad, they however need orientation and training in adapting their skills to medicinal chemistry research. The supply of biologists of various types is more restricted and those available need to be exposed to the stringent requirements for detecting and assessing the activity of candidate drugs. Basically, the expertise to set up proper tests and more importantly to have a correct appreciation of results is needed, which is just as true for toxicology. Biochemists having training in drug metabolism are not readily available. This area would need expertise in the synthesis and handling of radioactive compounds and in devising 'cold' methods for the assay of drugs in biological fluids and adequate knowledge of biological and biochemical processes; very few institutions in the country can offer such a training. Turning to clinical investigation which actually characterises the properties of a potential drug in the humans, one notes that there is a good history of Phase IV trials in the country, but the record in the earlier phases which is critical to the indigenous development of a drug is less impressive. This is because clinical pharmacology is a young scientific discipline in the country and trained manpower is woefully inadequate. There is a clear need for more medical institutions to take up this subject and industry can perhaps help by endowing chairs in clinical pharmacology. Affiliation of industrial clinical pharmacologists to medical institutions could provide a fillip to the dissemination of this knowledge.

Materials for drug research

The complex nature of the process of drug development clearly calls for the availability of a vast array of materials. This list will be headed by chemicals and biochemicals of which only a small proportion is available locally. The rest have to be imported. Occasionally, one can try to synthesize some imported intermediate from less expensive or indigenously available starting materials. This can be illustrated by two examples from our own experience, when we ran out of imported stocks of 2-chloro-5-nitrobenzoic acid (VI) and r-chloro-p-fluorobutyrophenone (VIII) and needed them badly for our research programmes. These were synthesized from other available chemicals as follows :

It needs to be emphasized here that such approaches are acceptable and, in fact, required for rapid execution of research projects; but when it comes to production, serious factors like volume and cost of production will have to be balanced against the cost of importing. This factor plays a critical role in determining the price of drugs, which is under constant scrutiny both by the government and the public at large.



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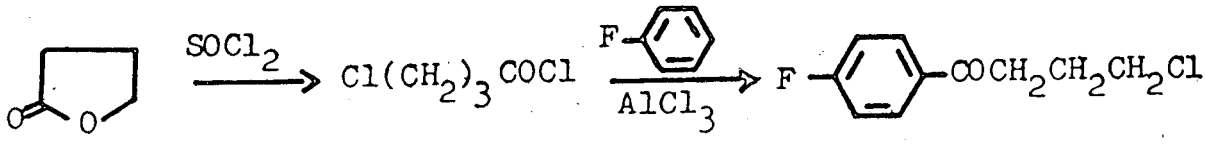


VII VIII

While a variety of glass, mechanical and electrical equipment is available in the country or can be fabricated, the situation is less favourable with respect to sophisticated electronic ware which is needed in abundance by any modern drug development laboratory. A partial list will include spectrometers, spectrophotometers and microanalytical facilities for structure and purity determination, EEG, ECG machines, scintillation counters, gas chromatographs, etc., all of which will have to be imported and properly serviced. In drug development, small animals in the biological laboratory, in a way, may be considered to be the equivalent of chemicals in a chemical laboratory. It becomes very important to have a proper animal house. This should provide different kinds of animals like mouse, rat, hamster, guinea pig, cat, dog and monkey, reared and kept under standard conditions. With appropriate investments, this is largely possible in the country. As regards clinical pharmacology, while laboratory facilities exist for clinical pathology and clinical chemistry in many medical institutions, these are set up to handle only routine problems. A strong case exists for creating special separate facilities for ensuring proper attention to problems of new drug development.

It has been noted that most chemicals and instruments are not locally available and have to be imported. In this context, it is heartening to note that the Government has replaced the earlier system of issuing ad hoc licences by a liberal provision for R & D institutions approved by the Department of Science and Technology to import goods worth upto Rs. 500,000. An additional provision of upto Rs. 200,000 for the rapid import of large quantities of starting materials for the synthesis of active substances is needed for multicentre, multinational trials.

It is also quite obvious that the present provision is adequate only for chemicals and medium-priced equipment. For more expensive items, special capital goods (CG) licences are needed and must be made available speedily. These licences must provide for charges for commissioning by experts from the suppliers and also for training of Indian service engineers deputed to look after them. Appropriate governmental rules and regulations must also be framed and administered in such a way that spare parts can be imported quickly. This is needed to cut down the idle time of costly instruments. Occasionally or rarely, an Indian R & D institution may need to obtain some pieces of special equipment from abroad through its collaborators. In such cases, the government must view the case for granting a customs clearance permit

with sympathetic understanding. The country has already invested heavily in regional sophisticated instrumentation centres. Many R & D institutions, including those of the drug industry, can advantageously use their facilities, but this would need the strengthening of these centres for prompt customer service.

Power Supply

Adequate power supply is a problem that all Indian industrial units face. For the sophisticated instruments that drug development employs, power supply must be not only adequate but also stable. Bombay is fortunate to have a fairly stable power supply, ensuring reasonable life time for equipment. But there are seasonal or perennial curbs on power supply of moderate to severe nature; an auxiliary generator becomes thus a necessary adjunct.

Investment in drug research

We could now pass on to much larger problems facing basic research in India on drug development, namely, investment and investment climate. In 1972, the total international investment in pharmaceutical research was computed to be 550 million pound sterling[20]. This has been going up all the time and the figure stood at 2 billion dollars in 1976[21]. In W. Germany alone, the budget was 1 billion DM in 1975[1]. The current cost of developing one drug is estimated to vary around 40-100 million dollars[20 22]. The German study[1] placed it at 89 million DM in 1975, while the 1976 figure for the total international effort is 55 million dollars[21]. These figures are to be compared with investment in India which was estimated in 1976 to have been about Rs. 80 million or 1.5% of the total turnover of the pharmaceutical industry. By international standards, this covers barely a **fraction** of the cost of developing **one drug**. A sizeable stepping up of investment is clearly called for. While undoubtedly, the **quality** of research plays an important role in discoveries, it must be borne in mind that the multi-disciplinary requirements of drug discovery and development call for a **minimum** investment for the realization of meaningful results.

It is instructive to have an idea of how the financial investment in drug development is distributed. Table 1, reproduced from the German study cited earlier[1], represents one such analysis.

In basic research for drug development, investment in time is as important and critical as in money. In figure 1, an attempt is made to analyse the time needed to develop a drug, which takes anywhere from 8 to 11 years, **after** the active compound is obtained. It is to be noted that the time needed for discovery of the active compound itself is an unpredictable factor, given the nature of the process of drug discovery. It is equally important to ponder over the period during which the drug will enjoy profitable sales in the light of the well known propensity for obsolescence in this field.

Chances of drug discovery

The chances of developing a drug once this investment in time and money is made have also to be carefully evaluated. Table 2 illustrates this aspect in the case of the malaria problem[23]. It has been stated that "in more recent times, only 1 out of 5,000 to 20,000 has become a clinically useful agent". The current view point tends to place the odds at definitely lower than 1 in 10,000.[22]

Table 1 : Where does the money go in Basic Research for Drug Development?

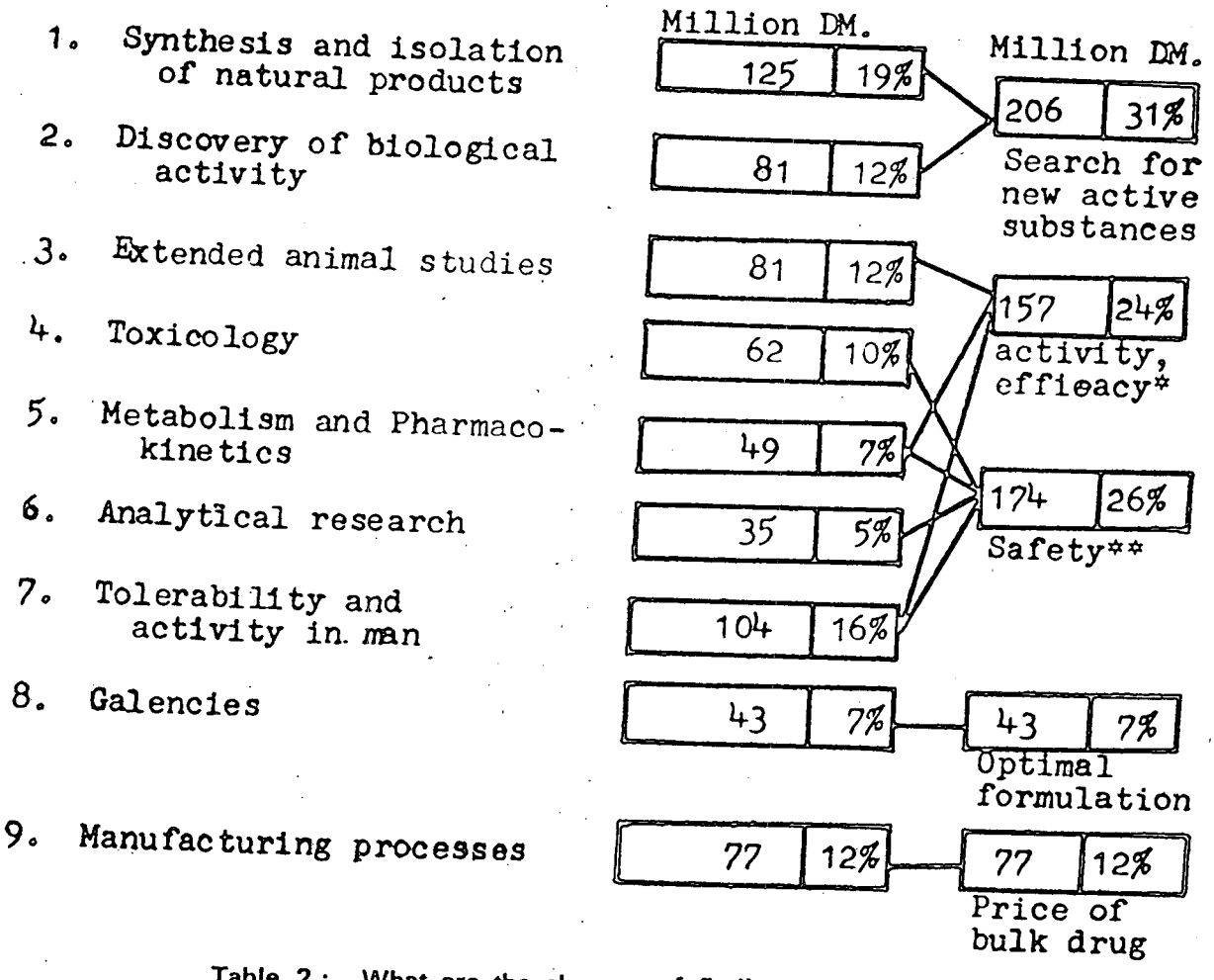


Table 2 : What are the chances of finding a drug ?

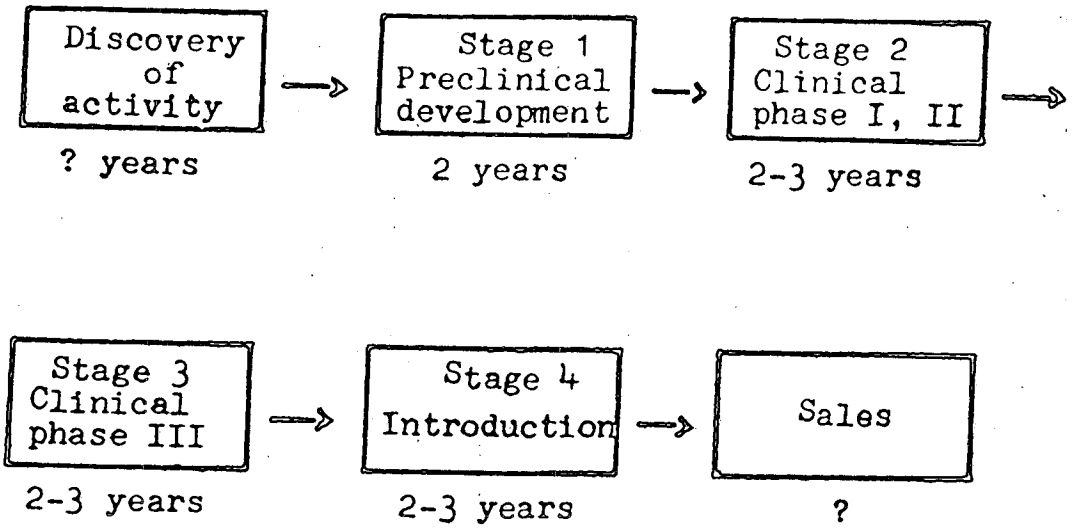
The Malaria Problem

The Walter Reed Institute Research Programme—

Tested since 1964	:	380,000 compounds
Active in mice	:	3%, 11500
Tested in the new owl-monkey model against P. falciparum & vivax	:	200
Clinically tested	:	29
Effective in humans	:	7 drugs, 2 combinations

Mefloquine chosen as the best one.

Fig.1 : Time needed to develop a drug



Government policies

Given the problems that basic research for productive drug development involve, it is obvious that in developing countries like India, investment can be stimulated by the government only by generous incentives. Such encouragement is needed to utilize the countries' undoubted potential of scientific talent and to give the country its rightful place in the comity of nations. It is also only proper that we should accept the burden for developing drugs for diseases peculiar to the tropics. Some comments are thus warranted on policies of the government which have a direct bearing on investment in research.

Positive factors arising out of the government's current policies are generous income-tax rebate on R & D expenditure and liberal provision for import upto Rs. 500,000 worth of chemicals, equipment and spare parts. However, the regulation concerning granting of licences to manufacture drugs arising out of Indian research are unnecessarily restrictive now. These restrictions must be removed and such products should be guaranteed commercial exploitation free of encumbrances.

The patent problem

The patent system has been internationally recognized as one which ensures for a discoverer or inventor adequate time for recovering his investments in research; this has played a valuable supportive role in encouraging investment in drug research. We have noted already that the time needed for discovering and developing a drug ranges between 10 and 15 years, with the odds at less than 1 in 10,000. The current Indian patent regulations, affecting foods and drugs particularly, which were introduced by the Indian Patent Act of 1970 and which came into force on April 20, 1972, have as salient features :

Product by process

Unitary process

5 years life time from date of sealing, or

7 years from date of filing, whichever is shorter

Provision for compulsory licensing and licence of right.

It is quite obvious that these disincentives for investment in basic research for drug development need to be removed. In this context, it is pertinent to note that in Britain, the life time of a patent has been increased from 16 to 20 years and the compulsory licensing clause has been removed[24].

"Indeed the costliest type of research cannot be justified without expectation of strong patents. The tendency of some governments to degrade the patent law or to substitute price or other controls for normal free market forces is bound ultimately to be disastrous to consumers who need invention as well as industry".[20]

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* The costs of activity and efficacy are calculated by adding the costs of item 3 and half the costs of items 5 and 7.

** The cost of safety is obtained by adding 4 and 6 to half the cost of 5 and 7.