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Pre-Clinical Development of Drugs

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INTRODUCTION

The purpose of this paper is to present a brief outline of the essential requirements in the post-research phase of drug development. At present evolution of new drugs, is largely a responsibility of the pharmaceutical industry and deployment of resources in Research and Development is inevitably linked to the profit-motive. Without this, the resources and, possibly the practical incentive, would not be readily available to support further endeavour. The dilemma arises when, as at the present time, moral and humanitarian considerations of drug development for specific purposes conflict with the monetary basis of viability of the industry.

Stages in Drug Development

The development of new drugs in industry falls into four broadly distinguishable stages:

1. On-going research programmes in search of leads.
2. Pursuit of the lead in chemico-biological elucidation of optimal structure-activity of the molecule.
3. Development of the preferred candidate compound to the point of use in man and animals.
4. Entry into production with subsequent extension to marketing, sales and profitability.

The organizational pattern related to progression through these stages is very similar and is likely to differ in procedural detail only as between different companies.

On-Going Research Programmes.

At any point in time in any large research organization, research programmes will be numerous and varied, with pharmacology and chemotherapy departments competing for available chemistry as a basic element for future progress. In all instances the objective of the research is the discovery of chemical leads of more or less novel character which might be anticipated to offer advantage either in a field poorly equipped with therapeutic agents or to present significant progress in comparison with existing agents of less than adequate performance. The method of approach to such leads may be either through basic biological research or through what may be termed the Selective Approach from known molecular configuration of established activity or the Empirical Approach which is aimed at novel discovery arising from no established source. The empirical approach may be roughly divided into two categories; that based on selection and synthesis of structure influened by the background knowledge and speculative initiative of chemist and biologist or the unimaginative of chemist and biologist or the unimaginative and unintelligent large-scale screening of coded compounds.

In those parts of the pharmaceutical industry deploying significant R. & D. investment, the familiar pattern of research is a balanced programme of long-term basic research coupled with a "Bread and Butter" activity related to selective or empirical screening.

Regarding the test systems within any screening programme. These are usually established on the grand scale adapted to routine challenge of laboratory induced infections, by new chemical compounds given up to maximum dose levels tolerated by the host. The reading of the screen involves recognition of significant deviation from the normal pattern of infection. This provides the lead.

Pursuit of the Lead:

This is perhaps one of the more exciting and frequently frustrating stages of research. It is dependent upon the intuition, original thought, experience and synthetic ability of the chemist associated with the test system. It is a period of intense activity among all associated disciplines where the initial lead is pursued to the point of determining maximum structure-activity related to molecular configuration.

This will then be optimized by relating structure to other parameters such as ease of chemical synthesis and acute toxicity etc. Frequently such leads get nowhere, due either to demonstration of inadequate activity, unacceptable levels of toxicity or unacceptable costs in synthesis. In those instances where adequate performance is indicated there may one outstanding compound or, perhaps, several with little observable difference in biological merit. Selection from compounds of apparently similar therapeutic potential will be made on greater or lesser likelihood of unwanted side effects or relative ease of chemical accessibility and hence, cost.

Concurrently with this phase of activity which, according to complexity of the chemistry, may take anything from one to several years, the chemistry department is also much involved in exploration of alternative synthetic approaches for purposes of establishing patent cover to protect the invention. This facet of resource involvement is likely to continue over an extensive period to meet the requirement of patent filling in both producer and user countries. A high proportion of such patent applications may never serve the hoped-for purpose but, when published do form a literature source which can be of intellectual stimulus to the research chemist and biologist and also provide a legitimate source of information on trends within competitive industry which might otherwise have no basis for more objective otherwise.

Development of the Preferred Compound

Decision to proceed with the development of the preferred compound is of considerable moment because to do so implies the commitment of extremely costly resources over a period of at least 5 years and possibly 7 or even 10 years. Clearly, the resources are finite and, according to merit, the compound will be subject to some order of priority in competition with others within the general research programme. Several factors contribute to the establishment of priority ranking but among them is the compararive potential for return on investment.

Assuming that the decision is to go forward along the protracted course of determining suitability for use, it is customary, to establish a critical pathway inter-relating the development money and the detailed requirements of national regulatory bodies in those countries where the future drug is to be made or marketed. In large research establishments where the number of such operations will be many and at a varying stages of progression, the co-ordination is frequently monitored by computer, and regularly updated. The range of activities linked to the critical

pathway are essential to registration requirements in several territories for determination of purity, safety and facility of administration to the patient. In almost every instance, failure to meet essential standards in any of the studies will lead to cancellation or deferrment of the project or to return to research. It must be noted that the chemical development, purity control and pharmaceutical development must proceed to production standards before toxicological work can commence. Similarly, the toxicology and drug metabolism studies must be not only satisfactorily completed before clinical investigation but, together with all other date relevant to the compound must be compiled and submitted to pertinent regulatory bodies before permission for trial in man can be given.

The time taken to complete this stage of investigation will vary with the order of unforseen problems as they arise and to conflicting priority claims for particular resoruces by other projects. Also, it is the area of greatest failure rate. A popular figure is 90% failure over the hurdles of toxicology and clinical efficacy.

Production and Sales

While obviously a very important stage and the one which provides the finance of research as well as the profit incentive, it is of little interest in the present context except to emphasize that it is too costs money both in capital investment in specialized plant and in sales promotion.

This also enters the priority rating and can influence policy on selective investment in competitive fields of interest.

DISCUSSION

It will have been appreciated that success in the R & D section of the pharmaceutical industry is based on highly speculative investment where continuity in drug development is dependent upon a reasonable profit margin both to offset the failure rate and to finance further work. Many factors have conspired to increase the difficulties in expanding investment. Significant among these have been great increases in regulatory requirements following the thalidomide disaster and in inflationary tendencies which are particularly acute at the present time.

With increased and largely highly desirable expenditure on safety and manufacturing standards the costs of developing a compound have increased materially over the last decade. deHaen[1] indicates a steady fall in the number of new single chemical entities marketed in the U.S.A. since 1959.

1959	63	1966	13
1960	45	1967	27
1961	41	1968	14
1962	28	1969	11
1963	18	1970	16
1964	17	1971	14
1965	23	1972	11

The post-war period has seen very large increases in R & D expenditure. In 1973 the total R & D expenditure world-wide in the pharmaceutical industry was estimated to be almost $1,150 million with approximately two-thirds of this in U.S.A. alone. The U.S.A. figure for 1972 is given as $750 million. Against this, according to the Stanford Research Institute[2], the rate of increase in R & D in U.S.A. has been falling in recent year:

	Increase over previour year
1970	+ 12.6%
1971	+ 10.6%
1972	+ 6.5%
1973	+ 4.5%

If true, this falling rate of increase matched against inflation may imply less resource available in real terms than existed previously and may not offer evidence of increase expansion.

It seems possible that these examples of the influence of events on the economics of drug research account in some measure for the concentration in USA on the health needs of sophisticated countries to the disadvantage of the needs of underdeveloped countries as is evidenced by considerable withdrawal from the tropical medical fields.

This trend apparent in the USA has not yet been so obvious in Europe.

Sufficient has been said on the pattern of drug development to appreciate that in research and development terms, the only realistic unit of time is 10 years. With this in mind the future in drug development has to be viewed over, say, a 20-year period, i.e. about two drug generations away. It is estimated that by 1990, the world population will be round 5.5 billion if the present rate of increase continues and that 80% will be in the present underdeveloped countries. In philosophical terms it seems inconceivable that the pharmaceutical industry will not be involvedsin the well-being of 80% of the world population. The problem now is to find the economic basis for maintenance and expansion of research involvement.

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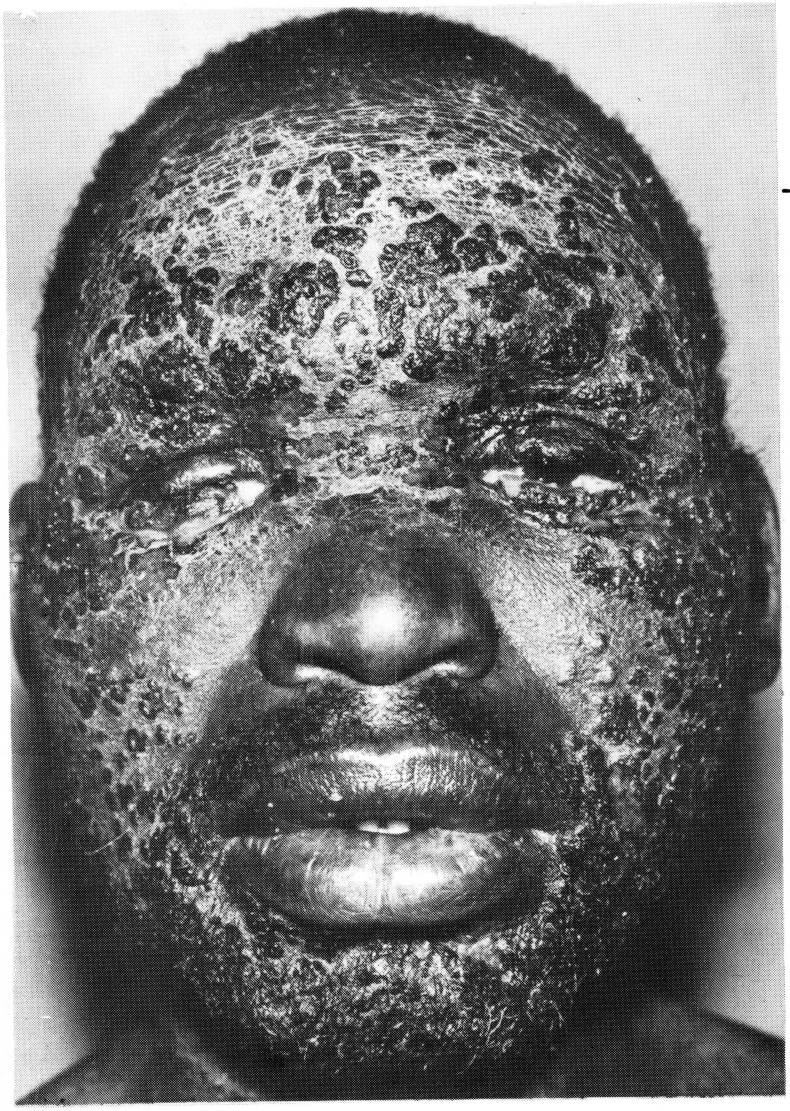
Basically, industry is not faced with a problem but rather with dilemma over choice to invest in programmes with hitherto poor financial return or to concentrate their resource allocation to more obvious sources of reasonable reward. This is a conflict between humanitarian outlook and the basis of economic viability. The solution to the problem lies in the developing countries themselves and with those international institutions with the responsibility of promoting the well-being of the peoles of these countries. Solution is likely if the essential requirements of industry are recognized and means found to meet them satisfactorily. Indeed, it could be that the greatest incentive to industry for investment in this field would be evidence of obvious intent to utilize drugs already developed and at a level which would indicate the prospect of reasonable return on potential future development. How this may be achieved is not clear at present.

SPOT THE DIAGNOSIS
A dermatological problem



This patient had an extensive Seborrheic eczema. His condition responded very well to oral prednisolone treatment initially. However on the 4th day of treatment there was a sudden and profuse vesicular eruption in all the seborrheic areas. The vesicles changed to umblicated pustules during the next 3 days. The oral prednisolone was stopped and the lesions healed spontaneously after 10 days leaving varicella like pitted scars. The general condition was unaffected during this acute episode.

Can you spot the diagnosis?

If you can't, turn to page 53 for the answer.

Answer

KAPOSIS VARICELLIFORM ERUPTION

Named after the discoverer this condition is a complication of any form of extensive eczema due to super infection with either Herpes Simplex (ECZEMA HERPETICUM) or Vaccinia Virus (ECZEMA VACCINATUM).

In our patient it was due to Herpes labialis which can be seen faintly on the lower lip. The eczematous skin and the prednisolone treatment are the two factors responsible, for the dissemination of the virus. The grouping of small vesicular eruptions on the lip noticed in the early stage gone the clue to the diagnosis of ECZEMA HERPETICUM.

Eczema vaccination has a similar clinical picture and differentiation can not be made from the morphology of lesions. However a definite diagnosis can be made by determining the nature of inclusion bodies. Among the two eczema vaccination is the most serious and needs careful management.