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The Development of a Drug of Plant Origin*

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There is a Korean proverb, saying that *Kwon Un Sip Nyon I Yo Sye Nun Paik Nyon I Ra* (權不十年 勢不百年) meaning that power lasts ten years and influence less than a hundred. A really good drug may last several hundred years, but it also takes a rathe longr time and a great sum of money to develop it.

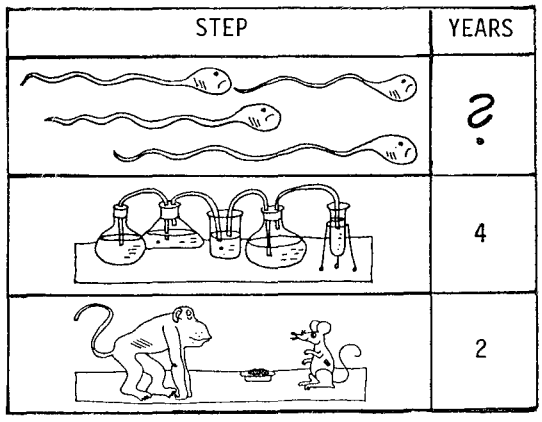
Although it has ben repeatedly stated (Djerassi 1969, 1970, 1979; Diczfalusy 1978, 1979a) it appears to be shocking news to many scientists to learn that the development of a new fertility regulating agent, for instance one of plant origin, is likely to take some 20 years and may cost as much as 50 million dollars. Why is it so? Let us examine the process of drug development for a moment, since it is important for us to understand the limiting factors, time frame and financial constraints in order to formulate a proper strategy.

In the development of a fertility regulating drug of plant origin, the major steps may be ethnobotanical identification on the basis of a computer search, a critical evaluation of the literature information, collecion of the selected plants, then screening of their extracts in bioassays, and-in case there is antifertility activity in two or more animal species-a case can be made for starting fractionation, isolation and identification of the active constituent.

However, the isolation and identification of a new chemical entity exhibiting antifertility activity is not the end, but rather the beginning of the process, and we can say with Shakespeare that what is past is prologue. From here on we are still facing a development process with a time frame of 15 to 20 years. Why? To appreciate the problem, let us go through the major steps of the drug developmental process, as shown schematically in Figs. 1-6.

WHAT DOES IT TAKE TO DEVELOP
A PILL FOR MEN ?

I



Let us assume that a group of phytochemists isolated a new chemical entity which inhibits specifically sperm motility, so that at last we have a real chance to develop a pill for men. Is the isolated compound the best possible one? This is the first question. To provide an answer, we must initiate a large scale synthetic and screening programme (Fig. 1); a large

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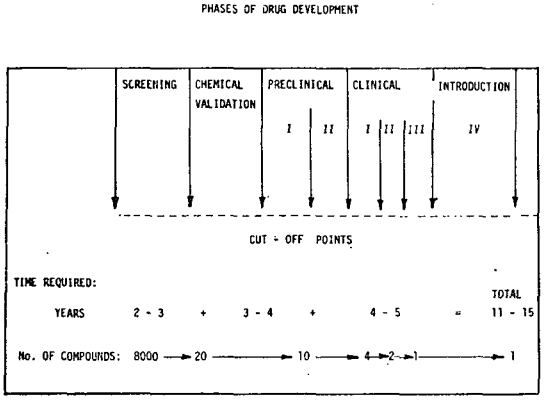
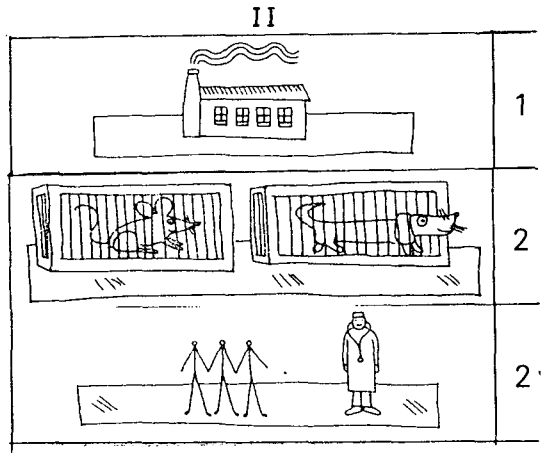
number of analogues, perhaps several hundred, are prepared and subjected to animal testing. To find the most suitable compound may easily take 5 to 6 years.

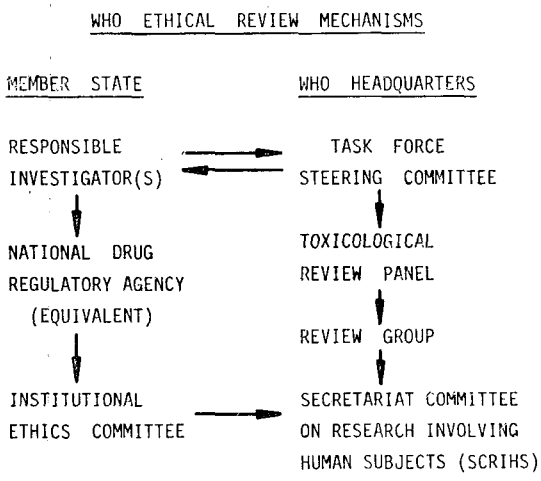


As indicated in Fig 2, it may happen that as many as 800 to 1000 new compounds are synthesized before a proper selection is made for continued developmental work.

Now the candidate compound must be synthesized on a much larger scale (as shown in Fig. 3) to enable us to conduct the so-called "Pre-Phase I" animal toxicological studies in at least two species for, say, 6 months, after which the new substance will be tested very, very carefully on a few volunteers (who have signed



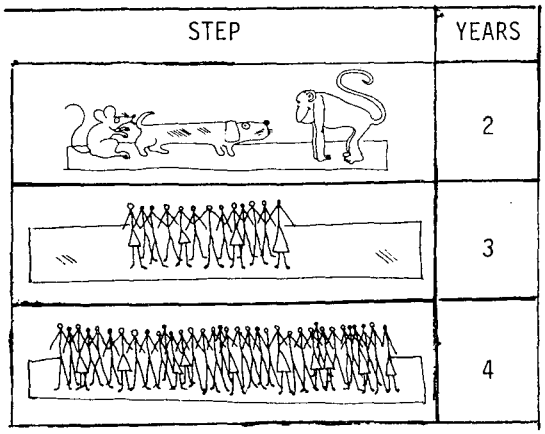
forms of informed consent), not more than 5 to 10 subjects, in a hospital setting under very careful medical supervision. This is called a clinical Phase I investigation, a kind of human tolerance study; we want to ensure the absence of unexpected adverse effects. However, such a clinical trial cannot be initiated unless the protocols are approved by the local Ethical



Committee and the Drug Regulatory Agency of the country in question, as indicated in Fig. 4. In the World Health Organization's Special Programme on Human Reproduction, the protocols must also be approved by the Steering Committee of the Task Force, the Toxicology Review Panel, the Review Group, and finally, the Secretariat Committee for Research involving Human Subjects (SCRIHS). As indicated in Fig. 4, the SCRIHS will not consider any proposal unless it has been approved by the National Drug Regulatory Agency, or its equivalent, and the Institutional Ethical Committee. There will always be a few critics who may feel that this procedure is too slow, too bureaucratic, and unnecessarily complicated; however, in practice this is by no means the case. The system functions very well and provides an adequate guarantee that the volunteers are not being exposed to any health hazards.

WHAT DOES IT TAKE TO DEVELOP A PILL FOR MEN ?

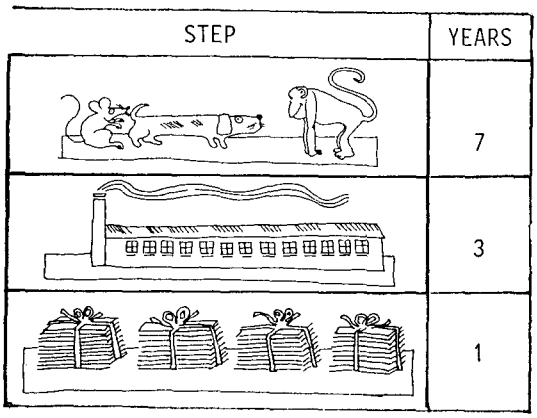
III



What next? As indicated in Fig. 5, now two years animal toxicological testing is needed, in say, three species, for instance rat, dog and monkey, before the adequate human dose can be established in a so-called clinical Phase II study on some 50 to 100 subjects Subsequently, the optimal dose is evaluated in a large scale, so-called Phase III study on several hundred (up to a thousand) individuals. The number of years needed for these steps is also indicated in Fig. 5.

WHAT DOES IT TAKE TO DEVELOP A PILL FOR MEN ?

IV



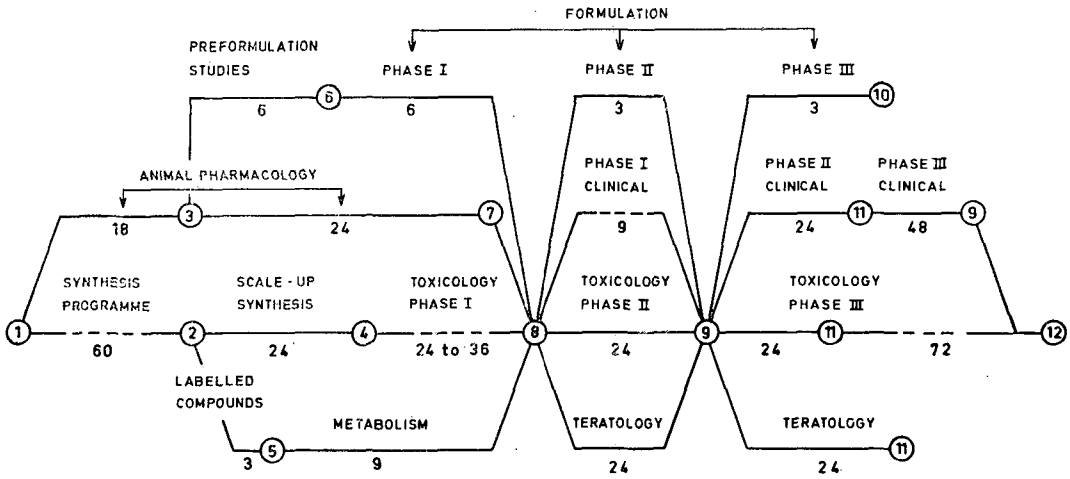
However, in the case of new fertility regulatingagents, before the initiation of a Phase III study, we must have started life-time toxicological studies, for instance 7 years in dogs and 10 years in monkeys, and a series of special studies must also be conducted to exclude any carcinogenic, mutagenic or teratogenic potential (Fig. 6). Then the synthetic methods must be scaled up to enable fabrication in large quantities, which may frequently present unexpected technical problems.

At this stage, methods must be developed for quality control, the stability of the product be must ascertained(it must be stable upon storage under various environmental conditions), and finally, the great moment arrives when a tre mendous amount of documentation is submitted to the Drug Regualatory Authorities. It is no exaggeration to say that by this time some of the inventors of the new drug must have reached retirement age.

Several of the steps discussed can and should be taken simultaneously, according to a so-called critical path map, as shown in Fig. 7 which is a simplified version (Diczfalusy 1979a) of the original one published by Djerassi (1969). The numbers below each phase indicate the number of months required for the completion of that specific step. The figure of the critical path map illustrates the planning and co-ordination of the different activities required for the successful completion of the task. Dr. Djerassi(1969) calculates that in this particular example the stage of registration (and of Phase IV field trials) will be reached in 17 years.

Although registration may be considered as the end of the process, in practice it represents the beginning of the life saga of the new drug, going through the classical phases described by Eisenberg, frm early enthusiasm, the first evidence of adverse reactions, growing criticism,

CRITICAL PATH MAP FOR THE "MALE PILL"



calls for discard, and-hopefully-final sobriety.

Since fertility regulating agents will be used by millions of healthy individuals during prolonged periods of time, it is easy to see that the safety regulations are rather demanding and that the animal studies on safety play a predominant role in the development of the new agent.

In the best of possible worlds it would be expected that these studies could be conducted in an animal species in which the pharmacokinetic and pharmacodynamic properties of the new drug approximate those found in man, but this is a very difficult requirement, which can only exceptionally be met. The pharmacokinetic behaviour of the new drug in an animal model may be dramatically different from that in the human. There are sad examples of this, for instance the famous issue of mammary "nodules" induced by certain contraceptive steroids in Beagle dogs (Diczfalusy 1979b), which resulted in the withdrawal from the market of valuable compounds in several countries. With the possible exception of some qreat apes (which are endangered species and therefore cannot be used for toxicological studies), there is no ideal animal model for the study of the safety of fertility regulating agents; hence, in want of any better solution, several animal species are used (rat, mouse, rabbit, dog, monkey, etc.) for toxicological evaluation.

For instance, as shown in Table I, in most Western countries, the Drug Regulatory Authorities request that the acute toxicity should be investigated in at least two rodent and one non-rodent species, and not only by the route of administration proposed for use in man. Furthermore, as indicated in Table II, the minimum requirement for subchronic and chronic toxicity studies is one rodent and one or two non-rodent species dosed at three levels, namely the expected human dose, a maximum tolerated dose and a high enough dose to produce toxic manifestations.

This lastmentioned requirement raises of course a fundamental question, namely, how much is too much when it comes to the administration of excessive doses? And when such "unrealistically high" doses do produce toxic reactions, can we really completely disregard this in the subsequent assessment of the risk/benefit ratio of the new drug?

ACUTE TOXICITY

SPECIES:

AT LEAST TWO RODENT
(e.g. RAT AND MOUSE)

AT LEAST ONE NON-RODENT
(e.g. DOG)

ROUTES OF ADMINISTRATION:

a) THAT PROPOSED FOR USE IN MAN

b) ANOTHER ONE PRODUCING
DEFINITE ABSORPTION

REPEATED DOSE STUDIES

SPECIES:

ONE RODENT (e.g. RAT)

ONE NON-RODENT (e.g. DOG, OR PRIMATE)

ROUTE OF ADMINISTRATION:

THAT PROPOSED FOR USE IN MAN

DOSE LEVELS:

a) LOW = EXPECTED HUMAN DOSE,
OR HIGHER

b) MEDIUM = MAXIMUM TOLERATED DOSE

c) HIGH = SHOULD PRODUCE TOXIC RESPONSE

How long should be the duration of administration in such studies? Asindicatedin Table III, this depends on the proposed duration of therapeutic administration; hence, agents expected to be administered over prolonged periods of time, like contraceptives, must be evaluated during two years in rodents, and during at least 6-12 months in non-rodents. Furthermore, because of the special concern with regard to the use of fertility regulating agents by very large numbers of healthy human beings, the Drug Regulatory Agencies in most Western countries demand life-time toxicological studies, i.e. 7 years in dogs and 10 years in monkeys, as indicated in Fig. 6. In addition, special studies are also requested to exclude any teratogenic, mutagenic and carcinogenic potential. Some of these are multigeneration studies in which two or three subsequent generations are evaluated (cf. Table IV).

SPECIAL STUDIES

TYPE:	SPECIES:
FERTILITY	ONE
TERATOLOGY	TWO
PERINATAL	ONE
POST-NATAL	ONE
MUTAGENICITY	-
CARCINOGENICITY	TWO

DURATION OF ADMINISTRATION

PROPOSED DURATION IN MAN	DURATION OF TOXICITY STUDY
SINGLE DOSE	1-2 WEEKS
UP TO ONE WEEK	4 WEEKS
ONE TO FOUR WEEKS	3 MONTHS
OVER FOUR WEEKS	6 MONTHS
LONG-TERM USE (OVER 6 MONTHS)	2 YEARS IN RODENTS AND 6 MONTHS IN NON-RODENTS

It is fair to say that only the animal safety studies indicated above represent an expenditure of some 5 million U.S. dollars. Furthermore, the various types of clinical investigations (for instance the extensive pharmacokinetic and pharmacodynamic studies and metabolic investigations) are a great deal more expensive than the animal toxicology. In view of these considerations, it is easy to see that the devlopmental time of a new agent is very long and the cost very high.

A few carefully calculated general estimates are presented in Table V; the estimates were given in U.S. dollars in year 1978 and do not refer specifically to fertility regulating agents, which, as indicated above, may be more expensive. Hence, with the prevailing rate of inflation, one can envision an expenditure of 50 million dollars or so in case of each new agent. The problem is compounded by the fact that in the developing world there is a major need for several new agents, not only for a single "perfect" one. Why is it so? Because there are major differences in the acceptability of any given method, due to the cultural, socio-economic and religious heterogeneity, because of the changing needs of the couples during the various phases of their reproductive life, because of the great differences in terms of health services available, because of the possibility of an expected appearance of long-term adverse reactions, and because-due to the polymorphism of human populations-rare adverse reactions will occur with every method in a few individuals.

Who should then develop such an array of new agents? What a strange question! Why not the Drug Industry with its competence, know-how and impressive record of past achievements? Simply because Industry does not see a reasonable chance to recover multiple investments of the order of 50 million dollion dollars

Table V. Estimates of the investment needed to develop a new drug, calculated in terms of 1979 or 1977 $US. (Source: Diczfalusy, 1979a).

Years	Investment ($ × 10^6)	Source
10~17	20~35	Djerassi(1970, 1978)[a]
7~10(minimum)	20~30	Merck & Co (1977)[b]
	24~53	R.W. Hansen(1977)[c])
>10	63	Zaffaroni and Pharriss (1978)[d]

[a] Dr. Djerassi suggests that his cost estimates be multiplied by a factor of 2.2 to validate them for 1978 (personal communication).
[b] First Quarted Report, 1977.
[c] Comments on the proposed change in the US Food and Drug Administration's Secrets Policy PS7706, October 1977. The Center for the Study of Drug Development, University of Rochester Medical Center Publication Series.
[d] Personal communication; estimates based on the Prescription Drug Industry Factbook (1976)

for the development of agents which will mainly be used in developing countries. This has forced several public sector agencies-the most important ones being WHO and NICHD-to initiate drug development programmes for the benefit of the public sector, especially in developing countries. The question is then: do these agencies have the required funds? No, not if left alone. This appears clearly from a Ford Foundation Study (Greep *et al.* 1976) published a few years ago; in 1972, mankind had spent some what less than $100 million on research on reproduction, of which probably 25~30% was related to drug development.

What is then the solution? As an advertisement of the Caterpillar Corporation states, "there are no simple solutions, only intelligent choices". An intelligent choice seems to be to bring a public sector agency, such as WHO, together with Industry into joint ventures with some form of cost sharing. This may turn out to be in the best interest not only of the

developing world (of the 156 member states of WHO 118 are developing countries), but also of several pharmaceutical companies. It should be borne in mind by Industry that WHO has a great deal to contribute to such joint ventures, due to its proven ability to mobilize the most outstanding intellectual resources in any discipline and in any country. Indeed, it may be of some interest to note that several patent applications have already been filed by groups of scientists from several countries working together with the WHO Special Programme in Human Reproduction, and that all rights to these patents have been assigned to WHO to be used for the benefit of developing countries.

It has been stated fairly recently by Simone Weil (La Pesanteur et la Grace, 1967) that "la science, aujourd'hui, cherchera une source d'inspiration audessus d'elle ou périra" (Science, today, must find a source of inspiration above itself, or it will perish). It appears that scientists from more than 80 countries find this new source of inspiration by collaborating with the WHO Special Programme in Human Reproduction, in order to improve the human condition in developing countries.

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