Kor. J. Pharmacog.
생 약 학 회 지
12(3):171~176 (1981)

Extracts versus Pure Compounds Ethnomedical or Folkoric versus Synthetic Chemical Approach*

Helmer Kofod
Royal Danish School of Pharmacy, Copenhagen, Denmark

The title provided by the organizers of this seminar, poses some questions about strategy.

As all good titles it is slightly challenging in its formulation.

I realize, of course, that competent views have already been put forward by Dr. Farnsworth in 1976(Am. J. Pharmacy 1976, 46-52) and by Bonati (J. Ethnopharmacology 2 (1980) 167-171).

My professional platform is that of a natural product chemist educating pharmacists in one of the donor countries, Denmark.

I propose to outline briefly the philosophy behind the two extremes: the traditional ethnopharmaceutical approach and the socalled modern, rational drug design, based more or less on synthetic chemical approach.

Subsequently I shall try to discuss, where to my mind, the WHO project should be strategically placed in between the two extremes, taking the given parameters into account.

The Ethnomedical Approach

Once upon a time it was believed that the divine creator in his infinite kindness had made a specific healing plant species for every disease and disorder, inflicted upon man by his surroundings or by his own stupidity. It was further believed that a proper plant could be picked simply by studying the exterior such as shape and colour. Heart shaped leaves were good for cardiac disorder, red flowers for the blood, and the testis-shaped tuber of Orchis indicated aphrodisiac properties etc.

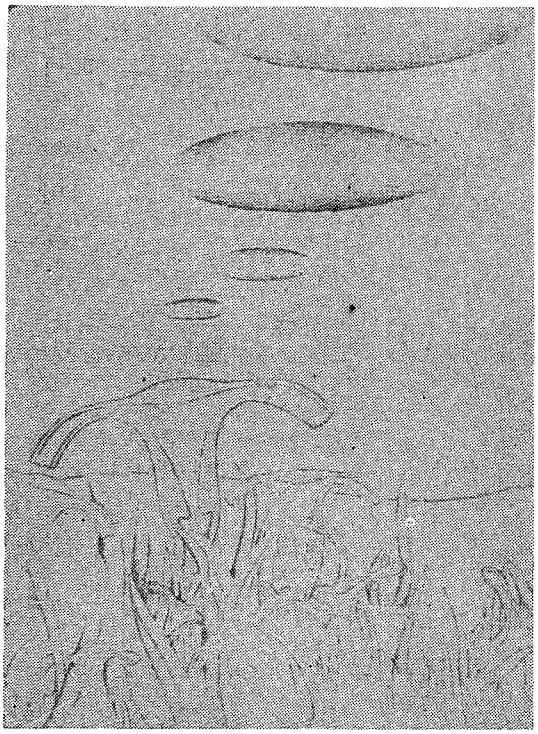
This socalled doctrine of signatures was advocated even by PARACELSUS, who otherwise may be regarded as one of the early pioneers of modern pharmacology, based on chemistry. If the steering committee believed in the signature doctrine we would probably recommend looking into the plant species shown on fig. 1 a drawing by the French artist Frederique Court, who obviously knows something about anatomy! Unfortunately this species does not appear in the Linnæan systema naturae; as a matter of fact not even in the Chicago computor !

We are fortunate in having at our disposal more adequate screening methods for tracing the right plant species.

It is a fact, however, that naive concepts from the signature doctrine and a strong belief in divine providence survive in the minds of large populations also in the industrialized countries. The renaissance of "nature-medicine" in these countries is an amazing fact.

The Danish Parliament in 1975 yielded to a

* Presented 26 February 1981 at the Seminar on Research on Plants and Plant Derived Products for Fertility Regulation, Seoul, Korea. The Seminar was sponsored by the Natural Products Research Institute, Institute of Reproductive Medicine and Population, Seoul National Univerity, the Korean Society of Pharmacognosy andsWorld Health Organization.



firm political pressure and legalized marketing of "nature medicine", exempt from the rigorous scientific proof of identity, efficacy and non-toxicity, which as a sine qua non for registered, official medicine.

This legislation was passed against the advice of all competent scientific authorities. The "green wave" has ideological and political overtones, and it shows how deep-rooted the belief in nature's own products is. Drugs of natural origin are *per se* felieved to be good for you, harmless and suitably balanced in composition, synthetics are "artificial" and by definition bad for you. A "Pure chemical" is in some people's mind almost synonymous with spoiled and unn atural." Chemicals are in wide circles associated with pollution. The "naturists" ignore the fact, that some of the most deadly poisons are produced by nature, not in chemical laboratories, and it is not easy to convince them that ben zoic acid synthesized from toluene and benzoic acid, sublimated from benzoe-resin, are in fact identical in every respect. I mention these observations to show that the psychosocial aspects and acceptability of drugs are perhaps not so different in the industrialized and the developing countries as we often think.

I need not remind this audience that in spite of some naive and primitive deadweight the immense treasures of ethnomedical traditions contain a core of empirical therapeutic knowledge handed down and crystallized through generations. Knowledge which in many cases has been proved by natural science.

In this way we have already got a number of valuable drugs which have either become part of=become part of our armamentarium or opened up new fields for therapy. The far East gave us Ma-Huang (Ephedrine), India gave us Rauwolfia (reserpine). South America gave us chinine and curare, morphine, cocaine,digitalis, vinblastine are other well known examples. Chemical modifications of muscimol made by freezing this molecule in an active conformation seem extremely promising in the development of effective drugs against psychic and neurological disorders, against which only symptomatic therapy has hitherto been available. The last example is taken from my own laboratory.

It is a scientific fact,that plants are far more carable of synthesizing than the most ingenious laboratory chemist. The plant cell performs miracles in overwhelming variety and abundance, working quietly, without high temperatures, without high pressures and without corrosive reagents.

These natural resources are far from being exhausted and I agree, with Dr. Farnsworth, when he speaks of "Higher Plants as the sleeping giant of drug development." To be quite correct the giant does not sleep. We are the

ones that sleep, if we do not make use of the immense resources.

The fact that the giant never sleeps, but produces continuously throughout life very often give rise to difficulties. Contrary to the laboratory chemist the plant does not always finish off the synthesis and present the product. Extraction of an active substance from plant material normally means is breaking into a sequence of processes, hoping that the substance we want, is present in a fair amount before it is transformed into something else. Snapshot of a dynamic situation.

I may perheps add the Dr.Farnsworth in my opinion is too modest when focussing only on higher plants. Those parts of the plant kingd om which we call the lower plants are just as clever synthetic chemists. Think of the ergot alkaloids or yeast or bacteria. In the light of future genetic technology applied to this part of the plant kingdom we may expect wonders.

The Synthetic Chemical Approach to Drug Development

A special klan of pharmaco-chemists, who ften internationally call themselves medicinal chemists, have a dream of what they call rational drug design. Generally and briefly described its philosophy is accumulation of detailed basic insight into the complicated mechanisms of pathogenesis, expressed in chemical language, i.e. in terms of three-dimensional structure of receptor sites, processes and equilibria, including membrane passage. With this knowledge the molecular architect is supposed to go to his desk and design a molecule, which has the desired effect at the proper site in the proper organ. The substance should be stable in its dosage form in the patients bottle, and, when administered orally or otherwise, it should penetrate membranes and other barriers unchanged, reach the target and preferably the target only, exert its effect by releasing a welldefined concentration over a welldefined period of time and finally be eliminated without having done any harmful effects neither on its way to the target nor on its way out.

This kind of rational construction of a chemical missile sounds like science fiction, but so did the idea of military guided missiles only a few decades ago. As a matter of fact various sophisticated pharmaceutical technology is already at hand or rapidly developing, under the general heading DRUG DELIVERY. It includes Molecular manipulations, various new approaches to the prodrug principle, the active substancebeing "carried through" membrane barriers by a protein carrier, subsequently split off at the site of action. It includes controlled-release tablet technology, microencapsulation, covalent attachment to polymer backbones, site-directed chemotherapy with cell specific antibody-drug conjugates, use of erythrocytes as drug carriers, nanoparticles, gelatin microspheres, use of emulsion systems for parenteral delivery and the liposome technique. These key words are actually taken from a symposium on Optimization of drug delivery to be held in Copenhagen round the 1. of June this year by the Alfred Benzon Foundation.

Other interesting techniques are encapsulation of a drug in an iron-oxide-containing microsphere and directing the "missile" by a magnetic field. Transdermal controlled delivery systems are adhesive plaster constructed of polymer membranes, one of which contains the drug, e.g. a hormone. Microsealed delivery devices (MMD) can be implantated subcutaneously and often work as a diffusion pump.

In some cases the "missile" can be placed at the target quite simply by a manual procedure.

This is true of ophthalmological depots and of intrauterine devices. But as we heard this morning fertility regulation has almost a dozen more possible targets less accessible. In these cases modern drug delivery technology may eventually be of interest to reduce quantity, frequency of taken, and toxicity.

Let us come down to earth. Although in the eighies a break-through is anticipated with some of the pharmaceutical techniques mentioned, the ideal, rational drug design is still a dream. Some pharmaceutical companies are deeply interested in the progress in drug delivery systems, but the synthetic approach to the development of new active substances is still largely the classical trial and error method: systematic synthesis of a large number of analogues with or without a natural product as a model, and systematic bioscreening for activity. If you are lucky, perhaps there is something of a lead in one out of 2000 compounds. I think I am right in saying that pharmaceutical companies still feel that searching for the needle in the haystack is more profitable than the immensely costly basic science. Even then the investment in developing one new drug is almost prohibitive due inter alia to the heavy requirements before registration can take place.

After this review of the present situation in drug research in general, let us look at our specific task. WHO

Pregnancy is not a disease. But according to the official definition of health, overpopulation may well be regarded as a social disease in the large body called society.

Neither WHO nor we are indeed to discuss population policy, but only to provide adepuate means for its implementation.

Obviously none of the extremes outlined above are acceptable as such. The question is where in between them are we to place the strategy of the task force project, in order to obtain the most favorable cost/benefit and taking all the rational and irrational parameters into account.

I feel there should be no doubt whatsoever that as scientists our aim and duty is to supply to the third world rational, safe,effective stable chemically welldefined antifertility compounds, formulated in pharmaceutical preparations, designed according to the most advanced technology. There has been incidenses of export to developing countries of drugs (in general) that were not up to standard for registration in the producing country but considered "good enough" for export. From an ethical and scientific point of view this is unacceptable.

Extracts versus Pure Compounds

Scientific aspects: There is in my opinion no scientific arguments whatsoever for using extracts in stead of pure compounds. I fully agree with the response recently given by representatives of the task force to the Advisory group, that "biologically reproducible extracts may have clear advantages in terms of local acceptability and production costs,but they pose formidable problems of standardization and toxicology". It is often postulated, that natural mixtures of compounds often contain secondary or related compounds, which may enhance, potensate or solubilize the active ingredient. In my opinion this is too often marketing arguments for inferior products rather than scientific truth. And if in a few cases there might be something in it, I should strongly recommend to isolate the active ingredient and the alleged supporting compounds, remix them in well defined proportions. Form a scientific point of view I must regard extracts as inferior to pure compounds. When this is said clearly, I admit that

there might be non-scientific reasons for staying satisfied with extracts and not to the highest technological level. The reasons are economic, psychosocial (acceptability by the local population), and institutional strenghtening, which is an integrate part of the WHO object, Let me comment the last aspect first.

Institutional strenghtening (selfreliance, self confidence): Many failures have been experienced by the donor countries in their attemps to transfer highly advanced technology to developing countries, where the population was not yet motivated or educationally prepared to handle it. t has therefore been common in at least Danish administrative language to talk of "appropriate technology" that is a degree of sophistication adapted to the present situation. This aspect may in some cases count in favour of extracts, since they represent—in history of natural product chemistry and in the history of the individual drug—a good step forward and the production can be implemented with relative simple technology.

Economic aspects: Obviously it is cheaper to produce extracts than pure compounds alth ough there are exceptions. It should not be overlooked, however, that the savings in extraction costs may well be lost in time consuming standardization and toxicology test, which for pure compounds often may be executed once and for all, but must be currently made on all batches of extracts, due to the variations. It should also be remembered, that the advantage of a pure compound accomodated in a "guided missile", is that we need only the minute quantity at the site of action, whereas the old fashioned systemic administration requires much larger and wasted quantities in order to obtain the adequat concentration at the target site. In the case of very expensive active substances this may at least in the future be cost saving and balance excess money used in obtaining a pure compound.

Psychosocial aspects: Modern pharmaceutical education has introduced a new concept: patient compilance, i.e. the extent, to which the patient actually follows instruction, verbal and printed. This has something to do with ability to read, with selfdiscipine and with acceptability of the dosage form. It has become almost a ritual to take "pills" in the western countries. Some claim it a part of the therapy, distracting you from your symptoms, and call it placebo effect. In other cultures other rituals prevail as natural. I am not capable to evaluate whether an extract is more acceptable than a tablet or a device, but such emotional, religious and traditional attitudes are obvious important for patient's compliance. I have been told that chinese tradition e.g. does not distinguish between food and medicine in the way we do in the western countries. The chemists answer to the first "versus" therefore must be: Pure compounds, unless economic and/or psychosocial indications force us to compromise and choose extracts or even decoctions.

Folkloric versus synthetic chemical approach: Those advocating the synthetic approach strongly, may well postulate that local institutional strenghtening, cost-saving of psychosocial arguments are the only ones in favour of the ethnomedical approach.

Contrary to this attitude I believe there are genuine scientific reasons to continue the ethnomedical approach. In the later phases of the development it will, however, invariably involve synthetic work as part of structural elucidation and/or molecular manipulations with the aim of improving efficacy, reducing toxicity and optimizing drug delivery. But I have no doubt whatsoever that much inspiration is still to be found in nature's own laboratory.

In fact we are planning the 19th Benzon symposium to be held in Copenhagen in 1983 with the working title: Natural products as leads in drug development.

A prominent scientist has pointed out that this type of research on fertility control is exceedingly complicated. He concludes that even though fertility regulating compounds may be used predominantly in developing countries, they will almost certainly be generated in North America or Europe. Even if this turns out to be correct, there is ample justification for the ongoing work in the task force with its dual object of research and research development and education.

You would hardly expect me to conclude otherwise at the end of the seminar. But I emphasize that I have reached the conclusion not by loyalty to the steering committee, but on the basis of scientific judgment. I was therefore happy to learn just before I left Copenhagen, that the Danish contribution to the Special Programme in 1981 had avoided the drastic budget cuts, which we experience in almost any research funding today.