# New Drug Development — The Indian Scene☆

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'Medicines for the masses' and 'Health for all by 2000 A.D.' are slogans with which we are all familiar. The importance of the theme is underscored by the fact that the Indian Government is at the threshold of announcing a new Drug Policy. This is expected to give a fillip to the Indian drug industry which for a variety of well-known reasons has not grown recently at a rate which would have let it attain the targets of the sixth and seventh five-year plans. The subject is also the theme of several symposia organised by different cross sections of the society.

The pharmaceutical business stands apart from other types because of the much higher rate of obsolescence of it's products. The business has still thrived well in the western countries, because of their heavy investments in new drug development. This in turn has bee possible because of the industries' good profitability arising from relatively fewer government restrictions and the possibility of having full proprietary rights on new discoveries for periods long enough to allow reasonable pay-backs. The Western Society and even more so, the entire world community has benefited from their R & D discoveries, as witnessed by the availability of a large number of valuable drugs for a variety of diseases, including those from the group labelled as 'tropical diseases'.

It shall therefore be a natural matter of concern for us to monitor continuously and assess frequently the status of new drug development in India. This activity itself is relatively new to this country, if we think of 'allopathic' drugs, i.e. new chemical entities developed along modern and scientifically and statistically validated lines, used singly or in known combinations. This is in contradistinction to 'Ayurvedic' drugs, which have an ancient history in the country and have made their own known contributions to health care. Systematic attempts at new drug development may be considered to have started after our independence at Central Drug Research Institute, Lucknow. Other institutions devoted to this pursuit were established subsequently.

The results of their efforts were reviewed by the author in 1981 (K. Nagarajan, 32nd Indian Pharmaceutical Congress, Nagpur, January 23-26) and in 1982 (K. Nagarajan and V.P. Arya, J. Sci. Ind. Res., 1982, **41**, 232). More recently, Prof. Harkishan Singh and coauthors have brought out a monograph (Medicinal Chemistry Research in India, published by National Information Centre for Drugs and Pharmaceuticals, Central Drug Research Institute, Lucknow, 1985) which covers the area exhaustively and documents the results.

The subject matter of new drug development crops up again and again in seminars and symposia. Matters like the areas of research, orders of investments and responsibilities of various sectors of the Indian Drug Industry — Public and Private, big and small, national and multinational are discussed with a degree of seriousness commensurate with the relevance of the subject to the community. Unfortunately, rather more frequently than what is desirable, the discussions tend to get tinted with sectoral emotions, producing more heat than light. Thus as recently as on March 9, in a symposium on 'Future trends in the Pharmaceutical Industry' organized by the Indian Pharmaceutical Association in Bombay, some speakers identified problems associated with new drug development by the Indian industry, such as insufficient investments arising from inadequate profit margins and drug regulatory and pricing restrictions. A letter to the Times of India of April 1, provides an amusing sequel, which is also illustrative of the utter confusion clouding the subject: "Even if we pool 5% of our total turn-over of Rs. 1800 crores, it will provide Rs. 90 crores to introduce two new drugs every year... What have they (Indian Pharmaceutical Industry) done all these years? This was certainly an 'eye-wash' show by the IPA, when the new drug policy is soon to be announced. If the pharmaceutical industry and especially the multinationals honestly desire to develop new drugs for tropical diseases, they should con-

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tribute at least 5% of the total turnover as R & D to be handed over to the national research laboratories. Only then should they be allowed to squander the present 2% as R & D expenditure towards unethical promotion of unwanted and hazardous drugs".

It will be useful for us first to take a quick look at what is involved in developing new drugs. We shall then expose ourselves to what has been achieved so far in India and evaluate it in terms of our inputs and requirements. We can further recognize possible lacunae and ponder over remedial action.

The process of drug development is complex in nature and multidisciplinary in requirements. The subject has been reviewed by several people including the present author (in Research and Development in the Pharmaceutical Industry, Current Trends, OPPI, Bombay 1977). Stated briefly it is as follows: Research programmes and projects are identified by drug development groups taking into account medical needs of the environment, marketing inputs, financial considerations, divisional policies and state of the art research ideas. The actual process begins in a chemical laboratory, where, after interaction of chemists with biologists and based upon folk-lore medicines, biochemical concepts or novel chemical ideas or insights, a new synthetic compound or a plant extract or pure plant product is prepared. These are handed over to various biologists for preliminary screening in a variety of animal models or other test systems for various indications. Often a blank is drawn in this process, but once in a while a lead is found. The chemist intensifies his efforts now and using institution and semi-empirical or quantitative methods or molecular modelling, optimises the lead — viz. prepares a compound which has an optimal level of desired activity in chosen test systems, comparable to that of a standard if one exists. From this point onwards, the candidate drug follows well-defined stages. Thus the compound undergoes extensive toxicological studies in several species of animals, to ensure that eventually humans can take it without risk. Biochemical information is also gathered about the fate of the drug in experimental animals — how long it stays in the system and how it is distributed, how much of it remains intact and how much of it is transformed into 'metabolites'. The galenical group gets busy around this time in formulating the preparation in the form of tablets or capsules for human administration. The enormous amount of data generated is presented to the Drugs Controller of India with a request for permission to do Phase I clinical trials in the humans — through accredited clinical pharmacologists of leading medical colleges. With this permission, trials are initiated in volunteers in hospitals. Under careful medical supervision, the tolerability of the preparation is ascertained. If this goes through uneventfully, the preparation proceeds to Phase II. Again with the DCI's permission, the efficacy of the preparation in a given disease is investigated in dose-searching studies. These are usually followed by a double-blind comparison of the preparation with a standard drug in patients through doctors. Both would be kept ignorant of the identity of the pill they are handling to prevent biased evaluations. Successful trials would let the preparation advance to the next stage, Phase III clinical trials. Long-term toxicity studies involving feeding of the preparation for 3-6 months to two species of animals (rats and dogs) would have been initiated by now, as also detailed biological studies as well as metabolic studies, some of them in humans. Based on these data, the DCI gives permission for multicentric Phase III trials which are carried out in different parts of the country. The data are pooled and analysed and, if favourable, presented to the DCI who will give registration for the drug and allow it to be marketed. These three phases of drug development take from 8 to 10 years and presently, internationally the odds are about 1 in 15,000 for a new preparation to reach the market, and the cost of developing one is placed roughly at around Rs. 60, crores. The actual introduction of a new drug in India requires additionally an industrial licence from the Government.

The time frame for the development of a new drug is shown schematically in Chart 1. Table 1 gives a rough breakup in % of the cost in terms of the various activities involved. It is to be noted that safety assessment is as costly as the discovery process as well as establishment of activity/efficacy. In fact, increasingly stringent government regulations have pushed up the cost of safety assessment to phenomenal heights. Table 2 illustrates the heavy odds of finding a new chemical entity with clinically useful antimalarial properties.

CHART — I

**Time needed to develop a drug**

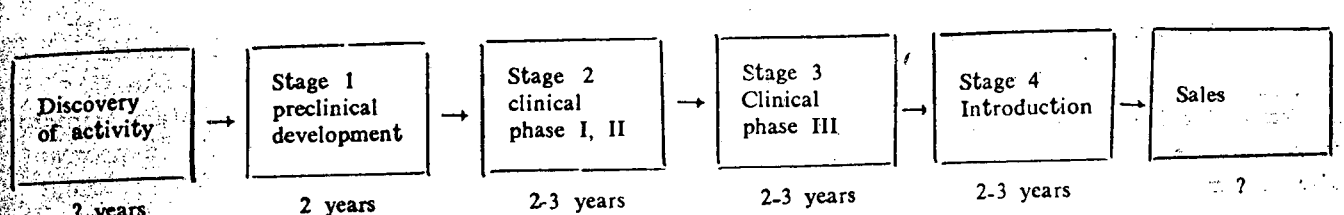



**TABLE 1 WHERE DOES THE MONEY GO IN BASIC RESEARCH FOR DRUG DEVELOPMENT?**

**(J. Thesing, Industrielle Arzneimittel Forschung, Voraussezungen and Moeglichkeiten, Edito Cantor Aulendorf 1977)**

1. Synthesis/isolation of natural products — 19%
2. Discovery of biological activity — 12%

→ 31% — Search for new active substance

3. Extended animal studies — 12%
4. Toxicology — 10%
5. Metabolism and Pharmacokinetics — 7%
6. Analytical research — 5%
7. Tolerability and activity in man — 16%

→ 24% — Activity, efficacy*

→ 26% — Safety**

8. Galenics — 7% → 7% — Optimal formulation
9. Manufacturing process — 12% → 12% — Price of bulk drug

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

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

TABLE 2

What are the chances of finding a drug?
The malaria problem

| | |
|---|---|
| The Walter Reed Institute of Research Programme : | |
| Tested since 1964 | 380,000 compounds |
| Active in mice | N 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.

The Indian scene can now be surveyed with respect to new drug development. It is obvious that in assessing the outcome, only laboratories with the requisite multidisciplinary set-up would be in a position to contribute. The earliest such institution was the Central Drug Research Institute, Lucknow, set up after independence. IDPL Research Centre at Hyderabad came much later. In between, a few members of the private industry established basic research centres. The more important ones are those of Hindustan CIBA-GEIGY, Hoechst, Sarabhai, SKF and Boots. Of these, SKF Research Centre has confined its activities to antibiotics, while the Sarabhai Centre is reported to have closed their new compound synthesis programme. The outcome of their research activities which span a period between 6 to about 35 years (depending upon the institution) has not been insignificant. Overlooking compounds that failed in the clinic or which were only hot leads and discounting new ones that are at a very early stage of development, those that have been registered as drugs or which are under clinical trials in some phase are noted in Charts 2-8. It is immediately seen that the activities cover an entire range of indications of 'tropical' and 'non-tropical' diseases. Among these preparations, **1, 4, 5, 6, 9, 10, 12, 14, 17** and 24 are drugs which have been offered registration by the Drugs Controller of India. The rest are in various phases of clinical trials.

The proof of the pudding lies in the eating and hence for the purposes of our study, we have to look at the drugs that are actually sold, which have arisen out of the new drug development efforts of our country. We then find that the following are available :

| | |
|---|---|
| Urea Stibamine (5) | Antikala Azar |
| Methaqualone (14) | Hypnotic |
| Hamycin (6) | Antifungal |
| Tromaril (17) | Antiinflammato |
| Sintamil (10) | Antidepressant |
| Cibemid (4) | Antiprotozoal |

The following are to be noted : Urea sti mine and hamycin are mixtures. Sales of former are either negligible or nil, perhaps cause of nonincidence of Kala Azar in the co try now (although there was an outburst so years ago). Methaqualone was discovered in dia, but the actual development and market were carried out from abroad. Cibemid is lik to be marketed only in 1987, while many ot registered drugs have not been commercialis for various reasons. The total sales of hamyc sintamil and tromaril are likely to be less th Rs. 3 crores per annum. The last two were d covered in 1964 and 1966 respectively, but ma keted in 1982 and 1981.

Before this performance is assessed, so other essential inputs need citation. The fi and foremost is the investment. The turnover the Indian Pharmaceutical Industry was arou Rs. 2000 crores in 1985, with a growth rate 13.3%. A new era of growth is expected due the new, hopefully progressive and liberal Go ernment Policy to be announced. Investment basic research for new drug development is p bably less than Rs. 15 crores per annum at t moment. This is to be contrasted with t international scene, where a firm like CIB GEIGY alone spent about Rs. 150 crores on pha maceutical R & D, and the turnover of the pha ma division of this single, multidivisional co pany exceeded the total turnover of the Indi Drug Industry in 1984. Among various oth factors responsible for the much lower inve ment in research for new drugs in India are t related to the Government policies concerni product and intellectual proprietary rights new drugs (brand names and patents). The are both restrictive in nature and consequen detrimental to investment in innovation.

Another factor meriting our attention is t following. Major new drug developments abro have now come about as a result of basic d coveries in understanding disease processes the cellular and molecular levels. Breakthroug

in genetic engineering have also contributed significantly. Instant awareness of the latest developments coupled with the availability of expert biologists of different hues has played a pivotal role in the West in dramatic developments in drug research. Unfortunately, we are neither blessed abundantly with such schools of research nor is the country in the path of international lecture circuits which offer vicarious experience to the listeners.

Taking all these factors into consideration, we find that the progress we have made has been satisfactory but not exciting. It is obvious that greater incentives are needed from the Government to encourage and sustain innovation and more investments are needed from industry. It is certainly a far cry from the 10-15% international figure to the 1% Indian figure (about 2%, developmental expenditure is also included). A favourable pricing policy from the Government, reintroduction of weighted tax deduction and relaxation of curbs on proprietary rights may spur such increased investments. The 'national' sector of the Indian Drug Industry has certainly come of age and there are a number among them now whose turnover would permit them such investments. Having scored commendable victories in the arena of process development for 'imported' drugs, it can turn its sight to developing new 'national' drugs. At any rate, there is no justification for us to beat our breasts and cry that others are not bearing our cross!

This in turn leads one to the question concerning the areas of research for new drug development. We have to look at the problem from two major angles which have been mentioned earlier; namely, market analysis and medical needs. Table 3 gives a break-up of the major share of different classes of drugs in India accounting together for about Rs. 710 crores. Table 4 names the top ten pharmaceuticals in the Indian Market. We note with interest that antibiotics/antibacterials and vitamins are carrying the day; and apart from these, Brufen, an anti inflammatory drug is the third largest selling drug. The total market in fact for the latter drug (brand name and generic) is over Rs. 15 crores!

Let us look at our medical needs on the other hand. We have heard repeatedly about the 'tropical diseases', to which research is exhorted

**TABLE 3**

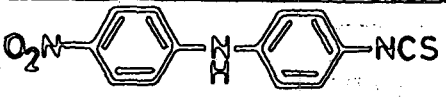
**MARKET SHARE OF DIFFERENT CLASSES OF DRUGS IN INDIA (1985)**

| Group | Rs. (crores) |
|---|---|
| ANTIBIOTICS | 260 |
| VITAMINS | 098 |
| ANTIRHEUMATICS | 057 |
| COUGH, COLD REMEDIES | 055 |
| ANTIPARASITICS | 049 |
| ANALGESICS | 047 |
| ANTIAMOEBICS | 045 |
| ANTACIDS | 040 |
| TONICS | 037 |
| ANTI-TB | 031 |

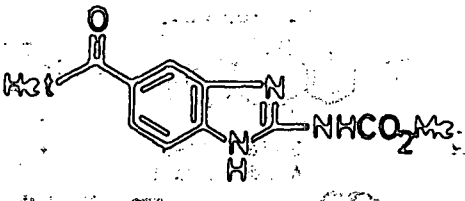
**TABLE 4**

**TOP TEN PHARMACEUTICALS IN THE INDIAN MARKET (1985)**

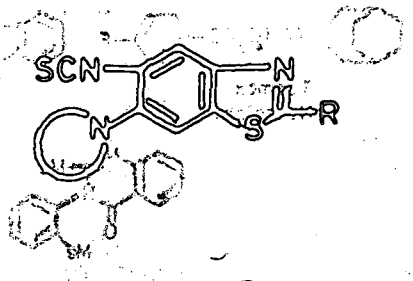
| Name Of Drug | Annual Sales (Crore Rs). |
|---|---|
| SEPTRAN | 18.71 |
| BECOSULES | 13.01 |
| BRUFEN | 09.84 |
| DEXORANGE | 08.44 |
| RESTECLIN | 08.01 |
| BARALGAN | 07.82 |
| BACTRIM | 07.71 |
| AMBISTRYN | 07.36 |
| ROSCILLIN | 06.98 |
| TERRAMYCIN | 06.76 |




Amoscanate - Anthelmintic, Antifilarial.

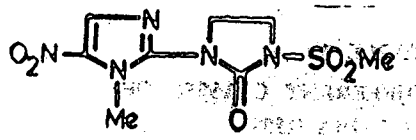



Anthelmintic




Antifilarial.

CHART 2



Clbemid
Antiprotozoic

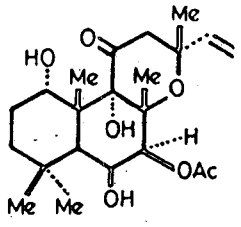
Urea-Stibamine (1922) (for Kala Azar)

Mixture of Urea $p\text{-AcNHC}_6H_4SbO_3H_2$ $(p\text{-}H_2O_3SbC_6H_4NH)_2CO$
Unknown Sb.org.compd.

Hamycin (1961)

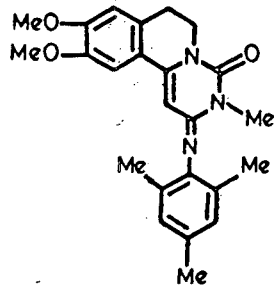
Polyene Antifungal
(Mixture of A,B,C and D)

## CHART 3



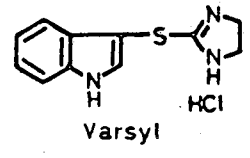
Forskolin (Coleonol)
from Coleus forskohlii
Antihypertensive, positive inotrope
Clinical trials for glaucoma.

7



Trequinsin (Antihypertensive)

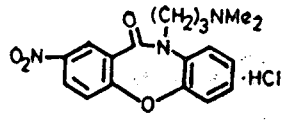
8



Varsyl
(Nasal Decongestant)

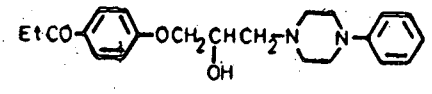
9

## CHART 4



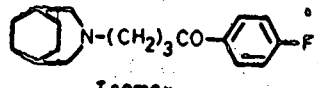
Sintamil (1964)
Antidepressant

10



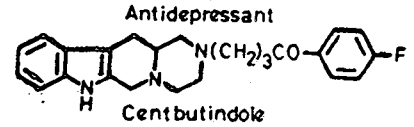
Centpropazine
Antidepressant

11



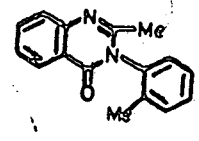
Taomex
Neuroleptic

12



Centbutindole
Neuroleptic

13



Methaqualone (1955)
Hypnotic

14

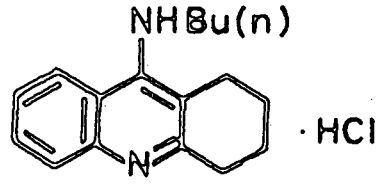
## CHART 5

to dedicate itself. According to WHO, these diseases are (1) Filariasis; (2) Leishmaniasis (Kala Azar); (3) Leprosy; (4) Malaria; (5) Schistosomiasis; and (6) Trypanosomiasis. Of these, Leishmaniasis may not be a serious problem now, while schistosomiasis and trypanosomiasis are not endemic to India. On the other hand, parasitic infestations like helminthiasis and amoebiasis and bacterial infections like tuberculosis have come to be identified as 'national' tropical diseases'. Additionally, although fertility is neither 'tropical' nor a 'disease', drugs or devices for fertility control ought to be considered to have national priority.

If we juxtapose these against treatment available, we find that satisfactory and relatively 'modern' products are on hand for most indications, with the possible exception of filariasis: Rifampicin, Ethambutol, Isoniazid, Pyrazinamide (for TB), Dapsone, Rifampicin, Clofazimine, (for leprosy), Mebendazole, Pyrantel, Laevamisole (for helminths), Metronidazole, Tinidazole, Diloxanide Furoate (for amoebiasis); Chloroquin, Primaquin, Daraprim, Sulphadoxine, Trimethoprim (for malaria), Diethyl Carbamazine (for filaria), Contraceptive steroids, physical barriers (for fertility control). We note parenthetically that all these drugs have been the discoveries of the "infamous Triple M", the much-maligned-multinationals, a large number of them introduced in the last two decades. Filariasis is still not satisfactorily conquered, but here again some important drugs like ivermectin, amoscanate, laevamisole, mebendazole, flubendazole and two benzothiazole isothiocyanate derivatives are under clinical trials. Resistant malaria does pose a problem; however, mefloquin is a

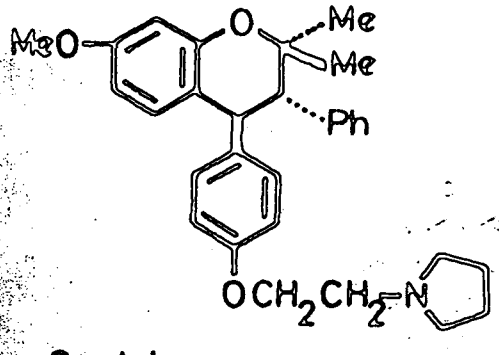
reserve drug for this purpose, while a new one, a derivative of dihydroratmesenin is on the scene. Moderate efforts for filaria and massive ones for malaria are also being increasingly deployed all over the world for developing prophylactic vaccines. Let us note carefully that for all the problems that have been outlined, important community measures rather than drugs will offer permanent solutions. Thus improved community hygiene and protected water supply can help us get rid of helminthiasis and amoebiasis, while adequate vector control can hopefully eradicate filaria, malaria and leishmaniasis. On the other hand, lapses in such measures will contribute to the vexatious problem of reinfection. Increase in the national nutritional status together with improved hygiene can control the TB problem. Similarly, with respect to fertility control, the difficulty is not one of availability of tools (drugs or physical barriers) but reaching them to the masses in the far flung villages of India and persuading the rural women to practise family planning.

It is often said that drug prices are high in the country. This is incorrect, since our prices




15

Centbucridine
Local anaesthetic




16

Centchroman
Antifertility agent

CHART 6

are some of the lowest in the world. It is possible that in relation to the low living standards in India, drugs could be priced lower for masses to be able to afford them, but it should not be forgotton that the cost of drug inputs is high in India and has been increasing steadily, productivity is low and economies of scale are unavailable. Drug prices have also to be compared with prices of items of daily life like cereals, milk, oil, etc, which are admittedly very high. It is a fact that sections of our population cannot afford drugs. This calls for subsidies from the Government.

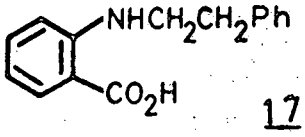
From the point of view of new drug development in terms of national needs, we have noted the status with respect to filaria, malaria and leprosy. But let us not ignore the fact that these are areas wherein the returns will not be commensurate with the investments. We must also give weight to the well-known fact that increasing urbanization, competition, stress and crowded living are responsible for increased incidence of the diseases of the "affluent" — cardiovascular disabilities, central nervous system disorders, allergy, arthritis, ulcer and diabetes. Marked increase in longevity of the average Indian has exposed him more to such problems and even to cancer. To cap it all, increased awareness helped by modern physical and biochemical diagnostics has resulted in greater appreciation of the incidence of the maladies and this is the segment of the population that can afford treatment to at least some extent. Simultaneously, these are also areas which offer scope for the introduction of better and safer drugs.

It is, therefore, desirable, if not mandatory, that efforts towards developing new drugs for these diseases are alloted and these should not be considered as 'antinational' We should also not be blind to the fcat that unique and useful products like the antiulcer drug, Cimetidine, enjoy a world market of nearly one billion dollars of Rs. 1200 crores. It should be more profitable to discover, develop and export such drugs than drain the brains which may produce them. In fact entry into the international market may even be a prerequisite for the viability of ventures of new drug development in India. However, this would require an extensive organizational set-up and reciprocal subscription to intellectual proprietary laws.

Before concluding this article, a few words must be said about drugs from natural products

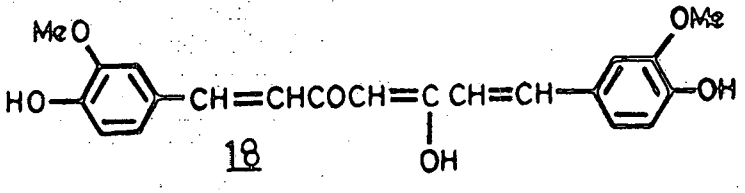
(Natural Products and Drug Development Ed. P. Krogsgaard — Larsen, S. Brogger Christensen and H. Kofod, Munksgaard, Copenhagen 1984) The Ayurvedic system uses many crude plant extracts singly or in combination. Validation of their claims by modern clinical methods and standardisation in terms of active constituents using spectroscopic analytical techniques are very difficult and it is gratifying to see that efforts and resources are being increasingly employed towards realizing these objectives. Isolation of pure, single substances, with desirable biological activities and their subsequent development pose equally difficult problems, but may be more rewarding in the long run. The odds of finding a useful, new plant product are not good, but probably not very much worse than a synthetic compound.

The story did not end with reserpine; vi cristine appeared on the scene some years ag But these Indian plant products were develop abroad. Forskolin promises to be a new add tion. From the Guggu lipids, active ingredien have been isolated in the pure state. Curcumin usefulness as antiinflammatory agent is und clinical verification. These are all of Indian or gin, while the recently discovered antimalaria artemesenin is from a Chinese plant. We hav several plants belonging to this species awaitin examination. Indian researchers engaged in ne drug development need not shy away from pla products, because these have been abandone elsewhere in the world, but they must try t wreast new useful drugs from an unwilling bu abundant natural resource which the country blessed with.



17

Tromaril ( 1966 )
Anti-inflammatory



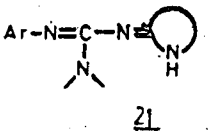
18

Curcumin from Curcuma longa ( turmeric )
Anti-inflammatory.

Guggulipid from Commiphora mukul resin - Antihyperlipidemic 19

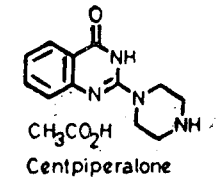
Salai guggal - oleoresin of Boswellia serrata - Antihyperlipidemic 20

## CHART 7



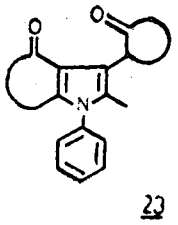
Antihyperglycemic

21



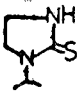
Centpiperalone
Antihyperglycemic

22



Hypoglycemic

23



Centimazole
Antithyroid

24

## CHART 8