

*G. Richter*

# THE HUNGARIAN PHARMACEUTICAL INDUSTRY (N 1980)

Although, there was a large-scale drug production on progress in Hungary already in the past century, 1901 can be considered as the year of birth of the Hungarian pharmaceutical industry, the year when Gedeon Richter has received the authorization to produce drugs in his pharmacy of Budapest.

The aim of this publication is to demonstrate concisely the Hungarian pharmaceutical industry, its production and research activity, and the part it plays in the international commerce of pharmaceutical and related products.

**PRODUCTION**

# The development of pharmaceutical production on industrial scale in Hungary

In Hungary, initiatives for the starting of pharmaceutical production on industrial scale had been taken relatively early.

In 1867 was founded the first pharmaceutical enterprise under the name of Hungarian Pharmaceutical and Technical-Chemical Company. At that time, in Europe, only in London, Paris, Milan and Brussels were functioning associations of similar tasks.

The first Hungarian pharmaceutical company mentioned worked for 45 years, it was liquidated in 1912. In the meantime however, in particular after the turn of the century, new industrial enterprises were established mainly out of chemist's laboratories. To the most successful ones belonged the firm of Gedeon Richter, incorporated in 1901, then the company of Dr. Emil Wolf, the Alka Chemical Works founded in 1910, adopting in 1913 the name Chinoin, further the subsidiary company of the Swiss firm Dr. A. Wander founded in 1912 in Budapest, the aim of which was to supply Austria-Hungary, the Balkan states and Russia with the well proved preparations of the parent company in Bern.

The rapidly increasing internal demand on human and veterinary preparations and the export possibilities focussed on the countries of South and Eastern Europe aroused the interest of entrepreneurs in pharmaceutical production. In this field they could rely upon the home raw materials necessary for the production of preparations of vegetal and animal origin. Since there was no organic che-

mical industry in the country, the organotherapeutical and phytochemical products played the decisive part, and synthetic preparations have come into prominence gradually only later.

In 1927 the Alkaloida Works were founded, based on the licence of János Kabay, which started with the processing of dry poppy-heads, and this permitted—for the first time in the world—the starting of the production of morphine alkaloids on industrial scale without needing opium further on as a raw material. Since that time the balance of the Hungarian drug foreign trade has become permanently positive and remained favourable even during the world economic crisis in 1929–1933. Thus, the development of the pharmaceutical industry, by overcoming many difficulties, could be made continuous. At the end of the thirties, that is in the period immediately before the outbreak of the Second World War, 36 drug manufacturing firms were working in Hungary, some of them had subsidiaries abroad, too. Drug imports constituted 60 percent of the exports. Forty-two countries were supplied with drugs produced in Hungary.

The Second World War has broken the progress of the Hungarian pharmaceutical industry. The ravages by war have caused immense material and personal damages to the country, included the pharmaceutical industry, too. The efforts made following the first post-war years were concentrated on the liquidation of damages and on the reconstruction. The factories, plants and laboratories have been

nationalized, and after reasonable amalgamations and reorganizations the Hungarian state drug industry has reached in 1949 its pre-war level (that of 1938).

The production was centralized in eight large enterprises, their production range was established and the necessary modernizations effected by means of a resolute policy of development and investment.

Six of the enterprises are functioning under the direction of the Ministry of Industries. The coordination of their activity is provided by the Union of the Hungarian Pharmaceutical Industry. The Phylaxia Veterinary Biologicals and Feedstuffs Ltd. is controlled by the Ministry of Agriculture and Food, the Institute HUMAN for Serobacteriological Production and Research by the Ministry of Health. The registration, authorization and control of the products for human therapy of all producers is effected, of course, by the competent organs of the Ministry of Health. As to the veterinary products this task is provided by the Ministry of Agriculture and Food.

The right of drug export and import was assigned to one enterprise, MEDIMPEX (Hungarian Trading Company for Pharmaceutical Products), controlled by the Ministry of Fo-

reign Trade. The home distribution is carried out through one wholesaler (Company for the Marketing of Pharmaceutical Products) and through pharmacy centers, of which 19 are to be found in the province and 1 in the capital.

### **Some data about the production of the Hungarian pharmaceutical industry**

The number of employees is at present nearly 24,000. The magnitude, number of staff, production line and product structure (assortment) of each enterprise are different, thus they represent a different proportion both in the production and exports (Fig. 1).

More than 80 percent of the production consists of the manufacturing of active substances and finished pharmaceutical preparations for human and veterinary use. These represent the majority of exports, too, although the proportion of plant-protecting agents shows a rising trend both in production and exports (Fig. 2—3).

# THE GROWTH OF HUNGARIAN DRUG PRODUCTION RELATED TO 1960

(1960: index = 1)

20 Index

15

10

5

1960

1965

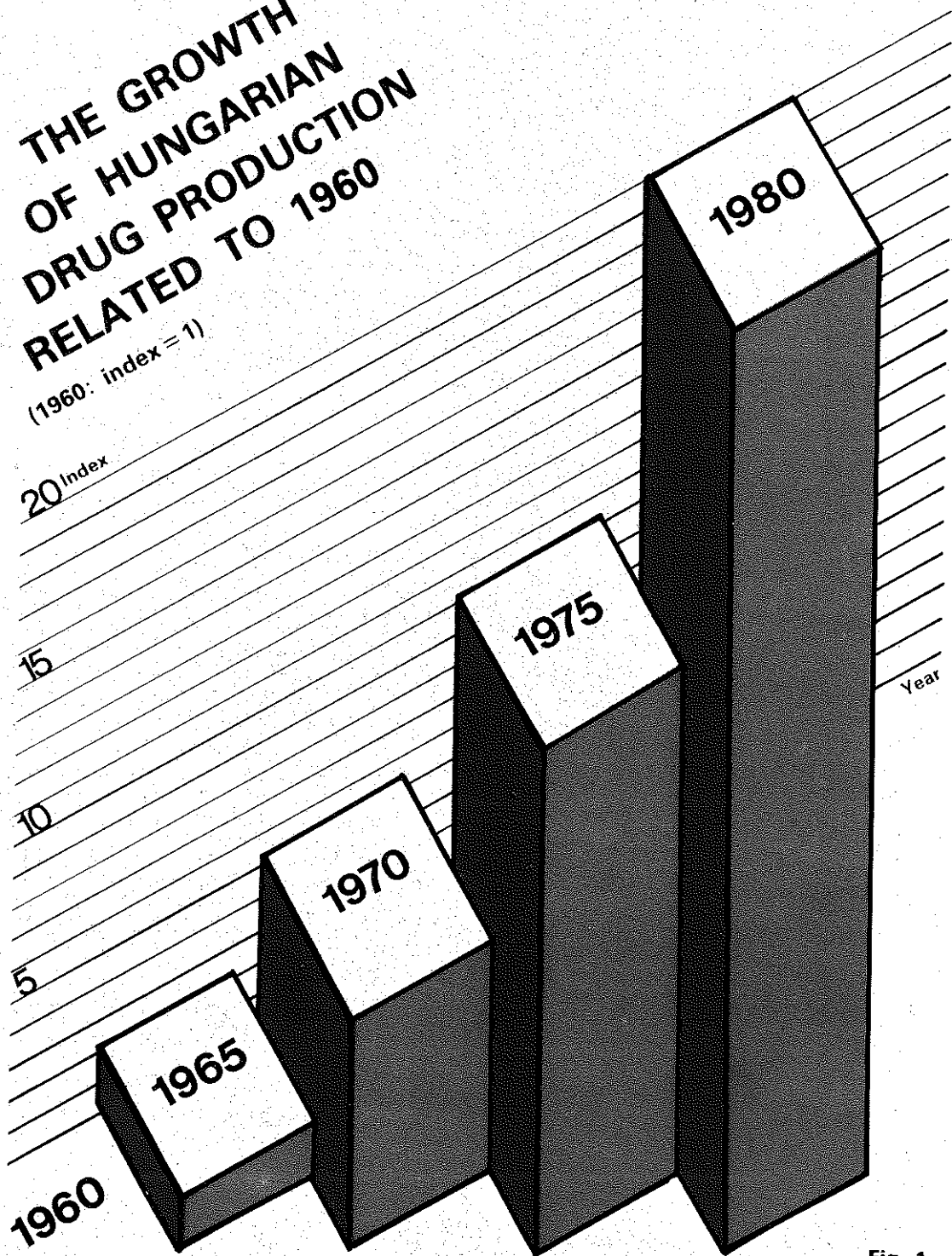
1970

1975

1980

Year

Fig. 1.



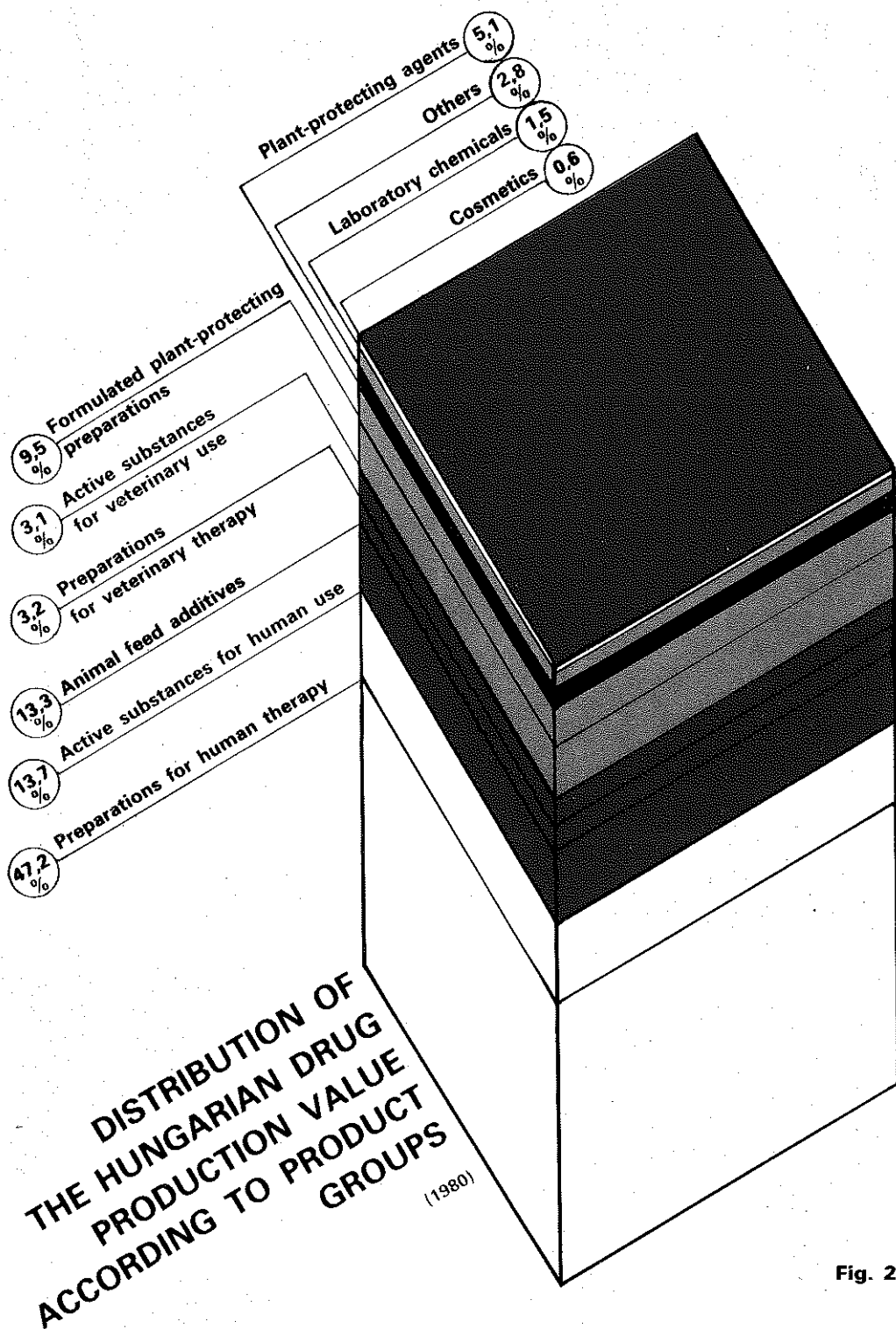


Fig. 2

# DISTRIBUTION OF THE HUNGARIAN DRUG PRODUCTION VALUE ACCORDING TO MANUFACTURING COMPANIES (1980)

UNION OF THE HUNGARIAN  
PHARMACEUTICAL INDUSTRY

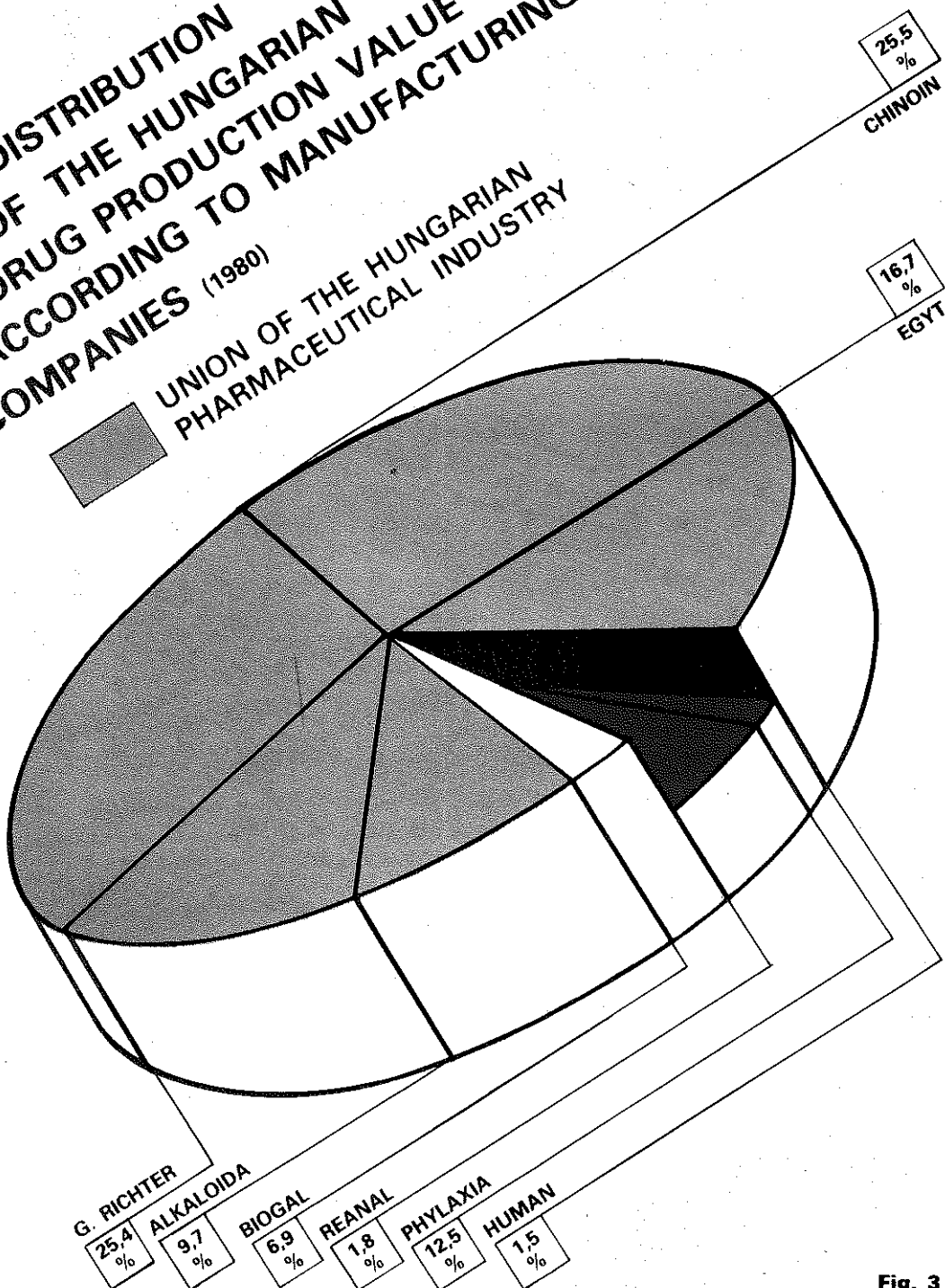


Fig. 3



# Production units of the Hungarian pharmaceutical industry

(in order of their foundation)



## CHEMICAL WORKS OF GEDEON RICHTER LTD.

1103 Budapest, Gyömrői út 19–21 (central establishment)  
1475 Budapest, P.O.B. 27 (postal address)

The CHEMICAL WORKS OF GEDEON RICHTER Ltd., founded in 1901 is the oldest among the pharmaceutical factories, working today in Hungary. Regarding the production value and exports they take the second and first

place respectively. As far as the staff number is concerned, they occupy the second place (almost 5,400 persons).

Among the *organotherapeutic* drugs belonging to their production range—apart from the traditional enzyme, liver and biliary acid preparations—it is the heparin which is produced in RICHTER's biochemical plant by using their own method; with this product the company has become one of the greatest heparin producers of the world. The raw materials required for the production of organotherapeutic products is covered by the expert collection of animal organs through a special country-wide network.

The manufacturing of a fairly high number of drugs with *vegetal basis* (*digitalis*, *ergot*, *Catharantus roseus*) is going on at RICHTER and the company's experts render agro-technical help to the large-scale cultivation of the used Hungarian medicinal herbs, too. For the processing of vegetal raw materials the continuously operating so-called "U" extractor was constructed by the experts of the company.

The manufacturing procedure of vitamin B<sub>12</sub>, based on non-sterile fermentation elaborated by the researchers of the enterprise occupies a prominent place among *fermentation* technologies. Ergot alkaloids and some steroid compounds are produced by sterile fermentation by the use of modern instruments.

Most of the products are manufactured by *synthesis*. The work of the well-trained staff and the modern equipment allow the implementation of such delicate procedures of high volume, as the manufacturing of semi-synthetic steroids (natural hormones and their synthetic derivatives).



*The Pharmaceutical Factory of Kőbánya (Budapest) is one of the largest and most up-to-date confectioning plant of Central Europe — packing and preparing plant of the Chemical Works of Gedeon Richter, Ltd.*



The modern oral contraceptives play a prominent part in family planning.

Among the synthetic preparations, representing a lower order, the production of peptide hormones is significant.

RICHTER produce about 150 active principles, a great part of which is marketed in form of proprietary drugs. Several hundred millions, of ampoules, several thousand millions, of tablets and coated pills, as well as other dosage forms are produced yearly in the finishing and packing plants of the company.

From the beginning of the year 1970, for a better exploitation of experience, acquired in the field of drug production and research, in addition to human and veterinary medicines, the company has extended its activity both in Budapest and in its provincial workshops to the manufacturing of other related products, too, like the production of biocosmetics, e.g. the Fabulon family of products, rather popular since that time, as well as of agricultural chemicals, primarily of plant-protecting agents and feed additives.



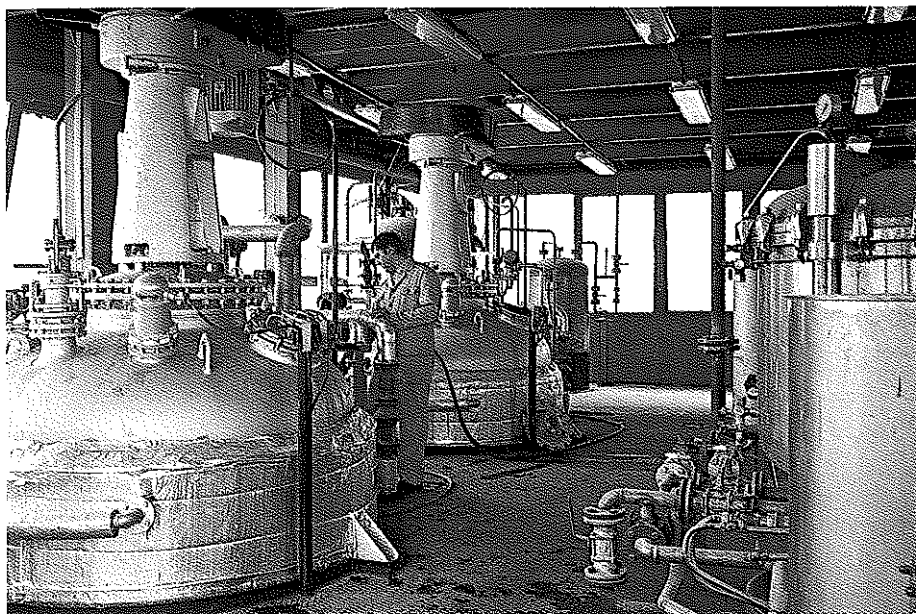
## CHINOIN PHARMACEUTICAL AND CHEMICAL WORKS

1045 Budapest, Tó u. 1-5 (central establishment)

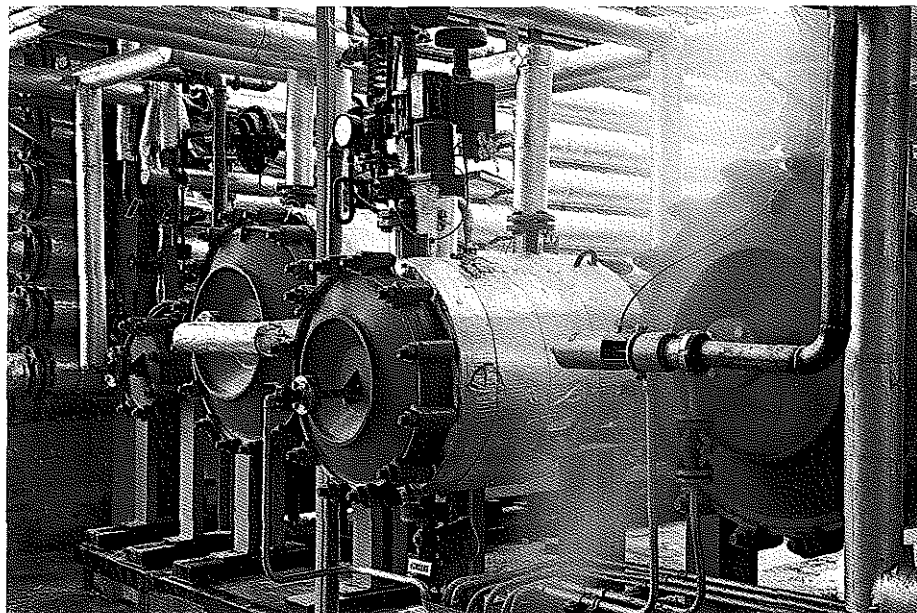
1325 Budapest, P.O.B. 110 (postal address)

CHINOIN were founded in 1910. The number of their staff is the highest among the Hungarian pharmaceutical companies, nearly 5,800 persons, their exports hardly match those of RICHTER.

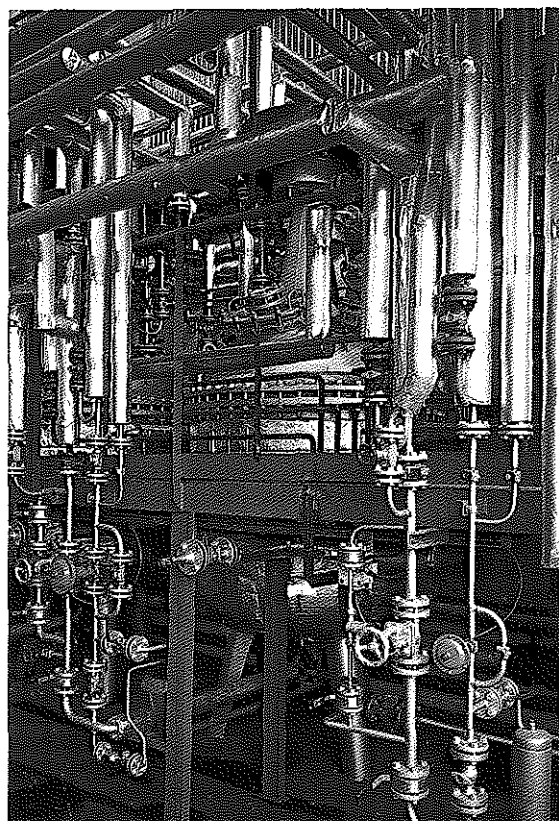
The company manufactures a wide variety of *synthetic* compounds. The most important of these are papaverine and its derivatives, the large scale production of which by synthesis was solved first in the world by CHINOIN. The enterprise has done a pioneering work in the development of the industrial production of sulfonamides. The multiple-stage high-volume synthesis of a number of antihypertensives, diuretics, analgesics, chemotherapeutics and other pharmaceutical fine chemicals is being carried out. The research and production of two important compound groups were effected at a quick



Chinoín (Budapest)  
— Fermentation  
plant — Factory unit  
preparing culture  
medium



Chinoi (Budapest)  
— Fermentation  
plant — Factory unit  
sterilizing culture  
medium



pace in the recent period, that of the antitumour sugar derivatives and of prostaglandins.

The large-scale production of antibiotics was started first by CHINOIN in Hungary. Although in 1950 a separate plant functioning under the name of BIOGAL was erected for this purpose, manufacture of *antibiotics* is still going on in the CHINOIN Works. The main products are nystatine, gentamycine, fumagilline and sisomycine.

In addition to the human preparations CHINOIN attach great importance to the development and production of *veterinary* ones, disposing similarly of considerable tradition and experience in this field.

CHINOIN are producing in their factory units about 100 different active substances serving the manufacturing of most of their pharmaceutical specialities in their finishing and packing plants of high capacity. More than hundred million ampoules and several thousand million solid drug forms (tablets, capsules, coated pills) are supplied by the factory yearly, partly for covering the home demand, partly for foreign markets.

In order to meet the increased demand of the agriculture, at the beginning of the 1970's CHINOIN introduced the production of feed additives and particularly of *plant-protecting agents*, being available already for exports. Among the plant-protecting agents they produce primarily fungicides and insecticides.

Chinoi (Budapest)  
— Fermentation  
plant — Feed-lanks



## EGYT PHARMACOCHEMICAL WORKS

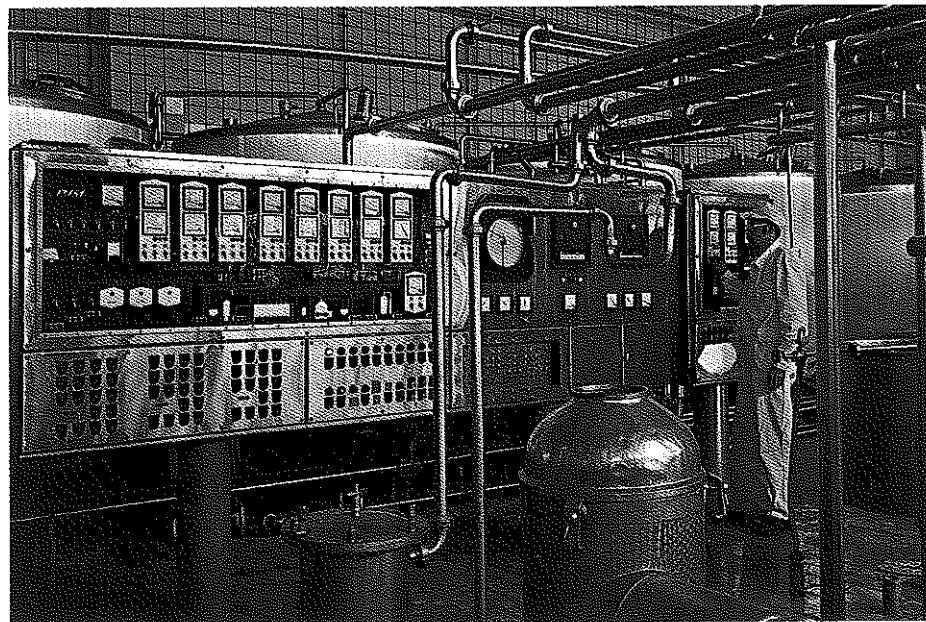
1106 Budapest, Keresztúri út 30-38 (central establishment)  
1475 Budapest, P.O.B. 100 (postal address)

The EGYT PHARMACOCHEMICAL WORKS had been developed after the Second World War of the subsidiary company of the Swiss firm Wander (Bern), established in 1912 in Hungary and of some other smaller pharmaceutical plants. Their production line consists today mainly of the manufacturing of pharmaceutical active agents and specialities. They remained however faithful to the production of food-preparations (medicinal and baby food-preparations), which is going on in their provincial factory unit in Körmend, called Lacta Factory for Food-Preparations. The staff number of EGYT amounts to 3,800 persons.

They produce first of all *synthetic* drugs, of which chlor-amphephenicol, a broad-spectrum antibiotic, represents the greatest volume. A large production capacity has been brought about for the manufacturing of different groups of chemical products, like halogenized oxyquinoline derivatives, phenothiazine derivatives, trimethoxybenzoic acid derivatives, etc.

In addition to the preparations serving veterinary purposes, feed additives (coccidiostatic and growth promoting agents) are also produced.

A wide range of pharmaceutical specialities is produced by EGYT from various active substances of which approx. 40 come from their own production. Modern antihypertensives, muscle relaxants and psychotropic agents are to be found among their preparations. About 100 million ampoules, several thousand million tablets, coated pills, ointments and other pharmaceutical forms, comprising spray preparations are produced in their modern finishing and packing plants.



LACTA (Körmend) —  
Dairy





## **PHYLAXIA VETERINARY BIOLOGICALS AND FEEDSTUFFS, Ltd.**

1107 Budapest, Szállás u. 5/7 (central establishment)

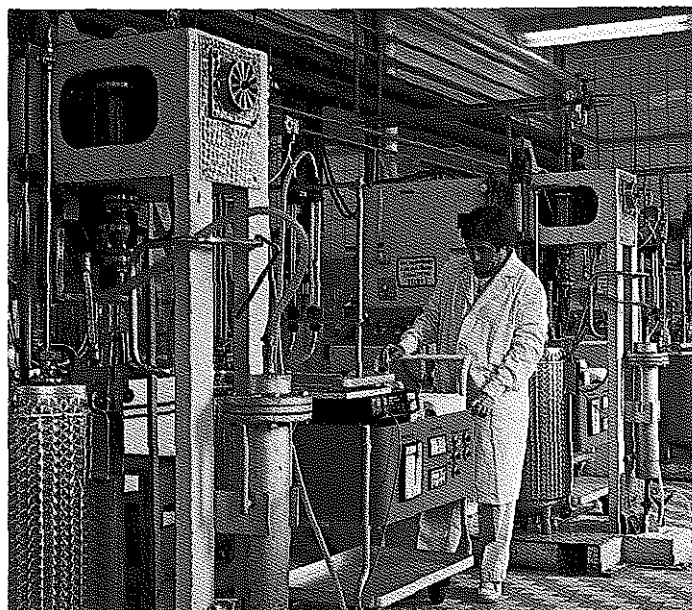
1486 Budapest, P.O.B. 23 (postal address)

The task of PHYLAXIA founded in 1912 was till 1954 the production of biologicals for both human and veterinary use. After the segregation of Institute HUMAN for Serobacteriological Production and Research, the line of PHYLAXIA consists exclusively of the manufacturing of products serving veterinary and stock-breeding purposes. The number of staff is at present already above 2,000 persons.

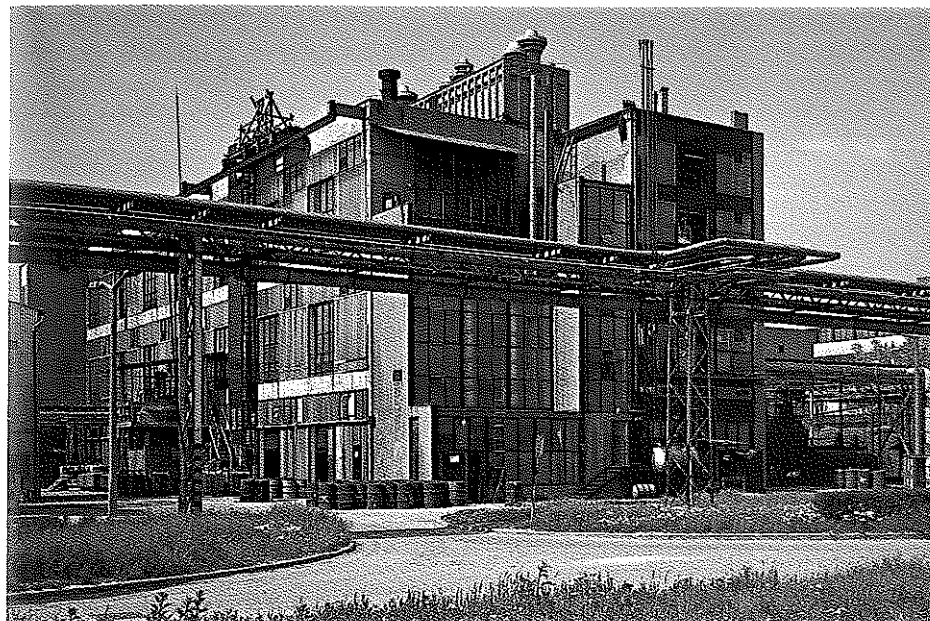
The structure of the production of biologicals is adapted to the veterinary and epizootic conditions of the country. Certain epizootic diseases, causing formerly severe damages, could be fully eliminated (e.g. swine-fever) and others reduced to a minimum level. The range of biological products was completed by various blood preparations and they are continuously engaged in the processing of newer vaccines and sera.

The active agents required for the production of feed additives and animal food-preparations are produced partly by fermentation.

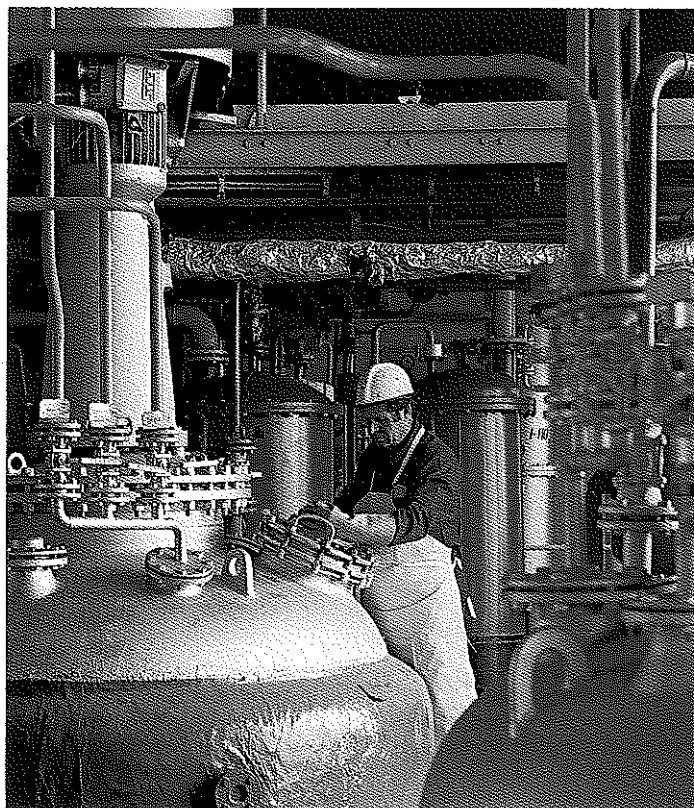
The export activity of PHYLAXIA shows an ascending trend. The swine-fever antiserum, the antiserum and vaccine against goose influenza and Aujeszky's disease have acquired international recognition. The company's experts co-operated in erecting a large-sized biological plant in Mongolia.



*Phylaxia (Budapest) —  
Production of vaccines  
against aphthous fever*



Alkaloida (Tiszavasvári)  
— Production of drug  
basic materials



## ALKALOIDA CHEMICAL FACTORY

4440 Tiszavasvári, Kabay János u. 16 (central establishment)  
4441 Tiszavasvári, P.O.B. 1 (postal address)

In the plant, established in 1927 was started first in the world the industrial production of opium alkaloids out of dry poppy-heads.

In addition to opium alkaloids and their semi-synthetic derivatives, ALKALOIDA is engaged in the production of several other *drugs of vegetal basis*. At the same time it co-operates in the organization of the cultivation and ingathering of vegetal raw materials.

At the end of the years of 1960 and at the beginning of the 1970's the transfer to the province of the manufacturing of certain products representing a high production volume of the Budapest pharmaceutical factories—limited in local expansion—has become necessary. On account of the existing favourable conditions, the modern manufacturing halls of synthetic compounds, in which, among others, the production of the antimalarial drug, chloroquine, as well as of various sulfonamides, barbiturates, etc. is going on, had been constructed with ALKALOIDA.

The provincial small plant has become by the second half of the seventies a pharmaceutical enterprise important even in European relation. The number of staff is today more than 2,300 persons.

The plant-protecting substances and preparations represent a considerable part, nearly the half of the production, manufactured partly on the basis of licence agreements.

The number of active principles made in ALKALOIDA amounts to 30. Apart from the development of these, the finishing and packing capacity is increasing continuously.



## BIOGAL PHARMACEUTICAL WORKS

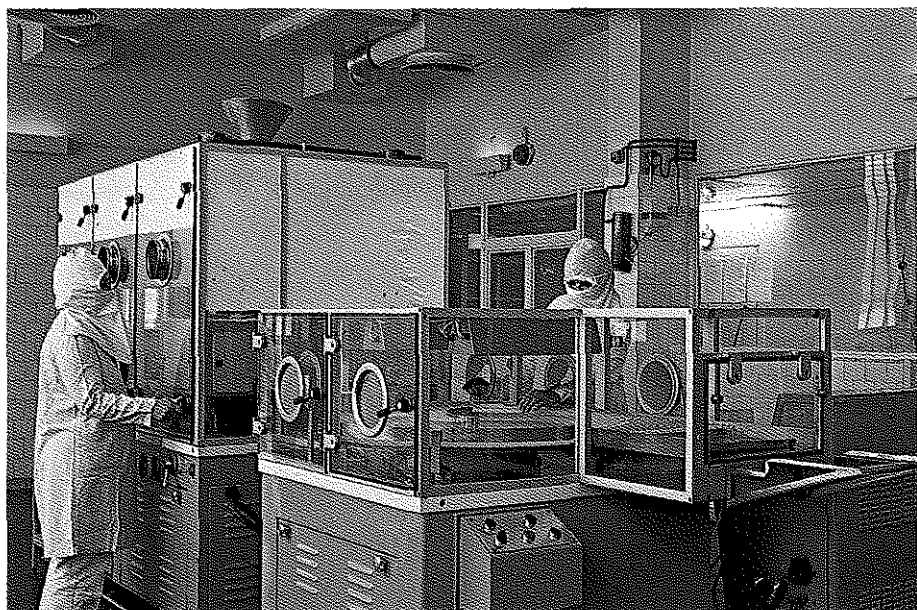
4042 Debrecen, Pallagi út 13 (central establishment)

4001 Debrecen, P.O.B. 197 (postal address)

Hungary has stayed out from the international development of the antibiotic fermentation industry during the Second World War on account of the pressure of circumstances. The deficiency, however, could be remedied relatively fast, and around the fifties the conditions were already matured for the construction of a modern antibiotic plant. This was ready in 1952 in Debrecen and since 1960 it is functioning under the name of BIOGAL. The number of staff amounts to 1,900 persons.

The capacity of the manufacturing of penicillin-G and -V grew to the manifold of the planned quantity during the subsequent years and, parallelly the production cost decreased. The fermentation of oxytetracycline was effected in fermenters of latest type (without agitator) and the list of products was increased by neomycine and tobramycine. In addition to the antibiotics for human and veterinary use, BIOGAL have extended their activity also to industrial enzymes used in the baking and food, textile and leather, as well as in the detergent industries.

BIOGAL produce about 20 different active agents and have constructed finishing and packing plants for the manufacture of ampoules, powder ampoules, tablets, coated pills, etc. The product development is tending, besides the fermentation of antibiotics and enzymes of new type, to the enlargement of the assortment of semi-synthetic products, and particularly to that of veterinary preparations.



*Biogal (Debrecen) —  
Powder-ampoule filling  
machine*





## INSTITUTE HUMAN FOR SEROBACTERIOLOGICAL PRODUCTION AND RESEARCH

2101 Gödöllő, Táncsics Mihály u. 82 (central establishment)  
2101 Gödöllő, P.O.B. 69 (postal address)

The firm PHYLAXIA founded in 1912 with the aim of producing only veterinary biologicals set up in 1922 a separate "Human Department" in order to start development and production of sera and vaccines exclusively for human use. After the nationalization in 1948 the work of all the other laboratories dealing with manufacture of human biologicals in Hungary was taken over by the Department which became independent in 1954 under the name of Institute HUMAN for Serobacteriological Production and Research.

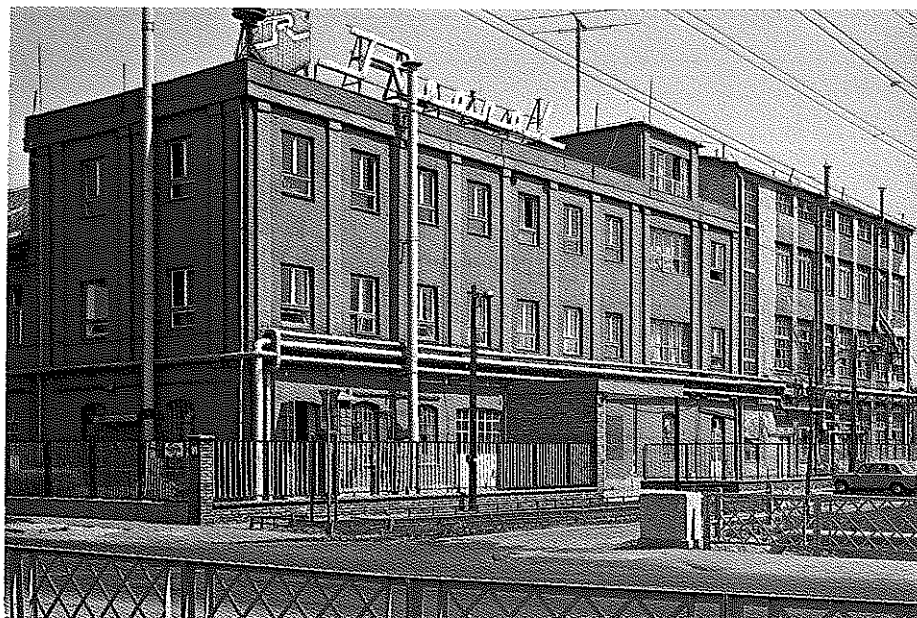
The production range of the Institute includes vaccines, therapeutic and diagnostic sera, blood derivatives, plasma expanders, infusion solutions and modern diagnostics for immunology and immuno-chemistry.

The Institute possesses actually 207 registered preparations and, besides these, it has on the market about 140 sorts of immuno-chemical reagents and culture media. Owing to its potent vaccines, the most important bacterial epidemics could be fought off in Hungary, like typhoid fever, pertussis, diphtheria, tetanus.

About 850 persons are kept employed in the Budapest and Gödöllő plants who carry out an important research and development activity besides their productive work.

Human (Gödöllő) —  
Freeze-drying  
(liophylization)  
of human blood  
plasma albumin





## REANAL FACTORY OF LABORATORY CHEMICALS

1147 Budapest, Telepes u. 53 (central establishment)

1141 Budapest, P.O.B. 54 (postal address)

The reorganization into a factory of fine chemicals of Bayer's subsidiary company which functioned under the name of "Magyar Pharma" Pharmaceutical Factory before the Second World War, was started after the nationalization. The right of manufacturing medicines was granted to other pharmaceutical enterprises, whereas the production of laboratory chemicals and reagents was transferred from these to the company functioning since 1957 under the name of REANAL. This firm was entrusted already in 1966 with the nation-wide storage and marketing of fine chemicals, too.

The number of staff amounting from 100 to 130 persons in 1949-1954 is today nearly 700. Compared to about 200 products at the beginning, the factory produces nearly 1,500 articles and is marketing about 6,000 substances for the home supply in fine chemicals through its commercial network.

The product range of the company includes chemicals for analytical and research purposes, kits of chemicals, photochemicals, plant-protecting agents and some pharmaceutical specialities. Particular attention is paid to the compounds used in the field of biochemistry, like aminoacids, aminoacid derivatives, peptides, enzymes, nucleotides, desoxy-nucleotides, sugar phosphates, ion exchangers of cellulose and dextrane base, gel filters of dextrane and polyacrylamide base and special chemicals of the modern instrumental analytics.



Reanal (Budapest) —  
Fermentation of  
antibiotica  
(Mythramycin,  
Oligomycin)



## BCR WORKS

2943 Bábolna, P.O.B. 30

The BCR Works are a joint venture of the Agricultural Combine of Bábolna, the CHINOIN Pharmaceutical and Chemical Works and the Chemical Works of Gedeon Richter Ltd. The aim of its foundation was the development and production of certain feed additives and medicated feed required for large-scale stock-breeding by joint effort.

The plant which will be followed by further units was put into operation in spring of 1978. They have a yearly output of 30,000 tons of feed additives which is sufficient for the preparation of 3 million tons of industrial mixed fodder.

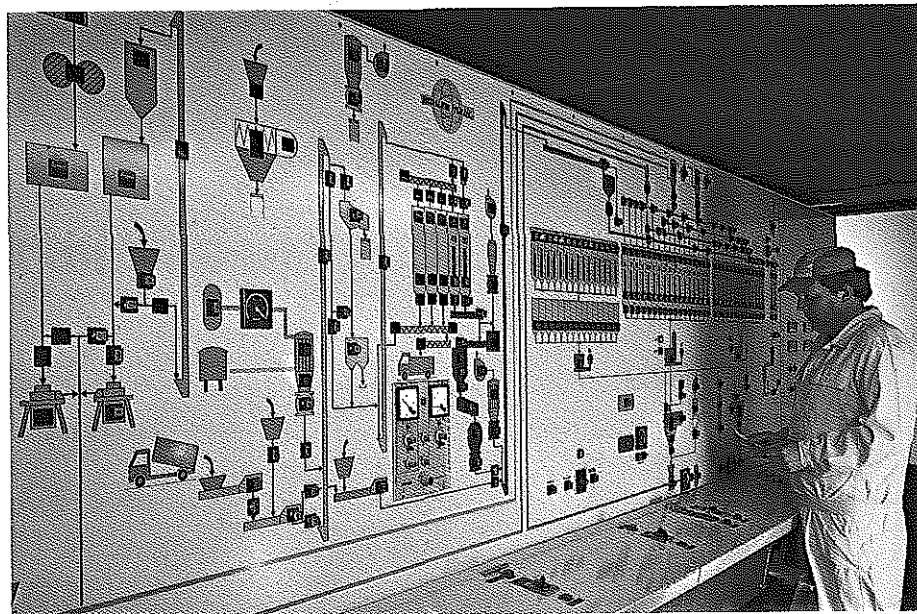
The plant is fully automated, having electronic control of punched card system. The production is based on the most up-to-date prescriptions and formulas, partly by using licences bought abroad. The most modern analytical instruments serve the control of the production and the finished products.

The works give employment to 110 persons; one third of these is performing analytical and other control tasks.

Among the partners of BCR Works the biggest Hungarian state farms and agricultural combines are to be found. The efficiency of the products is ensured by permanent experimental feeding and the analysis of industrial results.

Modern medicated feed is marketed in small (1 to 5 kg) packages, too.

Coccidiostatic agents take the first place among the products under development in BCR Works.



BCR (Bábolna) —  
Automatic control  
of manufacturing  
processes

## Foreign and Hungarian joint enterprises engaged in pharmaceutical production

One of the forms, becoming more and more important of the presence of the Hungarian pharmaceutical industry on foreign markets is the participation in foreign producing companies. The firms operating with Hungarian and local capital—apart from the concentration of material forces—have also the advantage of uniting the local contractors' experience and relations on the market with the technical knowledge of the developed Hungarian pharmaceutical industry. The governments of the countries, where joint ventures are functioning, appreciate this form of co-operation, particularly in the developing world, knowing that this would open new employment opportunities and promotes the growth of the technical level in the respective country.

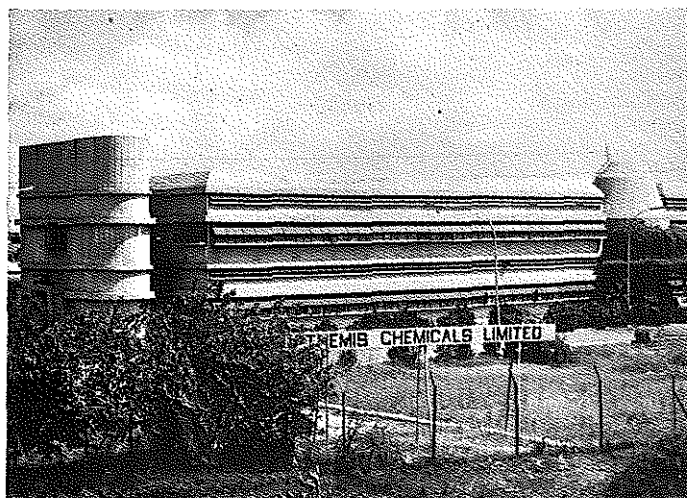
When establishing common enterprises, the Hungarian pharmaceutical industry is not confined only to the transfer of finishing and packing technologies, but also is not averse to cede the manufacturing processes of active substances to the party either. A good example for this is the Indian firm *Themis Chemicals*, engaged for a long time past in the pro-

duction of some important pharmaceutical fine chemicals (e.g. ethambutol, vitamin B<sub>12</sub>) on the basis of Hungarian know-how. The product obtained in this way is partly subjected to further processing, partly marketed. Its main pharmaceutical specialities are: Themibutol, Oxyrin, Themineuron, Sumetrol, Peritol, Dopagyt. As a result of the consistent developmental activity the enterprise has obtained recognition within the Indian pharmaceutical industry.

*Labatec Pharma* in Switzerland is one of the oldest joint companies of the Hungarian pharmaceutical industry. The pharmaceutical specialities produced (out of which the most important are: Dopatec, Mydocalm, Frenolon, Labamicol, Rheumycalm) are marketed both in Switzerland and other countries. They are carrying on an extended commercial activity, too.

The sphere of action of the Nigerian firm *Imarsel* can be characterized in the same way. This company is marketing its products, however, exclusively on the territory of Nigeria.

The endeavour to extend the network of productive companies of co-ownership is showed by the foundation of a Bangladesh company in 1980, working under the name of *Ambee Pharmaceuticals*. Their aim is to improve the provision of Bangladesh consumers with modern drugs (e.g. Klion, Ampicillin, Trofurit, Verospiron, Prednisolon, Sural).



THEMIS  
Pharmaceutical  
Factory — India

## Foreign co-operations serving the production

The Hungarian pharmaceutical industry readily takes part in manufacturing co-operations, looking for the mutually most advantageous solutions depending on circumstances and needs. The works under contract should be mentioned as a good sample, within the framework of which certain procedures are carried out by foreign companies under the severe quality control of the Hungarian consigner. These contracts allow the compensation of excesses and shortages of the production capacity between the partner enterprises. Such agreements could already be concluded with several firms—particularly with those of the socialist countries.

The licence agreements render possible the better exploitation of production capacities. These are usually connected with the transfer of certain technological steps to the licensee. The licence agreements are two directional, they may serve either the sale of Hungarian research results and manufacturing know-hows or the purchase of foreign technologies. The licence relations of the Hungarian pharmaceutical industry with some multinational concerns (Ciba-Geigy, Sandoz, Bayer, Astra, Organon, Syntex, Eli Lilly, Janssen, etc.) are already traditional.



**RESEARCH**

## Historical retrospection, traditions

The pharmaceutical research in modern sense is going on in Hungary for about 90 years. This activity was in progress till the end of the First World War mostly in the chemical and pharmacological departments of the universities. A steadily increasing number of results and scientific recognitions originated from this research work.

Between the two World Wars the bigger manufacturing companies had organized their own research units in close co-operation with the university institutions. In connection with drugs of vegetal base, the industrial production of morphine alkaloids out of dry poppy-heads, the isolation of vitamin C out of paprika, the elaboration of the cultivation of ergot by means of artificial contamination, the isolation of ergot alkaloids, etc., in the line of drugs of animal origin, the preparation of estrone out of pregnant mare urine, as well as the introduction of the manufacturing of various hormone products were of great importance. Also at this time was laid the foundation of the Hungarian synthetic drug industry, through the implementation of the production of many important active principles (papaverine, sulfonamides) by means of developed technology.

After 1945, besides the growing activity of the university institutes, the institutions of the Hungarian Academy of Sciences have increasingly taken part in drug research. The research laboratories of the pharmaceutical companies have also developed considerably. In addition to these, the central research organ of the Hungarian pharmaceutical industry, the Research Institute for Pharmaceutical Chemistry, was founded, later the Research Institute for Medicinal Plants was likewise incorporated organically into the pharmaceutical industry.

The more important achievements of the Hungarian drug research are shown in a separate table.

At present the supreme direction of research work is provided by the Board of Scientific Policy. Considering the

traditions, potentialities and requirements of the country, a particular importance is attached to the research of biologically active compounds serving the health protection and the curing of living beings (humans, animals, plants), further to the research of biologically active compounds, aimed at the increase of agricultural (plant cultivation, animal breeding) yields.

The co-ordination of the research work going on in the pharmaceutical industry is carried out with the enterprises (ALKALOIDA, BIOGAL, CHINOIN, EGYT, RICHTER, REANAL) united in the Union of the Hungarian Pharmaceutical Industry, by the Research Council of the Union. The members of the latter are, apart from the research directors of the enterprises, the directors of the two independent research institutes, the Research Institute for Pharmaceutical Chemistry and the Research Institute for Medicinal Plants. The President of the Research Council is the deputy director of the Union, who takes simultaneously part in the work of the National Co-ordinating Corporation engaged in the research of biologically active compounds.

In 1960 the number of research workers was more than 900 in the Hungarian drug industry (see table).

	1960	1965	1970	1975	1980
Number of research workers	902	1,270	2,200	2,660	2,800
Of these: graduated research workers.	250	320	590	775	950

During the past 20 years the expenditure for research represented 4 to 5 percent of the yearly turnover, whereas in 1981-1985, during the next Five-Year Plan, this ratio will rise to 7-8 percent.



The pharmaceutical factories utilize one part of the available amount for financing their own research, the other part will be remitted on the basis of research contracts, partly to the two independent industrial research institutes, partly to the more than 100 research laboratories, functioning independently from the industrial branch.

The research laboratories of the factories have developed wide relations with the research institutes of the Hungarian Academy of Sciences, various university institutes, medical research units and, last but not least, with the Clinical Pharmacological Network, operating under the control of the National Institute for Pharmacy. A co-operation in a number of scientific subjects is going on within the industrial branch, e.g. the development of operation technics, protection of the environment, instrumentation, automatization, etc.

### More important results of the Hungarian pharmaceutical research

Year	Result of research	Research workers
1866 1885	Discovery of the diuretic effect of Calomel and its combination with opium	Jendrassik
1897	Local anesthetic effect of chlorobutanol	Vámossy
1900	Discovery of the laxative effect of phenolphthaleine (this was the first synthetic laxative)	Vámossy
1916-17	Recognition of the decreased effect of quaternary tropeins on the central nervous system. Development of homatropine methylbromide. Introduction of the combination of tropeins and papaverine	Földi, Issekutz
1927	Discovery of the diuretic Novurit (mercurophylline)	Földi, Issekutz, Végh
1927-30	Elaboration of the method to produce morphine and related alkaloids of green poppy plant and later of dry poppy straw	Kabay
1928	Isolation of vitamin C of paprika (the first large scale production of the vitamin in Chinoin)	Szent-Györgyi
1929-36	Description of the coronary dilating effect of adenosine and adenylic acid	Drury, Szent-Györgyi
1932	Discovery of the spasmolytic agent Perparine (ethaverine)	Földi, Issekutz
1936	Discovery of vitamin P (citrine)	Rusznayk, Szent-Györgyi
1940	Discovery of Ultraseptyl (sulphamethylthiazole)	Földi, König, Gerecs, Wolf

Year	Result of research	Research workers
1940	Discovery of Salvoseptyl (sulphathiourea)	Földi, König, Gerecs, Wolf
1948-61	Microbiological transformation of steroids	Kráml, Horváth, Wix
1954	Isolation of primycine	Vályi-Nagy, Uri, Szilágyi
1955-69	Psychophysiological and psychopharmacological methodological research works	J. Knoll, B. Knoll, Kelemen
1955-70	Analysis of the interconnection between the effect and structure of tropeins. Development of Gastropine (xenytropium bromide), Gastrixon (trantellinium bromide) and central cholinolytics	Nádor, Gyermek, György
1955-73	Development of new cytostatic sugar derivatives [Degranol (mannomustine), Myelobromol (mitobromitol), Zitostop (mannosulfan), Lycurim (ritrosulfan), Elobromol (mitolactol)]	Vargha, Dumbovich, Horváth, Mrs. Horváth, Institoris
1955-75	Analysis of the interconnection between the effect and structure of aminoketones. Development of Mydocalm (tolperisone) and Karion (pimectione)	Pórszász, Nádor
1959-62	Development of Trioxazine (trimetozine), a minor tranquillizer	Vargha, Dumbovich, Borsy
1959-79	Research of the cerebral vasodilating Vinca alkaloids, Devincan (vincamine), Cavinton (vinpocetine)	Szász, Szporny, Szántay

Year	Result of research	Research workers
1961	Development of No-Spa (drotaverine)	Mészáros, Szentmiklósi
1961	Discovery of Pirazocillin (antibiotic)	Fehér, Koczka
1961-65	Development of the neuroleptic Frenolone (metofenazate)	Toldy, Borsy
1961-77	Development of the coronary dilator Sensit (fendiline)	Korbonics, Harsányi, Tardos
1962	Discovery of the antitussive Libexine (prednodoxazine))	Harsányi, Tardos
1962-68	Research of the anticoagulant, anti-inflammatory action of rare earth metals. Development of the local anti-inflammatory Phlogosam (samarium complex salt of sodium disulfosalicylate)	Jancsó, J. Gábor
1962-71	Analysis of the radioprotective effect of Cysteine	Hernádi
1963	Discovery of Depersolone (mazipredone) a water-soluble glucocorticoid	Tuba, Komen, Bor, Görög
1963	Discovery of the vasospasmolytic Halidor (bencyclane)	Komlós, Pallos
1965-79	Working out of Jumex (seligiline) of antiparkinson effect, the first selective inhibitor of the B-type monoaminoxidase	J. Knoll, B. Knoll, Ecseri, Magyar
1966	Working out of the antiseptic Reseptyl (Chloroseptyl)	Lugossy, Zsolnai, Jenei
1966-72	Synthesis of human ACTH	Bajusz, Medzihradsky, Kisfaludy, Gráf

Year	Result of research	Research workers
1966-74	Development of Grandaxin (tofizopam), a minor tranquillizer	Kőrösi, Láng, Komlós, Petőcz
1966-75	Development of the hypotensive Sanegyf (guanazodine)	Rákóczy, Beck, Komlós, Petőcz
1967	Discovery of the antiepileptic Perlepsine (morsuximide)	Seres, Tardos, Leszkovszky
1967-79	Homopyrimidazoles: working out of a new group of analgesic and anti-inflammatory compounds [Probon (rimazolium methylsulfate)]	Knoll, Mészáros, Füst
1968	Discovery of azidomorphines: working out of a new, potent analgesic group which possesses the lowest tolerance and dependency capacity known so far	Bognár, Makleit, Knoll, Füst, Rétsági
1970	Synthesis of prostaglandines. Mode of action analyses. Research of the interconnection between structure and effect	Mészáros, Kovács, Szántay, Knoll, Vizi
1971-81	Development of the $\beta$ -receptor blocking preparation Tobanum (cloranolol)	Hajós, Fekete, Kürti, Láng, Toldi, Borvendég
1972-81	Discovery of Arduan (pipecurium bromide), a compound of curarine effect	Tuba, Bor, Szerényi, Kárpáti, Szponny

# Organization of the Hungarian pharmaceutical research



## RESEARCH INSTITUTE FOR PHARMACEUTICAL CHEMISTRY (GYKI)

1045 Budapest, Szabadságharcosok útja 45-49 (central establishment)

1325 Budapest, P.O.B. 82 (postal address)

The theoretical and industrial drug research has come to a decisive turn after the Second World War, following the nationalization of drug industry. New research institutes were founded and the research possibilities on the level of university and academic institutions were extended, too.

In 1949 the Central Laboratory for Industrial Biochemical Research was established with the aim to lay the foundation

of the antibiotic industry, while in 1950 the Research Institute for the Drug Industry was formed. Since the amalgamation of the two institutes in 1952, the Research Institute for Pharmaceutical Chemistry has become the central organ of the Hungarian industrial drug research. At the beginning its task was the working out of industrial processes of high volume products which were modern, economical and independent from foreign patents, and important from the aspect of drug supply. As a consequence of the development of the factories' research laboratories, the Institute was enabled to proceed with fundamental research and the working out of original new preparations. It co-operates closely with the research laboratories of the enterprises not only in the solution of research tasks, but in the creation of new research capacities and in the realization of research conditions, too.

The Research Institute for Pharmaceutical Chemistry is at the same time also the biological test centre of the Hungarian pharmaceutical industry, possessing suitable units for carrying out modern pharmacological, toxicological, teratological, microbiological and radiological examinations. The need in experimental animals is covered mostly from own breeding.

The Institute takes a considerable part in the development of most of the new drugs and its activity is extended to synthetic, fermentation and biochemical research as well. In its modern synthetic and fermentation pilot plants the working out of semi-industrial and industrial technologies is alike possible.

In the Research Institute for Pharmaceutical Chemistry the modern technology of several important chemotherapeutics, oral antidiabetics, psychotropic agents of phenothiazine type and tuberculostatics has been worked out. From the successes of the research work aiming at the creation of new original compounds distinguishes itself the development of the anti-

*Institute for Drug  
Research (Budapest) —  
Evaluation of a thin-  
layer chromatogram  
(in UV-light)*



tumoral sugar alcohol derivatives (mannomustine<sup>1</sup>, ritrosulfan<sup>2</sup>), as well as that of metofenazate<sup>3</sup> (an antipsychotic agent), trimetozine<sup>4</sup> (minor tranquillizer), tofizopam<sup>5</sup> (developed in common with EGYT) and cloranolol<sup>6</sup> (a  $\beta$ -blocker). A fruitful field of research of the Institute is the peptide chemistry, where—in close co-operation with other research

laboratories—the elaboration of the industrial process for the total synthesis of oxytocine, as well as the synthetical production of the human adrenocorticotrophic hormone (ACTH) are the most prominent.

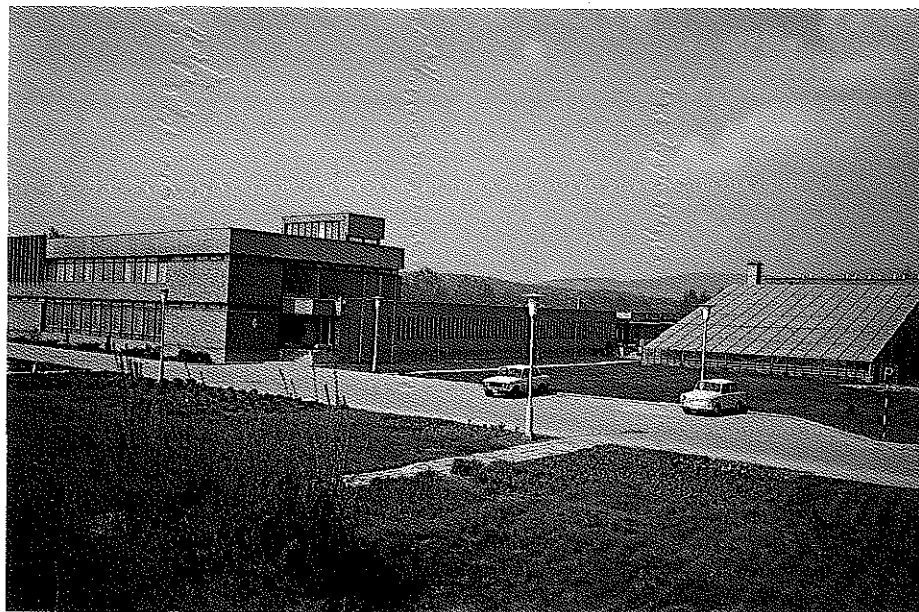
The activity of the Institute in the field of steroid research is rather outstanding, among which the implementation of the home production of estronè, metandienone, prednisolone and d-norgestrel (Ovidon®) are worth to be mentioned. The fermentation department has done a significant work in the production and isolation of oxytetracycline, streptomycine, neomycine, nystatine, 6-aminopenicillanic acid and vitamin B<sub>12</sub>, further in the microbiological transformation of steroids.

In 1952 the number of the Institute's staff was 315, today this number exceeds 700. Out of the 560 persons engaged in research work 227 are graduated. The most important research subjects are:

- agents acting on the heart and circulation;
- agents acting on the central nervous system;
- antibiotics and chemotherapeutics (anti-cancer drugs included).

<sup>1</sup> Degranol®  
<sup>2</sup> Lycurim®  
<sup>3</sup> Frenolon®

<sup>4</sup> Trioxazine®  
<sup>5</sup> Grandaxin®  
<sup>6</sup> Tobanum®



## RESEARCH INSTITUTE FOR MEDICINAL PLANTS

2011 Budakalász, József Attila u. 68 (central establishment)

2011 Budakalász, P.O.B. 11 (postal address)

The legal predecessor of the Institute was established in 1915 by the Ministry of Agriculture of that time. The Institute of a great past acquired considerable results in the research of morphine alkaloids, poppy improvement, the starting and

development of the home volatile oil production, the cultivation of ergot, as well as in exploration and enrichment of the home medicinal herb flora (revival of mint cultures, acclimatation of ricinus, the starting of the cultivation of *Digitalis lanata*). The Institute belonging since 1967 organically to the drug industry, has today a staff comprising 150 persons of which 35 are qualified researchers.

The research work of the Institute is extended to the study of the propagation, composition, utilization, biology, genetic properties, putting into cultivation, improvement, as well as to the implementation of the modern large-scale agro-technics and cultivation systems of plants used in the pharmaceutical, volatile oil industries, as well as in drug commerce.

The Institute, in co-operation with the agricultural institutions, has worked out and introduced the system of poppy and ergot cultivation on an industrial level in Hungary.

Its task comprises the production of the improved seed-grains of the more important medicinal herbs, the maintenance of the co-operation in the exchange of grains on an international level, the propagation of results obtained in research of medicinal herbs by means of publications (*Herba Hungarica*) and advising, as well as the supply of expertise for all problems concerning the matter of medicinal herbs. In addition to the field experiments, the modern phytotron technics are also used during the research work in the well-equipped laboratories.

The task of the Institute is the official qualification and control work in connection with the ingathering and cultivating of medicinal herbs.

Institute for Drug-plant  
Research (Budakalász)  
— Climate room

*Phytotron*



## Drug research in the factories

*(in alphabetic order)*

ALKALOIDA CHEMICAL FACTORY engages a research team of 110 persons of which 20 are qualified research workers. Their duty is primarily the development of production, the improvement of existing technologies, as well as the carrying out of laboratory and pilot plant trials in connection with the adaptation and starting of new manufacturing processes. With the execution of fundamental research work and experiments aimed at developing original new products other research organs (within or outside of the drug industry) are entrusted, though recently the ALKALOIDA researchers carry on already fundamental research, too, particularly in the line of plant-protecting agents.

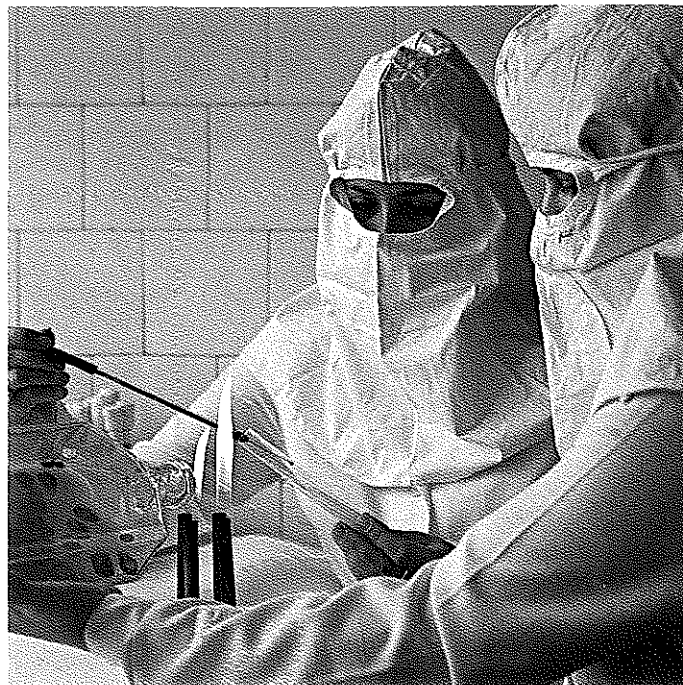
As a result of the relatively small research capacity, the major part of new preparations is produced on licence basis, where a notable activity of adaptation and improvement is displayed.

Great attention is paid to the isolation and analysis of the active agents of medicinal herbs, the elaboration of extraction technologies. A new product of ALKALOIDA is Tisasen, containing the sennoside A and B as active substances.

BIOGAL PHARMACEUTICAL WORKS are since the beginning of its functioning in close relation with the University of Debrecen and with other scientific institutions of the country. The establishment of an own research department, however, proved to be necessary and indispensable for



*Biogal (Debrecen) —  
Isolation of penicillin-  
producing strains*



further development. In 1954 a pilot plant, later research laboratories and microbiological research units were established, contributing considerably to the improvement of technology and the extension of the product range. The number of research workers amounts to 130, of which 40 are graduated ones.

Their attention is paid first of all to the maintenance and augmentation of the productive capacity of producing strains,

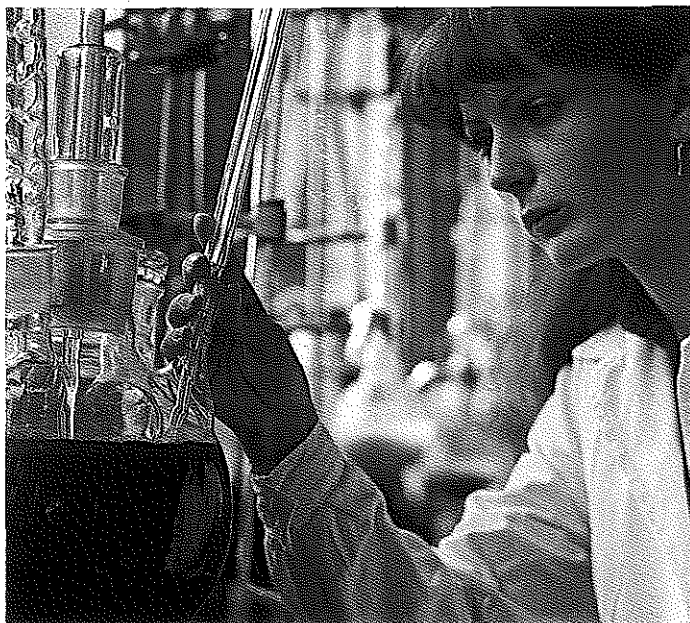
but the instrumentally well-equipped pilot plant provides an opportunity to the optimization and automation of technologies, too. Besides antibiotics they are carrying on experiments also with other fermentation products, like enzymes.

A considerable branch of research is the working out of manufacturing procedures for new antibiotics and semi-synthetic derivatives. In the research of antibacterial, antifungal and antiviral agents the company displays similarly an important activity.

The further development of galenic preparations, the development of modern human and veterinary drug dosage forms is the aim of the pharmaco-technological research, already traditional with BIOGAL.

CHINOIN PHARMACEUTICAL AND CHEMICAL WORKS have attached since their existence always a particular importance to research. Besides the implementation of the production in Hungary of numerous active agents of basic importance yet well-known, the efficiency of the CHINOIN research team is characterized by the development of many original Hungarian drugs, too. Among the original products elaborated during and after the First World War the homatropine methylbromide (Novatropine), mercurophylline (Novurit) and ethaverine (Perparine) are to be found. In 1930, the researchers of the works were the first to develop the synthesis of papaverine on industrial scale, and since that time CHINOIN are one of the biggest papaverine producers of the world. Soon after the appearance of the first sulfonamides (in 1940), they have put on the market their own, original sulfonamide preparation, the sulphamethylthiazole

*Chinoi (Budapest)  
— Pilot plant —  
preparatory laboratory*



*LATI (Gödöllő) —  
Housing of experimen-  
tal animals*



(Ultraseptyl). After the Second World War they have started the microbiological research in Hungary first, making possible the production of penicilline, streptomycine and oxy-tetracycline by fermentation. Since 1955, they have achieved success in the research of sugar alcohol derivatives of anti-tumorous effect (mannomustine, mitobronitol, mitolactol). Among the more important results of the sixties the development of drotaverine (No-Spa), a spasmolytic, various diphenylalkylamine derivatives, like the antitussive pred-noxdiazine (Libexine) and the calcium-antagonist fendiline (Sensit) may be listed. An original new analgesic and anti-inflammatory preparation is rimazolium (Probon).

In addition to the synthetic compounds, CHINOIN are engaged in the research of semi-synthetic derivatives of fermentation products and other natural substances. This work resulted in the implementation of the manufacturing of several penicilline derivatives (meticillin, oxacillin, ampicillin) on industrial scale and, recently, in successes in the field of prostaglandins.

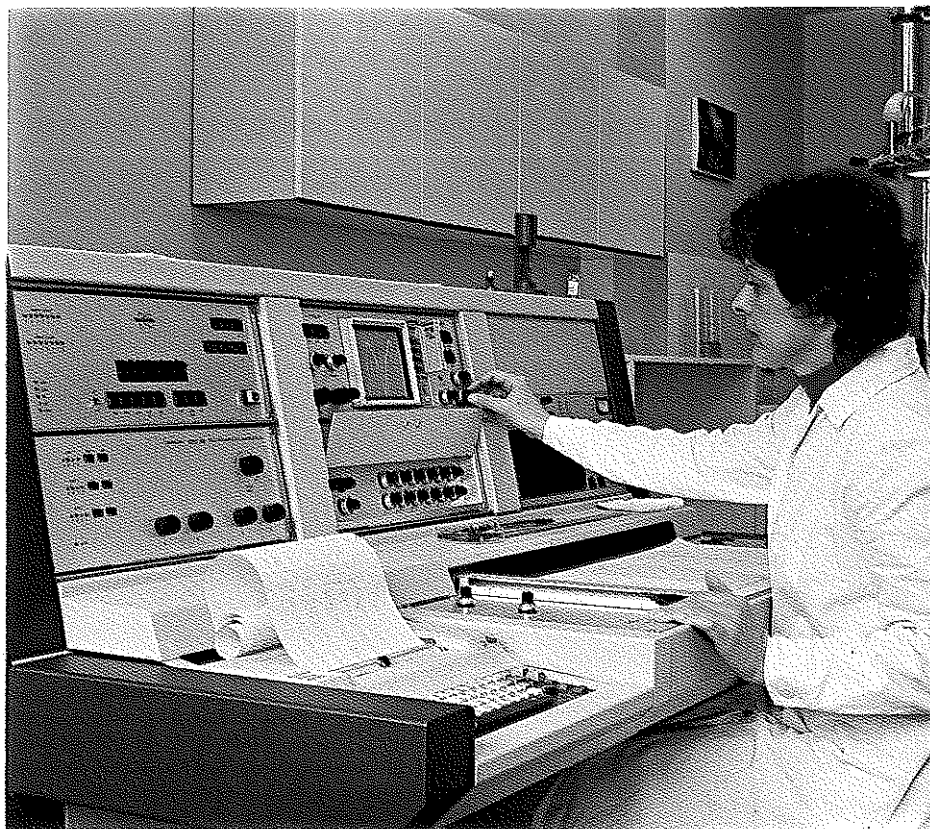
The works initiated vigorously the development of modern, original plant-protecting agents, among them that of synthetic piretroids.

Well-equipped pilot plants serve the speeding up and optimalization of laboratory procedures.

In the line of research CHINOIN are relying not only on their own research work, but they maintain co-operative relations with a number of outside research organizations, too. Their collaboration extends to foreign institutions and big industrial companies notable even on a world scale. In order to cover their need in experimental animals for preclinical research, they maintain a laboratory animal-breeding institute (LATI) in common with RICHTER.

In the domain of research CHINOIN keep employed approx. 700 persons, nearly one third of these are graduated.

EGYT PHARMACOCHEMICAL WORKS employ 350 persons in their well-equipped research laboratories, 145 of these



EGYT (Budapest) —  
Computer controlled,  
transforming magnetic  
nuclear resonance  
spectrometer,  
functioning with  
supra-conductive  
magnet, of 250 MHz,  
type Fourier, serving  
the detection  
of the chemical  
structure of various  
compounds, basic  
materials, reagents,  
intermediaries  
and drugs

are graduated research workers. In addition to this, they have investigations done by other research organs.

Chloramphenicol manufactured by their own technology represents the greatest volume in their production. Among the original products synthesized by their own experts the highest turnover is achieved in bencyclane (Halidor).

In the important domain of research, in the line of psychopharmacology, EGYT have realized the production of trimetozine (Trioxazine) and metofenazate (Frenolon), original Hungarian products, and developed tofizopam (Grandaxin), a minor tranquillizer. A new manufacturing process has been elaborated for the production of ethacrynic acid (Uregyt) and levodopa (Dopaflex), further a new, efficacious molecule, the guanazodine (Sanegyt) was discovered during the investigation of guanethidine derivatives.

In the seventies, a large-scale program was carried out by EGYT for the production of food-preparations, in order to

meet the increased home demand. Within the framework of this, the old products were withdrawn and replaced by a scientifically well-founded range of modern food-preparations. Mainly medicinal food-preparations of humanized milk base have been introduced in addition to those of cereal origin.

Similarly to the other important drug manufacturers, an operational laboratory, a pilot plant and an engineering laboratory have been established by EGYT as well. An efficient work is done in the field of the production of basic substances, the modernization and development of formulation and packing procedures. The successful amplification of the production range permitted the extension of foreign co-operation in the field of research.

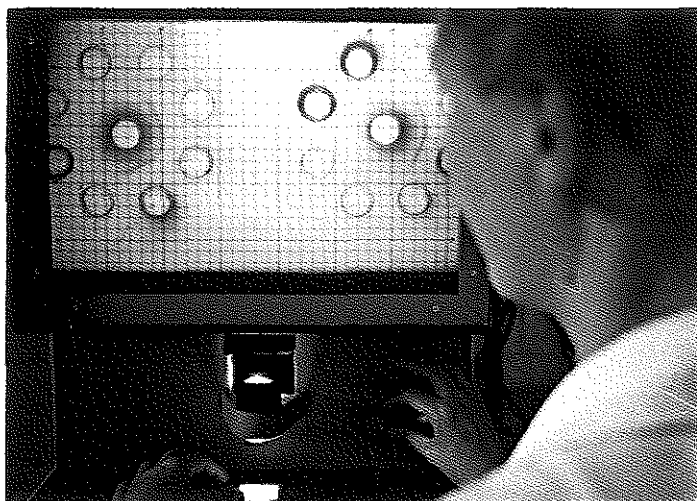
INSTITUTE HUMAN FOR SEROBACTERIOLOGICAL PRODUCTION AND RESEARCH had produced at the time of becoming independent (in 1954) primarily sera, vaccines and serobacteriological diagnostics. As a result of their purposeful activity, not only the number and level of these preparations improved considerably during the subsequent period, but new product ranges arose, too.

Right in 1955, the production of blood derivatives was started with the preparation of gamma-globulin, followed in 1957 by the production of solid (powder) culture media, and later of plasma expanders and infusion solutions. In the sixties the range of diagnostics increased considerably and, in the meantime, the composition and production methods of biologicals were almost completely changed. The large-scale extension of the range of most up-to-date immuno-chemical reagents took place only in the seventies.

At the time of the twenty-fifth anniversary of the existence of the Institute the activity was extended also to "non-traditional" fields, with the result of developing new hormone preparations and agents against burn injuries.

The number of their research team amounts to 40 persons, of which 20 are graduated.

*Humán (Budapest) —  
Analysis of  
immunochemical  
reagents*



The research work of the Institute is kept in evidence and recognized by the World Health Organization. In 1973 the Institute's Vaccine Department became a WHO Reference Laboratory for Bacterial Vaccines.

PHYLAXIA VETERINARY BIOLOGICALS AND FEED-STUFFS, Ltd. could owe even its foundation (in 1912) to a scientific discovery, to the preparation of the sérum against swine-fever. The enterprise established for the production of one single serum has become soon a serum-producing institute of international reputation. The fast development was due to the excellent researchers, the good organization of production, the careful and conscientious laboratory work, as to the foreseeing financial guidance.

PHYLAXIA have developed and marketed, since their existence, several new products, even on a world-scale. The

efficient work of their researchers, both theoretically and practically, has greatly enriched the veterinary and livestock-breeding skill. (Homologous swine erysipelas serum of high titre, hyperimmune serum and vaccine against Aujeszky's disease, goose influenza antiserum, hyperimmune serum and attenuated vaccine against viral diarrhoea, vaccine against infectious bovine rhinotracheitis (IBR), Gibberellic acid, pectinase, agar gel precipitation tests for the demonstration of swine-fever, foot and mouth disease, etc.).

The number of research workers amounts to 201 persons, of which 67 are graduated.

CHEMICAL WORKS OF GEDEON RICHTER, Ltd. keep employed in their research centre of great past about 570 persons, of which 225 are graduated. The development of research was considered with the enterprise as one of the most important tasks.

In the initial period, attention was paid primarily to the production of animal organ extracts, then to the development of purified hormone preparations. The natural substances were replaced later by products obtained in semi-synthetic and synthetic ways. The adrenal hormones, the male and female sex hormones, corticotrophine, insulin, thyroxine and their synthetic substitutes constitute even today an important field of research with RICHTER. A stable, water-soluble prednisolone derivative is mazipredone, marketed under the name of Depersolone.

In the course of the research work connected with fermentation technologies the works' experts have isolated own strains and achieved even internationally outstanding results in the biochemical production of vitamin B<sub>12</sub>, ergot alkaloids and steroid compounds.



*Chemical Works of Gedeon Richter, Ltd. (Budapest) — The pharmacological research laboratory provided with modern instruments and own animal colony constitutes one of the bases of the highly organized and developed research activities*

A traditional field of RICHTER's research work is the phytochemistry. A number of active principles of *Digitalis lanata* were isolated and put on the market, in form of preparations of high purity. Numerous ergot alkaloid products have been developed by using artificial contamination and special technologies. They played a pioneering post in the isolation, testing and development into a drug (Devincan) of the active agent of *Vinca minor*, the vincamine. A semi-synthetic derivative of this is vinpocetine (Cavinton), a specific drug for the cerebral tissue regeneration. Vinblastine and Vincristine isolated from *Catharanthus roseus* proved to be effective in the treatment of certain malignant tumours.

The researchers of the firm are efficient in the investigations of synthetic organic chemistry. They have achieved out-

standing results in the synthesis of polypeptides (total synthesis of oxytocin and synthesis of human ACTH) and in the discovery of many new compounds. These include tolperisone (Mydocalm), being not only a potent myotonolytic, but proved to be excellently useful in the treatment of peripheral circulatory disorders, too, further pimeclone (Karion), completing the range of respiratory analeptics. On the basis of a recent conception of antiinflammatory treatment, the samarium complex salt of sodium disulfosalicylate (Phlogosam, Phlogosol), an efficacious local antiinflammatory agent was made. They succeeded in developing a patent-independent process for diazepam.

As a result of the programmes of operation-development, new machinery was put into use both for the manufacturing of active principles and the finishing and packing of dosage forms.

The research team of the works maintains extensive co-operation on the one hand with Hungarian, on the other hand with foreign research organizations, scientific institutes and enterprises. They display recently an increased activity in respect of veterinary products and plant-protecting agents.

## Co-operation in research

The evaluation system of new products has developed in Hungary in such a manner that the experimental (preclinical) studies are carried out in the first place within the drug industry (in the Research Institute for Pharmaceutical Chemistry and in the enterprises, resp.), in the second place in university, academical and other scientific institutes. The fundamental experiments in men, called phases I. and II. human trials, are effected by a *Clinical Pharmacological Network (CPN)* consisting of 27 units, created in university clinics and special departments of hospitals with a total number of staff of about 110 persons, of which 65 are graduated research workers. The work of CPN is co-ordinated and managed by the *National Institute of Pharmacy*, its maintenance and development is provided jointly by the Ministry of Health, the State Committee on Technical Development and the drug industry.

The Hungarian pharmaceutical industry is carrying on research co-operation with foreign partners, too. The character of this may be manifold, starting from the widest, so-called general (frame) agreements to the mutual undertaking of strictly determined, concrete tasks.

Concerning the contents of the co-operation, it mostly cover the joint development (examination), and thereafter the transfer

or taking over of some new products. Co-operation can be brought about between a Hungarian enterprise and foreign clinics, institutes or between a foreign enterprise and Hungarian clinics, institutes for the carrying out of certain special, so-called target studies. The respective agreements with the foreign enterprises and institutes, resp. are concluded in such cases (in concert with the Hungarian producer) by MEDIMPEX Hungarian Trading Company for Pharmaceutical Products.

A "development" company may be established abroad by the Hungarian drug industry, in order to ensure the full conformity of the test results of new Hungarian products with the drug-evaluation requirements of the given country or of an economical community in a relatively fast way like e.g. *Optifaro*, functioning in the FRG.

The Hungarian drug industry takes part in the realization of co-operation agreements fixed in interstate conventions, as well as in the work of international organizations (UNO, WHO).

The favourable experience acquired so far inspire the Hungarian pharmaceutical research organizations to extend their co-operation in the research and working out of new products with any foreign partner who—on mutual basis—shows an interest in this.



## Hungarian drug patents

An index of the efficiency of drug research is the number of granted patents. In Hungary, according to the patent law for medicines, only the manufacturing process can be protected by a patent, the product itself not. Accordingly, the Hungarian patent applications refer to the manufacturing processes, but in foreign countries, where legal prescriptions allow it, the Hungarian inventors may ask, of course, for the protection of the product too. The number of pharmaceutical patents granted or applications being under judgement (resulting from Hungarian applicants) was the following on January 1st, 1980:

	Patents granted	Applications being under judgement
Alkaloida	18	12
Biogal	63	7
Chinoïn	357	148
EGYT	177	43
Reanal	29	18
Richter	234	144
R. Inst. for Pharm. Chem.	144	56
R. Inst. for Med. Plants	21	3

In addition to these, a number of patents granted abroad ensures legal protection to the export of the products of the Hungarian drug industry.



# **DRUG CONTROL**

# Traditions

State Pharmaceutical  
Institute (Budapest) —  
Examination of drugs  
by spectrophotometry



In Hungary, the organization of drug registration and control is closely correlated with the development of drug industry, drug supply and drug exports.

As mentioned before, the Hungarian pharmaceutical industry enjoyed in the second or third decade of the 20th century already a great international reputation. Thus, the National Institute of Public Hygiene and its Section for Drug Control were established relatively early, in 1925, almost as a spontaneous requirement; since 1933 the duty of this Section

was the registration, made obligatory on new pharmaceutical preparations and the quality control of drugs on a country level. After the nationalization of the pharmaceutical industry in 1948 and of the pharmacies in 1950, these tasks were taken over gradually by the *National Institute of Pharmacy* created for this purpose.

Thus, the National Institute of Pharmacy represents today the national drug control agency. Its main responsibilities are, as follows:

- selection of the “materia medica”;
- establishing of the requirements concerning drug safety and efficacy, control of the fulfilment of these requirements;
- management and co-ordination of the Clinical Pharmacological Network;
- authorization for clinical studies;
- assurance of the scientific (chemical, pharmaceutical, toxicological, pharmacological, clinico-pharmacological and clinical) evaluation of new drugs;
- drug registration;
- licensing of the manufacture of drugs;
- inspection of manufacturing plants;
- official quality control of drugs;
- ensuring of the objectivity of drug information;
- monitoring of adverse drug reactions;
- promotion of the rational drug therapy and correct drug utilization.

# Introduction of new drugs

State Pharmaceutical  
Institute (Budapest) —  
High-pressure thin-  
layer chromatographic  
examinations



In Hungary one of the basic principles of the introduction of drugs is that the unlimited increase of the number of pharmaceutical preparations does not serve public health.

The preclinical requirements are regulated by detailed prescriptions. Expert opinions, containing the methods and results of tests are controlled by the *National Institute of Pharmacy* and evaluated by two expert committees of the *Scientific Health Council*, the *Committee on Drug Administration*

and *Clinical Pharmacology and the Medical Committee on Research Ethics*.

The control and evaluation of the expert opinions are followed by a decision concerning the authorization for clinico-pharmacological research, i.e. for the so-called phases I. and II. human trials. It is prohibited to conduct non-authorized human experiments with a new drug.

Clinico-pharmacological tests are carried out by the units of the *Clinical Pharmacological Network* and the results are assessed by the two aforesaid Committees of the *Scientific Health Council*. Authorization for therapeutical experiments (phase III. human trials) depends on the evaluation results.

The *Clinical Pharmacological Network* consists of 27 research units, each unit is functioning as an integral part of a specialized health-institution (clinic or hospital) but its activity is fixed by a co-ordinated national research project for clinical pharmacology.

The positive evaluation of the results of therapeutical experiments, as well as the decision of the *National Institute of Pharmacy* in respect of "drug suitability" are equally preconditions of the registration of a new drug. The application for registration contains the data and expert opinions, on the basis of which the registration procedure is conducted by the Institute, in exactly regulated and prescribed forms.

The data and expert opinions are scrutinized by the Institute's sections for Chemistry, Biology and Microbiology, Pharmaceutical Technology and Pharmacopoeia and the quality requirements and control test methods are established in the *Quality Prescriptions*.

The text of label and package insert (directions for use) is also prescribed by the Institute during the registration procedure.

# Quality control

The reorganization of the pharmaceutical industry following the nationalization was extremely important, not only in order to rationalize production, but it favourably influenced the drug quality. As against to the limited possibilities of small production units (which disappeared), modern analytical, biological, microbiological and other control laboratories could be established in the seven large factories, completed by a central testing organ, the Control Laboratory of the Drug Industry serving the carrying out of certain special biological and microbiological examinations. The laboratories in question are well staffed and equipped, and they are subordinated to the manager of the factory's Department for Quality Control, who together with the director of the factory is personally responsible for the quality of drugs. This responsibility is extended not only to the duty that the quality of all drugs produced by the factory should meet the requirements of the Hungarian Pharmacopoeia and the registration prescriptions of the National Institute of Pharmacy, but in addition, that each of the substances and auxiliary materials used by the factory, as well as each batch (in process, semi-finished and finished) should be submitted to the prescribed examinations.

## Inspection of manufacturing

The Hungarian drug control authority has been entitled since 1936 to make inspections on the spot, but the execution of regular plant inspections is a relatively new activity.

In comparison with countries where the inspectors have to survey several hundreds of plants and laboratories, the work of Hungarian inspectors is considerably easier, since only seven big factories are engaged in the manufacture of human pharmaceuticals.

The "basic (overall) inspections" repeated every five years in the seven pharmaceutical factories constitute the starting point for the regular production control programme of the National Institute of Pharmacy. In principle 6 different forms of inspection are to be distinguished:

- authorization for drug production in a new plant;
- registration of a new drug;
- suspicion on drug quality defects;
- request of health authorities of a country importing drugs from Hungary (on the basis of bilateral or multilateral agreements or individual requests);
- "follow-up" controls;
- random inspections.

The Institute attaches great importance to the teaching and post-graduate training in the spirit of the so-called *good manufacturing practice* (GMP) of those drug factory experts who are implementing GMP in the everyday industrial practice and are engaged in internal factory control, resp. The GMP courses, where several hundreds of professionals from the drug industry took part and entered for an examination, were organized by the National Institute of Pharmacy in co-operation with the Post-Graduate Medical School and the Post-Graduate Institute of the Budapest Polytechnical University.

## **International co-operations**

### **Safety of drug application**

In Hungary, several methods have been introduced to make physicians acquainted with the new drugs and their appropriate application.

In addition to the centrally guided and controlled, but at the same time far-reaching informative activity about drugs, the deliberate observation of side effects and adverse reactions is stressed. In order to extend the work of detecting and preventing unexpected drug reactions, a Drug-monitoring Service was established by the National Institute of Pharmacy. The organized, spontaneous system, being in accordance with the recommendations of the World Health Organization, can look back to a short past, but its efficiency becomes more and more manifest.

The international relations of Hungary are important in every field, and drug control makes no exception either.

### **World Health Organization (WHO)**

Among the international organizations the World Health Organization deals on a world-scale with the problems of drug control, and Hungary endeavours to render help to the WHO in solving these tasks. Hungarian experts play an active part in the compilation of the International Pharmacopoeia, to which the National Institute of Pharmacy contributes with considerable experimental work. The WHO makes often use of Hungarian experts to perform duties as members of professional committees or consultative groups or as WHO consultants in developing countries. The Hungarian health authorities do their utmost for the implementation of WHO guidelines and recommendations serving drug safety in the country.

### **CMEA**

Hungary has undertaken a considerable task—in the framework of CMEA's standing Health Commission—in the field of the investigation evaluation and standardization of pharmaceutical preparations by the international co-ordination of the co-operation started with the participation of Bulgaria, Cuba, Czechoslovakia, GDR, Hungary, Mongolia, Poland, USSR and Vietnam. Hungarian experts take part very actively in the elaboration of the methods and prescriptions of the Compendium Medicamentorum, looking back at present already to great traditions (the aim of this publication is first of all the standardization of quality in drug foreign trade between socialist countries) and maintain working relationship with registration and control authorities of socialist countries.

## **EFTA Pharmaceutical Inspection Convention**

Hungary is member of the international convention elaborated by EFTA states (Pharmaceutical Inspection Convention: PIC\*), which over and above the GMP recommendations of WHO, regulates and makes compulsory the application of safe conditions in drug manufacture and the regular official control of the respective prescriptions.

Hungary is closely co-operating with the other Member States (Austria, Denmark, Finland, Iceland, Ireland, Liechtenstein, Norway, Portugal, Sweden, Switzerland and the United Kingdom) in implementing the provisions of the Convention. The co-operation and the uniformity of inspections are usefully served by the joint training and continuation courses of inspectors.

## **United Nations Industrial Development Organization**

Within the framework of UNIDO three courses of lectures were held by Hungarian specialists for technicians of developing countries. Hungary has actively contributed to the preparation and the work of the First UNIDO Consultation Meeting on the Pharmaceutical Industries (Portugal, December 1980).

## **International responsibility of Hungarian drug control authorities**

The Hungarian health authorities are aware of the international responsibility of the registration and control agencies of countries transacting considerable drug export businesses. In Hungary there are no "two different" registration procedures. The stipulations of the Hungarian Pharmacopoeia and the Quality Prescriptions of the National Institute of Pharmacy refer to the registered drug preparations, independently whether they are used in the country or abroad. In respect of the registered drugs, Hungarian authorities issue certificates on the request of the health authorities of importing countries, and both on multilateral or bilateral basis they undertake the guarantee-offering part, the fulfilment of which is made possible by the more than half a century traditions of the active regulatory drug control system and by the central organization of the pharmaceutical industry and foreign trade.

\* By the full name:  
Convention for the  
Mutual Recognition  
of Inspections in  
Respect of the Manu-  
facture of Pharma-  
ceutical Products



# FOREIGN TRADE

## Historical retrospection

The development at a rapid pace of the Hungarian pharmaceutical factories has created early the basis for exports. CHINOIN and the GEDEON RICHTER WORKS had delivered already prior to the First World War a considerable quantity of drugs to foreign countries, mainly to Russia and the Balkan countries. Later the export activity became more intensive and in the thirties European and even overseas subsidiaries were established, the latter first of all in Latin America.

The Hungarian pharmaceutical industry, reconstructed after the devastations of the Second World War, has become relatively fast able to produce—apart from covering the home needs—also for foreign markets. In the beginning the state enterprise KELIMPEX was engaged—besides other types of articles—in the export of their products, but already in 1949 the dynamical development has made necessary to establish a company specialized in pharmaceutical foreign trade. At this time MEDIMPEX Hungarian Trading Company for Pharmaceutical Products was founded which since that time

is representing the foreign trade interest of the Hungarian pharmaceutical factories.

Though, the export and import of pharmaceutical fine chemicals and specialities make up a decisive part of MEDIMPEX' activity, they achieve a considerable turnover in other fields too. Their export range is completed by feed additives, medicated feeds, biocosmetics, medicinal herbs, volatile oils, medicinal waters, laboratory fine chemicals, biochemical products and radioactive substances. As far as imports are concerned, they purchase important basic substances—apart from the drug industry—for 45 to 50 different enterprises.

The development of the pharmaceutical industry has early made necessary for MEDIMPEX to undertake tasks in the field of intellectual export-import. The licence and know-how agreements have contributed considerably to the extension of the industry's product range, as well as to the introduction in foreign countries of preparations resulting from Hungarian research (Fig. 4 and 5).

## Main markets

The commercial relations of MEDIMPEX extend almost to the whole world. They sell and buy nearly in 100 countries. Besides the socialist countries, the most developed non-socialist countries and those being on the lowest grade of development can be found among their partners.

### Distribution of the Hungarian drug export and import according to the main country groups (1980)

	Exports		Imports	
	Million Ft	%	Million Ft	%
<b>1. Socialist countries</b>	<b>5,656</b>	<b>57.3</b>	<b>967</b>	<b>15.0</b>
CMEA (Comecon)	5,631	57.0	940	14.5
Others	25	0.3	27	0.5
<b>2. Non-socialist countries</b>				
countries	4,213	42.7	5,474	85.0
Developed	2,729	27.6	5,144	79.9
EEC	1,610	16.3	2,925	45.5
Other European	696	7.1	1,602	24.8
Outside of Europe	423	4.2	617	9.6
Under development	1,484	15.1	330	5.1
<b>Total</b>	<b>9,869</b>	<b>100.0</b>	<b>6,441</b>	<b>100.0</b>

### Socialist countries

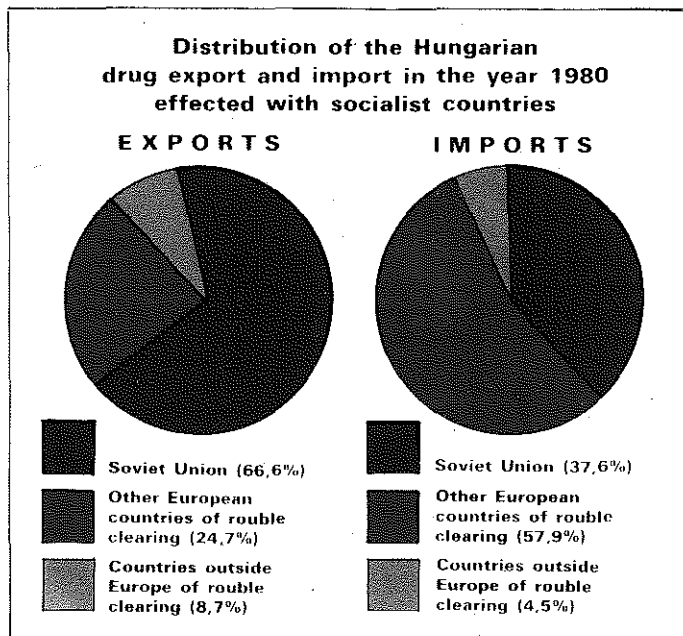
The Hungarian drugs obtained a good reputation in the socialist countries and are much in demand. This can be ascribed not only to their good quality proved in the course of years, but also to the systematic scientific publicity work carried on by MEDIMPEX. Scientific information bureaus are functioning in the Soviet Union, in Poland, in the German Democratic Republic, in Czechoslovakia, Rumania and Bulgaria.

The significance of drug consignments destined to the socialist countries is shown by the fact that their value exceeded 200 million rubles already in 1979.

The exports effected on the basis of bilateral or multilateral product specialization play an important part in the formation of the turnover.

The specialization is a tool to increase both the exports and imports. MEDIMPEX is constantly looking for possibilities to enlarge the range of the home drug supply by the must up-to-date preparations of the other socialist countries. Thus, the ratio of finished drugs is steadily increasing within the assortment of pharmaceutical products imported from the socialist countries.

Among the socialist countries the highest turnover is achieved with the Soviet Union. This is followed by the European CMEA countries, at the same time Vietnam, Mongolia, the Korean People's Republic and Cambodia are catching up more and more (Fig. 6).



# THE GROWTH OF HUNGARIAN DRUG EXPORT RELATED TO 1960

(1960: index = 1)

25 Index

20

15

10

5

1960

1965

1970

1975

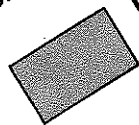
1980

Year

Fig. 4.

# DISTRIBUTION OF THE HUNGARIAN DRUG EXPORT VALUE ACCORDING TO MANUFACTURING COMPANIES

(data of the year 1980)



UNION OF THE HUNGARIAN  
PHARMACEUTICAL INDUSTRY

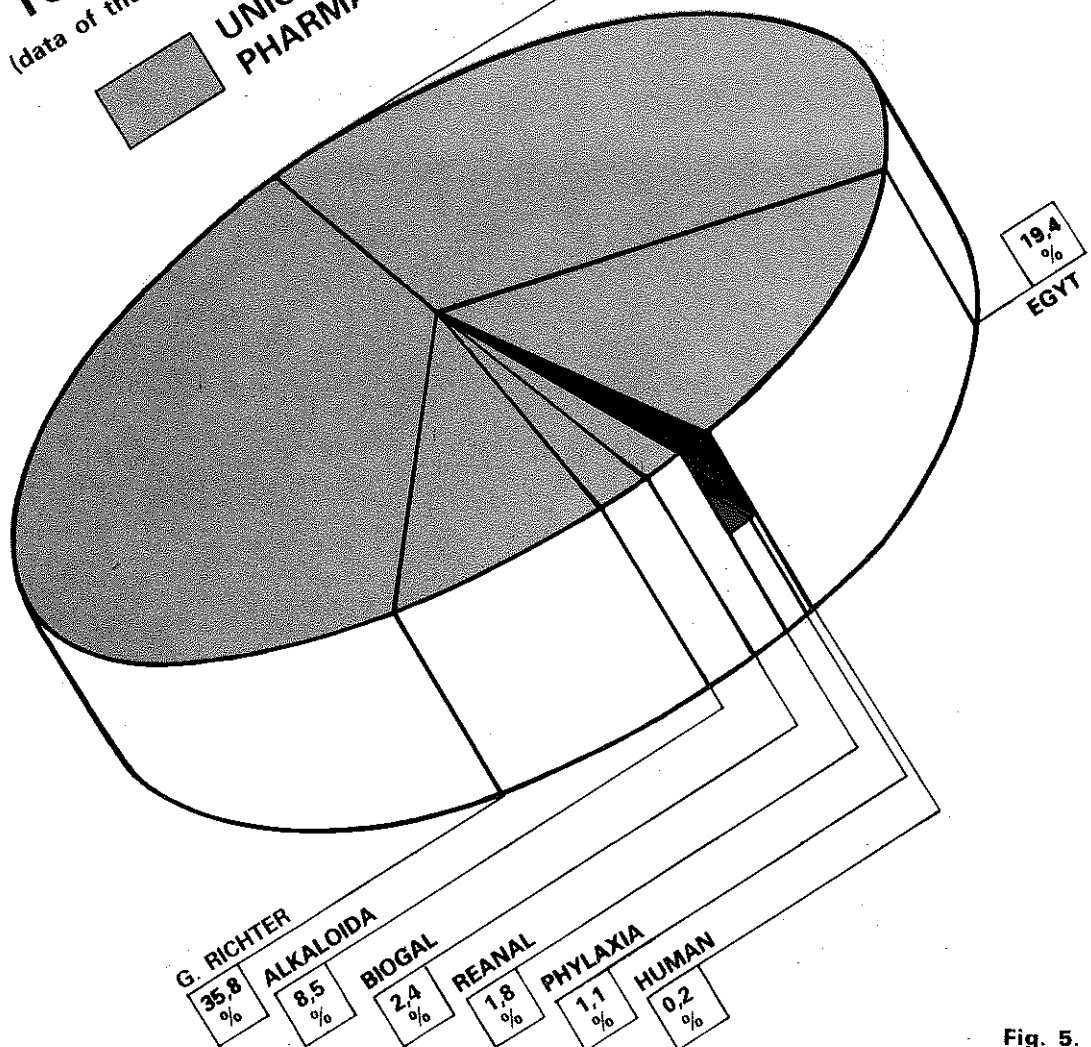


Fig. 5.



## Developed non-socialist countries

In 1980 about 65 percent of the export turnover of non-rouble clearing of MEDIMPEX was achieved with the developed non-socialist countries which circumstance accentuates the importance of this area in the Hungarian pharmaceutical foreign trade. The development of the commercial relations shows a firm tendency. In 1980 the average increase amounted to 6.2 percent related to 1979, the concrete rate of development shows, of course, a rather different pattern for each country. For the most dynamical markets e.g. these figures are the following:

Denmark	138 percent
Canada	100 percent
France	94 percent
Italy	37 percent
USA	33 percent

Since several years the German Federal Republic is the most important partner of MEDIMPEX. The firm *Pharma Haupt*, resident in Frankfurt/M, the local representative of the Hungarian pharmaceutical foreign trade, plays an important part in the realization of the high turnover. The local agencies of MEDIMPEX have done similarly much in the past of the above-mentioned countries.

In order to be present on the market in an increased degree, MEDIMPEX are developing steadily, systematically their commercial network. The result of the past efforts was the establishment of a trade bureau in the USA, the *MEDIMPEX North America*. The newly founded bureaus gradually follow the lead of the former representations which are already in possession of extensive connections, like e.g. *Enzypharm GmbH* in Austria.

The subsidiary and joint companies of MEDIMPEX in the non-socialist countries take part—besides the commercial

activity—in the development of production and research relations, too. The joint enterprise *Optifaro* was established in the German Federal Republic explicitly for the development of research.

The developed non-socialist countries represent a market not only for sales but are important for the purchases by MEDIMPEX. The import volume exceeds yearly US \$ 160 million which meets still the needs of many other industrial branches.

## MEDIMPEX's drug export and import data of 1980 in respect of some developed non-socialist countries (Million Ft)

	Exports	Imports
German Fed. Republic	643.3	1280.2
Italy	297.2	247.8
Switzerland	294.1	1021.6
Austria	111.9	240.0
United Kingdom	228.1	319.4
France	200.7	535.7
Holland	112.8	371.2
Finland	42.3	30.9
Belgium	96.4	150.3
Sweden	19.3	101.7

## Countries under development

The Hungarian drug export directed towards the developing countries is also characterized by a constant increase. Their share in total exports of MEDIMPEX to non-socialist countries is, however, lower (35 percent) than that to developed ones but the pace of the yearly increase of turnover is considerably greater. Of these the most prominent countries were the following:

Iran	2,000 percent
Indonesia	160 percent
Bangladesh	111 percent
Nigeria	80 percent
Algeria	50 percent
Egypt	50 percent

The running up of the turnover can be attributed to two factors. One of these is the increased interest and trust in Hungarian drugs, the other the co-operation in production based on Hungarian technology, established with local firms in more and more countries.

The steadily extending market network of MEDIMPEX serves the augmentation of the turnover as well. In addition to the representatives, trade bureaus, the number of scientific information centres and joint manufacturing companies increases, too. Among these latter, *Imarsel* in Nigeria and *Themis Chemicals* in India can look back already to a longer past (Fig. 7).

# **NETWORK OF MEDIMPEX**

(without agencies)



**PRODUCING  
ENTERPRISES**

- Nigeria
- India
- Bangladesh



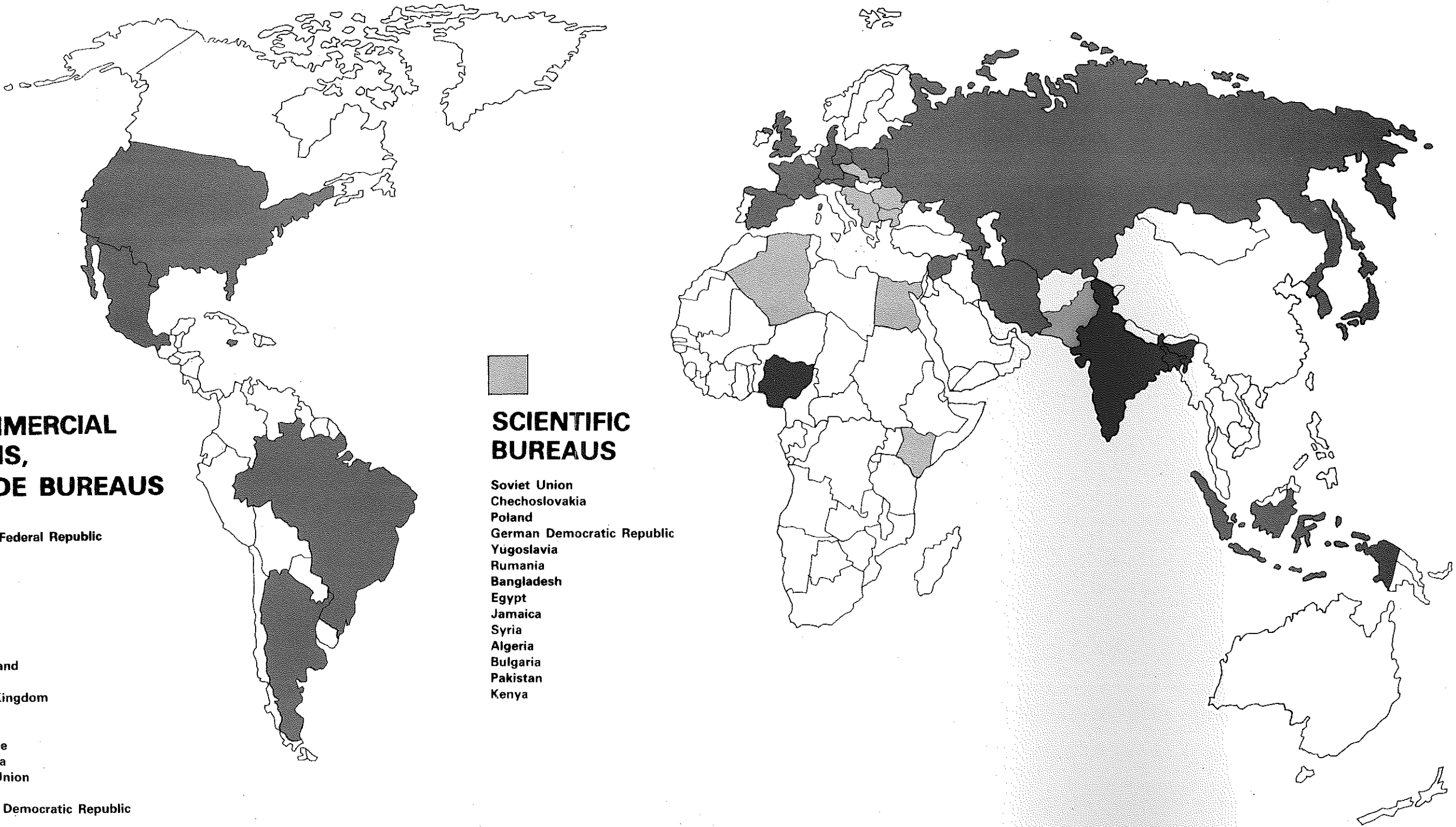
**COMMERCIAL  
FIRMS,  
TRADE BUREAUS**

- Austria
- German Federal Republic
- Spain
- Mexico
- Japan
- India
- USA
- France
- Jamaica
- Switzerland
- Brasil
- United Kingdom
- Iran
- Syria
- Argentine
- Indonesia
- Soviet Union
- Poland
- German Democratic Republic



**SCIENTIFIC  
BUREAUS**

- Soviet Union
- Czechoslovakia
- Poland
- German Democratic Republic
- Yugoslavia
- Rumania
- Bangladesh
- Egypt
- Jamaica
- Syria
- Algeria
- Bulgaria
- Pakistan
- Kenya



## Commerce of intellectual "products"

A full image of the Hungarian pharmaceutical foreign trade cannot be formed without taking into consideration —besides the transactions in goods—the commerce of pharmaceutical intellectual products.

In the past two decades MEDIMPEX have purchased licences, manufacturing processes and trade-mark rights for 42 products from 12 enterprises of 11 countries and sold the same for 80 products to 45 enterprises of 15 countries. In 1978 purchases were effected for 38.4 million forints and sales for 29.8 million forints. At that time the main customers were India, Denmark, Turkey and the German Federal Republic, the most important contractors were Belgium, Holland and the United Kingdom.

The real importance of the turnover in intellectual export-import is not represented by those sums which are paid for the licence, know-how, information, the right of trade-mark use, but by the effect which they exert on the research, development and sale, and for all parties taking a share in the trade it is difficult to demonstrate numerically the actual profit it brings in. The wide circle of partners of which MEDIMPEX is disposing in the intellectual export-import, expresses at the same time the readiness of co-operation characterizing the Hungarian drug industry and foreign trade in this field.



## ADDENDUM

Since putting the manuscript to press the realization of the targets of the pharmaceutical industry has made necessary to carry out some organizational changes. The main point of this change is the efficient realization of the so-called *innovation chain* (research—development—production—marketing—sales), to ensure the synergism between development and marketing. According to the Government's resolution the manufacturer would control the innovation chain. Thus, the sphere of activity and authority of the six factories of the pharmaceutical industry (Alkaloida, Biogal, Chinoin, EGYT, Richter, Reanal) have changed. The enterprises of the pharmaceutical industry possess several joint ventures which contribute to the realization of the innovation chain. The joint ventures are controlled by the Board of Directors, consisting of the company managers. The Union of the Hungarian Pharmaceutical Industry arranges the efficient strategical decisions of the Board of Directors of the industrial sector and co-operates in the execution. The Board of Directors of the individual research institutes is the controlling and leading organ of all three pharmaceutical research institutes (Institute for Drug Research, Medicinal Plant Research, Organochemical Development), forming a joint enterprise.

Concerning *the foreign trade*, several modifications have been effected, too. The producing companies have obtained the individual

right of foreign trade for technical-scientific collaboration (co-operations, licence agreements, etc.), and also "Medimpex" has been re-organized into a joint foreign trade enterprise. In its Board of Directors there is a seventh member beside the six directors of the pharmaceutical companies, namely the director of Pharmatrade Foreign Trading Company. This organization was established because foreign trade activity of Medimpex covered in the previous years not only the pharmaceutical industry, but also other industrial branches (medicinal herbs, medicinal mud, food industry, agriculture, cosmetics, perfumery, etc.).

The immediate superior authority of Medimpex Hungarian Trading Company is a Board of Directors, consisting of seven members, out of which every two years a president is elected, controlling the activities of the foreign trading company.

Medimpex Hungarian Trading Company for Pharmaceutical Products is thus a so-called *joint venture* and a joint property of the pharmaceutical factories, as well as of Pharmatrade Trading Company. With its marketing network extending to more than 25 countries, it helps and improves the steadily developing international relations of the Hungarian pharmaceutical industry.