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PHARMACEUTICAL INDUSTRY AND RESEARCH IN HUNGARY



BUDAPEST

1973

In the industrial production and export of Hungary the pharmaceutical industry is an important and steadily growing factor. Nearly three-quarters of the drug production is exported, a fairly high rate even by international standards. The rapid expansion of the pharmaceutical industry has been greatly promoted by the highly developed nation-wide health services. The national health scheme covering practically the whole population provides the benefit of free medical care and hospital treatment against a charge paid by the employer. Medicines are free for hospitalized patients

while the out-patients have to charge a small contribution (15% of the public price). Drugs for treatment of venereal diseases, tuberculosis, diabetes and other chronic conditions are available free of charge.

In Hungary there is at present one doctor to every 417 inhabitants, the number of hospital beds is 8.28 for every 1,000 inhabitants and the total number of doctors and nursing and hospital auxiliary staff for every 100 hospital beds is 50.

INTRODUCTION

The first Hungarian drug factory was founded in 1867 but after a few years it discontinued its activities, thus the very beginning of industrial drug production dates back to the turn of the century. These data cannot be considered as mere chance since they closely followed the birth of modern pharmacology and the creation of industrial drug production and research in Europe.

It was in the last decades of the past century that physiology, histology, microbiology and organic chemistry received a sudden impetus. The progress of these and of other medical specialities lead to a new discipline the formation of experimental pharmacotherapy. Drug therapy based earlier on empirical observations with medicines from botanical, animal and mineral sources was gradually superseded by modern pharmacology dealing with chemically pure substances tested in animal experiments. Simultaneously, dispensary scale drug manufacture was converted into industrial scale production which in turn involved extensive drug research.

The number of compounds made by synthesis has shown a steadily increasing trend from year to year and as a result the arsenal of drugs has been more and more dominated by synthetic substances, while the range of substances obtained from natural sources was constantly decreasing. It was only in the last decades that the propagation of biochemical techniques brought about a new expansion of natural substances (antibiotics, vitamins, enzymes) in the drug production.

DRUG RESEARCH

Drug research in Hungary is conducted not only in the two industrial research institutes, namely the Research Institute for Pharmaceutical Chemistry and the Research Institute for Medicinal Plants, and in the research departments of the five big factories: Chinoin, Richter, EGYT, Biogal and Alkaloida, but a number of Academy and University units are also involved. The latter are partly concerned with independent research subjects and they closely co-operate with industrial research units. A fine collaboration has been established with University Departments for Organic Chemistry, Pharmacology and Plant Chemistry.

The importance of clinico-pharmacologic evaluation becomes more and more evident, since it has to decide on the future of potential drugs under development.

The Ministry of Health has established for this sake the so-called network of clinico-pharmacologic units displaying a manifold activity.

1. Introduction of modern objective methods for the assessment of the effects of drugs in humans.
2. Investigation of the clinical efficacy of new original drugs.
3. Re-evaluation of some effects of old drugs.

It is a fact of common knowledge that pharmacological findings in animals can hardly be adapted to humans. A number of side effects are likely to occur in man which cannot be predicted on the basis of animal toxicology. There are even side effects which were recognized after some decades of practical use (e.g. agranulocytosis due to aminophenazone, inhibition of the aggregation of thrombocytes by acetyl salicylic acid, etc.).

RESEARCH INSTITUTE FOR PHARMACEUTICAL CHEMISTRY The Research Institute for Pharmaceutical Chemistry was founded in 1950. Since that time more than 150 technological processes have been elaborated and put into industrial practice by the Institute. An important part of the profit of the pharmaceutical industry is based on the technologies worked out and introduced by the Institute. These outstanding results can be attributed to a well-established collaboration between the highly qualified and properly skilled research teams. Alongside the Institute's initial staff of research scientists and technical auxiliaries who came from the industry, a valuable team of gifted junior specialists has gradually grown up. The steadily expanding scientific activities of the Institute's staff are reflected in the increasing number of patents granted and in the growing number of published papers and lectures. (The number of publications up to the end of 1972 was 739, in the same year staff members presented 83 lectures in Hungary and 28 abroad. The number of patents granted up to the end of 1972 was 385.)

RESEARCH INSTITUTE FOR MEDICINAL PLANTS The Research Institute for Medicinal Plants was set up in 1915. Its scope of activities includes research for a more intensive utilization of medicinal plants and their quality control. The research is conducted in the Departments for Cultivation, Biology and Plant Chemistry, in the Institute's well-equipped laboratories and its experimental station. The field of investigations covers distribution, agrotechniques, the problems of dissemination with special reference to the increasing of the content and quality of active constituents—as well as biochemical examination of medicinal plants. Investigation of the chemical structure of active principles of medicinal plants is dealt with by a special laboratory.

INSTITUTE FOR EXPERIMENTAL MEDICINE

The Institute for Experimental Medicine with a special Department for Drug Research was set up by the Hungarian Academy of Sciences in 1954. The Department has been concerned with basic research of fundamental relationships between chemical structure and pharmacodynamic activity, including the elucidation of the mechanism of action and in this way the search for new drugs.

The main research fields are: cholinergic actions with special reference to the central nervous system, pharmacologic investigation of the mechanism of circulation reflexes, spasm-inducing and spasm-inhibiting substances, the measurement of the parameters of some central nervous functions, the metabolism of amines in the central nervous system and some of their involvements. In the biochemical laboratory of the Institute electrophysiological investigations are also carried out.

UNIVERSITY INSTITUTES

The close co-operation which has been established with a number of University institutes and University teams for the last sixty years has provided a solid support for the pharmaceutical industry. After the nationalization of the industry a turning-point was reached also in research outside the industry as a result of planned co-ordination and specialization. This has brought about a closer co-ordination of research both inside and outside the industry resulting in the expansion and increased efficacy of research.

At present the Hungarian pharmaceutical industry maintains regular contacts with more than 70 University institutes and research institutes of University level. The aim of the research co-operations is the development of new medicines. Several institutes are engaged in the pharmacologic and toxicologic investigation of new drugs including teratologic studies as well. There is a close collaboration in the field of chemistry and microbiology further in analytical research implying micro-analysis, X-ray diffraction, IR and UV spectrophotometry, NMR, mass spectrometry and gas chromatography as well as the development of new analytical methods and pharmacokinetic studies. Research in medic-

inal plants and improvement of agrotechnical methods are also carried out in collaboration with several institutes.

An inestimable assistance is granted by hundreds of physicians in more than 120 clinics and hospitals where pharmacologic and clinical testing of new drugs is carried out.

The beginning of Hungarian drug research coincided with the turn of the century. It was in 1900 when Z. Vámosy described the laxative action of phenolphthalein which, since that time, has become a drug of current use and was also included in several pharmacopoeias. It was the first pharmaceutical preparation based on Hungarian discovery.

The following table gives a survey of medicines originating from Hungarian research:

YEAR	GENERIC (CHEMICAL) NAME	TRADE NAME
1900	Phenolphthalein	Phenolphthalein
1917	Methyl homatropine bromide*	Novatropin
1927	Mercurphylline*	Novurit
1928	Ascorbic acid*	Vitamin C
1931	Ethaverine*	Perparine
1936	Adenosine triphosphate	Atriphos
1936	Embryonic heart extract	Corhormone
1940	Sulphamethylthiazole	Ultraseptyl
1955	Tolperisone*	Mydocalm
1955	Pimeclone*	Karion
1955	Mannomustine*	Degranol
1956	Oxytocin, synthetic*	Oxycotin synth.-Richter
1958	Trimetozine*	Trioxazin
1959	Vincamine*	Devincan
1959	Mitobronitol*	Myelobromol

* International trade name accepted by WHO

YEAR	GENERIC (CHEMICAL) NAME	TRADE NAME
1960	Deprenyl *	Jumex
1960	Metofenazate *	Frenolon
1961	Mannosulphan *	Zitostop
1961	Drotaverine *	No-Spa
1961	Sodium disulpho-salicylate samarium-III anhydrous	Phlogosam
1961	1,-Dideoxy-1,4-Bis ([2-hydroxyethyl]amino) erythritol-1,4-dimethane sulphonate	Lycurim
1962	Fendiline *	Sensit
1962	21-deoxy-21-N-(N' methylpiperaziny) prednisolone hydrochloride	Depersolon
1962	3-(beta,beta-Diphenylethyl)-5-(beta-piperidinoethyl)-1,2,4-oxadiazole	Libexin
1963	Bencyclane *	Halidor

* International trade name
accepted by WHO

YEAR	GENERIC (CHEMICAL) NAME	TRADE NAME
1965	Mitolactol *	Elobromol
1966	alpha-Guanidino-methyl heptamethylenimine sulphate	Sanegyt
1966	Tofisopam *	Grandaxin
1966	alpha-Methyl-alpha-phenyl-N-morpholinyl-methylene succinimide	Morfolep
1966	(4-chlorophenyl)-3,4-dichlorobenzolsulphonamide	Perseptyl
1966	Rimazolium *	Probon
1970	Vinpocetine *	Cavinton
1971	Synthetic human corticotrophine 1-32	Humacthid-32

* International trade name
accepted by WHO

RESEARCH
ACHIEVEMENTS
OF THE
HUNGARIAN
PHARMACEUTICAL
INDUSTRY

ACTIVE SUBSTANCES OF PLANT ORIGIN

DIGITALIS 1924 The first pure extract from common foxglove was produced by the Chemical Works of Gedeon Richter Ltd. in 1924. After World War II, the Richter factory in close co-operation with the Research Institute of Pharmaceutical Chemistry and the Research Institute for Medicinal Plants achieved very important results in the research and production of digitalis glycosides. A wide range of glycosides including lanatosides A, B, C (Neo-Adigan), lanatoside C (Isolanid-Richter), deslanoside (Isolanid-Richter), digitoxin (Carditoxin), digoxin (Digoxin-Richter) and acetyldigitoxin (Acigoxin) have been produced in huge quantities.

MORPHINE 1930 The extraction of morphine from dry poppy capsules was first accomplished by the Hungarian pharmacist J. Kabay. Since Sertürner had first isolated morphine at the beginning of the 19th century, much effort was devoted to the isolation of morphine not from opium but directly from poppy. The

methods suggested, however, failed to be economical. J. Kabay was the first to work out an economical procedure for the extraction of morphine from poppy capsules which had been earlier regarded as worthless. This procedure was advantageous not only for its economical value but from the point of view of public health. By eliminating the opium-phase, the extraction of morphine and of other opium alkaloids was made possible from a non-opiate starting material. Its importance in this respect was emphasized in a statement of the Opium Committee of the League of Nations.

The Kabay method was subject to further improvement and utilization by various manufacturers all over the world.

The Alkaloida Chemical Factory produces a wide range of therapeutically important alkaloids (morphine, ethyl-morphine, codeine) as well as their derivatives (nalorphine, dihydrocodeine, dihydrocodeinone) and some of the by-alkaloids (thebaine, narcotine). According to the statistics of the UN Opium Board, Hungary is among the leading opium alkaloid exporting countries, especially of codeine and morphine.

ERGOT ALKALOIDS Investigations aimed at the isolation of ergot alkaloids were started simultaneously by Chinoin and G. Richter

1936 Ltd. Research resulted in the discovery of Sensibamine. Later M. Békássy succeeded in establishing ergot cultivation by means of artificial contamination enabling thus G. Richter Ltd. to use ergot in large quantities and of improved quality for the production of crystalline ergotoxine and of its constituent ergocristine, furthermore of ergotamine and ergometrine, which comply with the standards of the pharmacopoeias.

VINCAMINE 1959 Vincamine, the crystalline alkaloid of periwinkle (*Vinca minor*) was first isolated by K. Szász at the Chemical Works of Gedeon Richter Ltd. The compound received world-wide attention by its cerebral vasodilating effect.

ACTIVE SUBSTANCES OF ANIMAL ORIGIN

NEOPERHEPAR 1927 Prior to Whipple, R. Jeney was the very first to draw attention to the benefits of the antianaemic activity of the liver in a paper dealing with blood regeneration following blood losses. Unfortunately clinicians failed to check these findings in patients suffering from pernicious anaemia. As soon as the ingredient of antianaemic effect of the liver became measurable, Gedeon Richter, founder of the Chemical Works of Gedeon Richter Ltd., stated that the liver extract (Perhepar) issued several decades earlier was containing adequate quantities of the newly discovered principle. The standardized liver extract Neoperhepar contains declared quantities of cyanocobalamine.

ATRIPHOS 1936 A. Szent-Györgyi was the first to demonstrate that adenosine triphosphate (ATP), known as an important factor in muscle contraction and metabolism, is a potent dilator

of both coronary and peripheral vessels. Atriphos produced in Hungary was the first preparation containing adenosine triphosphate in a pure state and thus it constituted an important progress after organ extracts of unreliable therapeutic value. The preparation is used worldwide in the treatment of angina pectoris and of vasoconstrictions as well as for the control of paroxysmal tachycardia.

APROTININ 1965 The Chemical Works of Gedeon Richter Ltd. produces aprotinin, a polyvalent protease inactivator consisting of 58 amino acids, from cattle lung. This trypsin-kallikrein inhibitor is marketed under the name Gordox and is used for treatment of pancreatitis and other conditions.

HORMONES AND HORMONE-LIKE SUBSTANCES

HORMONES OF ANIMAL ORIGIN

The Hungarian pharmaceutical industry has its fine traditions in research and production of hormones.

ADRENALINE 1902 One year after the discovery of adrenaline by Japanese scientists, the Chemical Works of Gedeon Richter Ltd. marketed Tonogen, a product containing natural adrenaline.

This was followed a few years later by Glanduline, a standardized posterior pituitary extract. Since that time G. Richter built up its special hormone line covering a wide range of various hormone products.

STEROID HORMONES

An important step in building up this hormone line was the elaboration of various steroid hormones, as oestrogens, gestagens, androgens, adrenal steroids (DOCA, hydrocortisone, prednisolone), anabolics (methandienone, nandrolone). In the 1930s oestrogen derivatives produced by Chinoin from the urine of mares (Akrofolin, Hogival) and their semi-synthetic progesterone (Akrolutin) gained world-wide reputation.

Recent progresses in the steroid program of Richter are marked by Depersolone, a new glucocorticoid preparation of rapid onset of action, and a wide range of oral contraceptives (Infecundin, Bisecurin, Cervicundin).

SYNTHETIC HORMONES

OXYTOCIN SYNTH.— Shortly after the elucidation of the structure of oxytocin by Du Vigneaud its industrial synthesis was performed by the Research Institute for Pharmaceutical Chemistry. Since that time the Chemical Works of Gedeon Richter Ltd. has been continuously producing synthetic oxytocin.

ACTH SYNTH. On the basis of a successful co-operation between the Research Institute for Pharmaceutical Chemistry, the Institute of Organic Chemistry of the University of Budapest and the Chemical Works of Gedeon Richter Ltd. a fragment of human corticotrophin of the amino acid sequence 1–28 was synthesized. Later on another fragment with sequence of amino acids 1–32 (Humacthid-32), and recently also the full sequence was prepared by synthesis. Out of these compounds only Humacthid-32 has been put on the market because it is displaying a full hormone action. The full sequence compound is used only for scientific purposes.

VITAMINS

VITAMIN C 1928 Nobel Prize winner A.

Szent-Györgyi isolated a substance from the suprarenal gland called hexuronic acid, which proved identical with Vitamin C. The isolation of the same substance from paprika by Szent-Györgyi enabled the Chinoin Works to start industrial synthesis.

VITAMIN P 1936 The investigations into Vitamin C led A. Szent-Györgyi and I. Rusznyák to the isolation of Vitamin P. The substance reduces permeability and fragility of the capillaries. Szent-Györgyi and G. Bruckner evidenced Vitamin P to be built up from the flavonoids, namely from hesperidine and eriodictiol.

VITAMIN B₁₂ Both Chinoin and Richter have made

1955 some important contributions to Vitamin B₁₂ research by working out completely new fermentation processes to produce crystalline Vitamin B₁₂.

CHEMOTHERAPY

TUBERCULOSTATIC AGENTS

Several anti-tubercular agents, such as INH ((Isonnicid), Ethionamide (Rigenicide), Prothionamide (Tebeform), Cycloserine, Pyrazinamide, Ethambutol (Sural), are produced in large quantities by Richter and Chinoin, respectively.

SULPHONAMIDES

In Hungary, Chinoin has been the pioneer in sulphonamide research. At present, Alkaloida has also an important role in the production of sulpha drugs.

SULPHANYLAMID Almost contemporaneously with the appearance of Pron-

1939 tosil, Chinoin developed and issued its sulphonylamid under the brand name De-septyl. (For the time being no production.)

SULPHAMETHYLTHIAZOL, SULPHATHIOUREA 1940

Chinoin was the first manufacturer to synthesize and produce sulphamethylthiazol (Ultra-septyl) and sulphathiourea (Salvoseptyl).

COMBINATION OF SULPHAS WITH TRIMETHOPRIM, 1969

Combination of synergetic action, like a sulphamethoxazole + trimethoprim (Sumetrolim) and sulphadimidine + trimethoprim (Potesepyl) constitute new important developments of the chemotherapeutic drug production.

CYTOSTATICS

Search for antineoplastic agents is one of the most important tasks in modern biology. Researchers of the Research Institute for Pharmaceutical Chemistry did a pioneering work in the

preparation of cytostatic sugar alcohol derivatives.

From the numerous derivatives which proved active in experimental studies, the following have been introduced in clinical practice on the basis of wide-scale clinical investigations.

MANNOMUSTINE (DEGRANOL) 1955 Starting from the hypothesis that cytostatic groups, when bound to "natural" substances, will pass the cell membrane more readily and thus will reach more easily the tumour cell, where they have to display their action, L. Vargha synthesized a number of sugar alcohols substituted with biological alkylating groups. The second compound of the substances synthesized was mannomustine (1,6-bis β -chloroethylamino]-1,6-dideoxy-D-mannitol). Animal experiments by B. Kellner and L. Németh have brought the evidence of its high activity and a relative low degree of toxicity. Clinical observations made first by C. Sellei and later by a number of other investigators verified the effectiveness of Degranol in chronic lymphocytic leukaemia, Hodgkin's disease, lymphosarcoma and other haemoblastoses. Mannomustine is considerably less toxic than nitrogen-mustard and its practically unavoidable side effects are far less frequent in occurrence and less serious in severity. These findings have been evidenced by papers dealing with investigations in more than 20 countries.

MITOBRONITOL The cytostatic effect of mito-
(MYELOBROMOL bronitol (1,6
DIBROMO -dibromo-1,
MANNITOL) 6-dideoxy-*D*-mannitol) was
 established by Csányi and
 co-workers in the Re-
 search Institute for
1959 Pharmaceutical Chemistry. In clinical
 practice it has been found the drug of
 choice for the treatment of chronic myelocytic
 leukaemia.

1,4-DIDEOXY-1,4-BIS
([2-HYDROXYETHYL]
AMINO) ERYTHRITOL-1,4
-DIMETHANE SULPHO-
NATE (LYCURIM) 1961

The drug was worked out by the same team of
 the Research Institute for Pharmaceutical Chem-
 istry. Its action is directed to lymphoid haemo-
 blastoses, particularly to chronic leukaemia, its
 immunosuppressive action being also impor-
 tant.

MANNOSULPHAN 1,2,5,6-
(ZITOSTOP) 1961 tetramesyl-
D-mannitol.
 Its biologic
 action substantially differs from that of the cyto-
 statics known hitherto. In adequate doses it is
 mainly active against solid tumours, while blood
 picture is only affected by doses close to or
 within the toxic range. Its clinical features show
 therefore a certain selectivity.

DIBROMODULCITOL
(MITOLACTOL) 1965

In animal experiments Mitolactol inhibits the
 growth of a number of transplantable, resistant
 tumours. Its oral application in humans displays
 a potent antitumour action. Its toxicity is slight.

ANTIBIOTICS

Antibiotic research in Hungary started as early as the middle of the 1940s. Today the most important antibiotics, as penicillin, streptomycin, oxytetracycline, neomycin, bacitracin, nystatin and the semisynthetic penicillins (ampicillin, methicillin, oxacillin, penamecillin) are manufactured by modern technologies and in large quantities. Some synthetic antibiotics, as chloramphenicol and cycloserine, are also produced in considerable amounts.

T. Vályi-Nagy and collaborators in the Department of Pharmacology of the University in Debrecen succeeded in isolating Primycin, a polypeptid with antibacterial action, in 1951. Megacin, an antibacterial protein produced by *Megatherium* discovered by G. Ivanovics and L. Alföldi in 1951, and Flavofungin, an antifungal polyene discovered by J. Uri and I. Békássy in 1956, are only of theoretical value. E. Tóth-Sarudy and I. Horváth in 1969 isolated from *Streptomyces parvulus* PARVULIN, a mixture of three acidic peptides. The antibiotic of a rather broad spectrum of activity is used in animal feeding.

SPASMOLYTICS

NOVATROPINE In the course of investigations in 1917 to the relationship of chemical structure and pharmacological activity Prof. B. Issekutz demonstrated that quaternization of homatropine with methylbromide (Novatropine) abolished central nervous excitatory action, while parasympathetic blocking effect was maintained.

PAPAVERINE Since the quantity of papaverine yielded by opium was insufficient to meet continuously increasing demands, Chinoin was the first, more than 40 years ago, to start the synthesis of papaverine on a large-scale industrial level.

ETHAVERINE (PERPARINE) The discovery of ethaverine, a three times more active smooth muscle relaxant as papaverine, was the result of a close research co-operation of a Chinoin team (Z. Földi and co-workers) with Prof. B. Issekutz. Ethaverine is the ethyl analogue of papaverine.

DROTAVERINE Thirty years after
(NO-SPA) 1961 the implementa-
tion of industrial
papaverine pro-
duction a research team of Chinoin (Z. Mészáros
and coll.), in co-operation with Prof. B. Issekutz,
prepared the new papaverine-derivative, drotaverine, which is superior to papaverine and
ethaverine in spasmolysis and devoid even in
high dosage from cardiotoxicity.

DIURETICS

HYDRARGYRUM E. Jendrassik
CHLORATUM 1886 described in
biting the laxative ac-
MITE CALOMEL tion of calo-
mel by opia-
1886 tes, its diuretic effect can be used for
draining up of oedemas. Calomel was
referred to as a diuretic in the text-books over a
long period.

MERCUROPHYLLINE A re-
search
(NOVURIT) 1927 team of Chinoin
(Z. Földi and
coll.) synthesized in 1927 the β -methoxy- γ -
hydroxymercuripropylamid of camphoric acid.
Its favourable diuretic action was demonstrated
by B. Issekutz who also pointed out that this
effect could be strongly potentiated by associa-
tion with theophylline. The mixture of the two
compounds has been in current use all over
the world and included in several pharmaco-
poeias.

HYDROCHLORO-THIAZIDE (HYPOTHIAZIDE), 1958 In the course of their search for new nonmercurial diuretic agents L. König and Z. Földi prepared hydrochlorothiazide — coincidentally with but independently from foreign researchers — thirty years after the discovery of mercuraphylline. According to B. Issekutz the compound is fifteen times more potent than its forerunner, chlorothiazide.

PSYCHOTROPIC AGENTS

The Hungarian pharmaceutical industry has kept pace with the world-wide research work on psychopharmacologic agents. Most of the important psychopharmaceuticals, as meprobamate (Andaxin), chlorpromazine (Plegomazine), imipramine (Melipramine), levomepromazine (Tisercin), perphenazine (Thilatazine), trimipramine (Sapilent), amitriptyline (Teperin), nialamide (Nuredal), diazepam (Seduxen), are included in the production programme.

Out of this group the following original products are to be mentioned:

TRIMETOZINE (TRIOXAZINE) 1958 Trioxazine (Trimetozine; N-[3,4,5-trimethoxybenzoyl]-tetrahydro-1,4-oxazine) was synthesized by L. Vargha and co-workers in the Research Institute for Pharmaceutical Chemistry. Pharmacological and clinical testing demonstrated its activity as a minor tranquillizer together with a remarkably low degree of toxicity. Trioxazine has the advantage not to affect monosynaptic and polysynaptic reflexes and as a consequence it does not display muscle relaxing action. Trioxazine is a day-time tranquillizer, free of side effects, particularly suitable for treatment of neuroses and agitation due to emotional factors.

METOFENAZATE (FRENOLON) 1960 L. Toldy of the Research Institute for Pharmaceutical Chemistry demonstrated that esterification of the hydroxy group in perphenazine with trimethoxy benzoic acid results in the decrease of toxicity and increase of therapeutic activity. Pharmacologic trials showed Frenolon to have a therapeutic index more favourable than that of chlorpromazine or perphenazine. Open field clinical trials brought about findings which corroborated pharmacologic prognosis.

Frenolon has been in current use as a major tranquillizer. Its additional coronary vasodilating action makes its use justified also in cases where cardiac and circulatory failure is complicated by psychiatric or neurotic super-positions.

N-3,4,5-TRIMETHOXY- BENZOYL HEPTA- METHYLENE IMINE (ORIGEN) 1968

The potential antidepressant action of N-3,4,5-trimethoxybenzoyl heptamethylene imine was detected by the investigations of L. Szporny and É. Pálos. From the chemical point of view it is a new type of anti-depressant, which is not a MAO-inhibitor. It is active against the different forms of depression.

MISCELLANEOUS

TRICHLORO- ISOBUTYLALCOHOL 1897

Z. Vámosy was the first to point out the local anaesthetic property of trichloro-isobutylalcohol.

PHENOLPHTALEIN 1900

The laxative action of phenolphthalein was recognized by Z. Vámosy. Phenolphthalein has received world-wide acceptance and has been included in most pharmacopoeias. This was the first drug of Hungarian discovery produced on an industrial scale.

TOLPERISONE K. Nádor synthe- (MYDOCALM) sized 1-piperidino- 2-methyl-3-*p*- tolyl-propanone

1955 (tolperisone), an amino-ketone with pronounced anti-nicotine property. Pharmacologic tests proved its blocking effect on the polysynaptic crossed extensor and ipsilateral flexor reflexes, but without observing either curare-like or atropine-like actions. Extensive clinical trials verified its favourable influence in conditions accompanied by hypertonicity of striated muscles, as in sclerosis multiplex and postencephalitic syndrome. The tremor controlling effect has been evidenced in many cases of Parkinson's disease. According to later clinical findings, in addition to this, tolperisone proved extremely useful in peripheral vascular diseases, particularly in angioneuropathias.

PIMECLONE Out of the aminoketones
prepared by K. Nádor in
(KARION) 1955 the Department
for Drug Re-
search at the Institute for Experimental Medicine

of the Hungarian Academy of Sciences pimeclone (1-piperidinomethyl-cyclohexan-2-one) exhibited in pharmacological testing a lobeline-like but therapeutically more promising stimulating action on the respiratory centre. In contrast to lobeline the application of the new substance was not followed by drop in blood pressure. In artificial hypothermia the full activity of pimeclone is maintained.

In therapeutic dosage it has no influence on the cardio-vascular system and administration can be repeated without any risk. Due to direct stimulation of the respiratory centre and a consecutive increase of respiratory frequency and volume Karion can be given with good results in neonatal asphyxia, barbiturate and carbone monoxid poisoning, in respiratory depression during or after narcosis and to speed up the expiration of inhaled narcotics.

DEPERSOLONE It is a glycocorticoid, chemically 21-deoxy-21-N-(N'-methyl-piperaziny)-prednisolone hydrochloride, discovered and synthetized in the Research Laboratories of Gedeon Richter Ltd. It displays pronounced antiphlogistic action and is used as intravenous injection or drip in cases of emergency for traumatic shock and asthmatic state. When administered in form of ear-, nose- or eye-drops it exerts a marked antiinflammatory action.

LIBEXIN 1962 In the Chinoin Chemical and Pharmaceutical Works Ltd. K. Harsányi synthetized a

new oxadiazole derivative with marked peripheral spasmolytic and antitussive activity. The drug is devoid of respiration depressing and constipating effects.

BENCYCLANE (HALIDOR) 1963 In the Research Laboratory of EGYT Pharmacofactory Pallós and collaborators synthetized bencyclane (Halidor) as a result of investigating a series of basic cycloalkanole ethers. Relying on its vasoactive, myotropic, spasmolytic properties the drug is advantageously used in acute and chronic spasms of smooth muscles, furthermore in circulatory disturbances of the brain and of extremities. In several Western countries bencyclane is marketed as Fludilat or Ludilat.

PHLOGOSAM 1961 The importance of factors involved in blood coagulation in the inflammatory process directed attention to rare earth metals as possible antiinflammatory agents (Jancsó).

The complex salt of Samarium with sulphosalicylic acid (2 : 1) proved to be a highly potent antiphlogistic agent in both animal experiments and human trials.

From recently developed drugs mention should be made of PROBON (analgesic), NIOBEN (vasodilator), SANEGYT (a blood pressure lowering guanethidine derivative), GRANDAXIN (minor tranquillizer).

REGISTRATION FOR NEW DRUGS

1. Before starting with the production of a new drug, the manufacturer has to inform the National Institute for Pharmacy about his intention and to submit accurate data of specification including chemical and pharmacokinetic parameters and detailed descriptions of pharmacological and toxicological findings. The application will be carefully checked by the Institute and submitted to the Committee for Drug Research and Registration of the Scientific Health Commission. If preclinical data are accepted, clinical institutions will be appointed for clinical trials. In Hungary every substance approved for trials in humans has to contain well-defined active principle(s) and findings of animal studies have to be verified by adequate clinicopharmacological tests.

2. The experts entrusted with the clinicopharmacological and clinical investigation of new drugs have to assess the new substance on the basis of a trial implying a sufficient number of subjects. When, after evaluation of the reports, the National Institute for Pharmacy takes its decision giving its permission for the manufacture, it also accurately deter-

mines fields of indication, route of administration and dosage.

3. In this phase the process of registration begins. This involves the thorough chemical (biological or microbiological) testing, including activity, purity and stability tests. If the results of the controls are satisfactory, the Institute gives permission for registration indicating whether the new drug can be dispensed with or without a doctor's prescription and including the final, approved text of labels, and package inserts, etc. On the basis of registration, the Ministry of Health grants its permission for sales.

PHARMACEUTICAL PRODUCTION



CHINOIN
Chemical and Pharmaceutical
Works Ltd.



Chemical Works of
GEDEON RICHTER Ltd.



EGYT
Pharmacochemical Works



ALKALOIDA
Chemical Factory



BIOGAL
Pharmaceutical Works



PHYLAxia
Veterinary Biologicals
and Feedstuffs Ltd.



Institute for Serobacteriological
Production and Research
„HUMAN”

CHINOIN CHEMICAL AND PHARMACEUTICAL WORKS LTD.



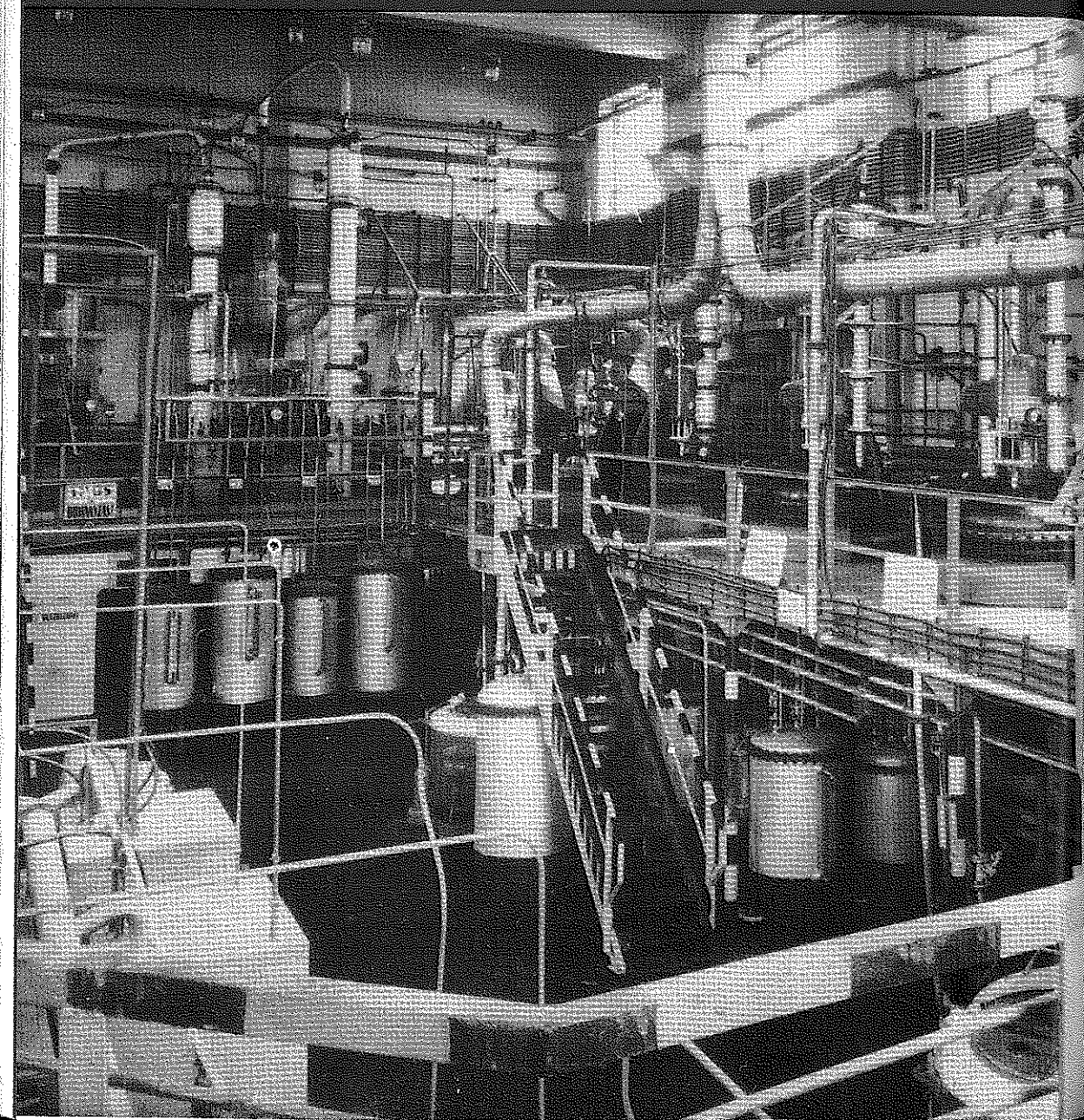
The factory was founded in 1910 by the chemical engineers Dr. Kereszty and Dr. Wolf in Újpest, then a suburb of Budapest, at present a district of the capital.

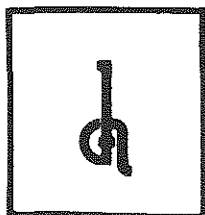
At the beginning the factory was manufacturing some simple substances and intermediates as well as some

specialities on the basis of foreign licences, it was also dealing with the packaging of some products bought in bulk.

After World War I the production of Chinoin became continuously and considerably expanding. Beside the manufacture of a few drugs of animal and plant origin, there was an important increase in the production of synthetic substances, as ether for narcosis, chloroethyl, bromoisovaleryl-urea, homatropine methylbromide, papaverine which not only permitted to comply with home demands but to operate export business at the same time. In the period between the two World Wars Chinoin built up an operative network of export agencies, representatives and subsidiaries.

Already in the early 1920s the Research Laboratory of Chinoin Ltd. established close co-operation with a number of university institutes. Out of these the Chemistry Department headed



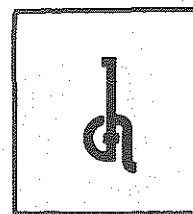


by Prof. Zemplén and the Pharmacology Department headed by Prof. Issekutz proved to be of valuable assistance.

During the years preceding World War II several successful new drug developments brought about a rapid expansion. The outbreak of World War II interrupted the process of progress; export markets had been broken off and war events, particularly bombings, caused grave damage to the factory. Production in 1945 practically came to a standstill. The nationalization in 1948, however, brought about a new, important, continuous expansion; the production programme was extended (antibiotics), which gave an important impetus to manufacture. A sudden increase in production set in, a number of new preparations were put on the market. Export rate began to increase successively, at present it makes about 70% of production.

In 1971 prostaglandin research and production were added to the programme. The preparation and production of the prostaglandins E_1 and $F_{2\alpha}$ have already been solved.

The product range of Chinoin includes beside drugs for human and veterinary uses also pesticides. The pharmaceutical industry set as an object into its programme the manufacture of modern pesticides in the interest of the chemization of agriculture. Chinoin has taken over the



biggest share in this section. The production of 25 products with herbicide, fungicide and insecticide actions are in the process of development, supplemented by substances regulating plant growth and maturation.

CHEMICAL WORKS OF GEDEON RICHTER LTD.

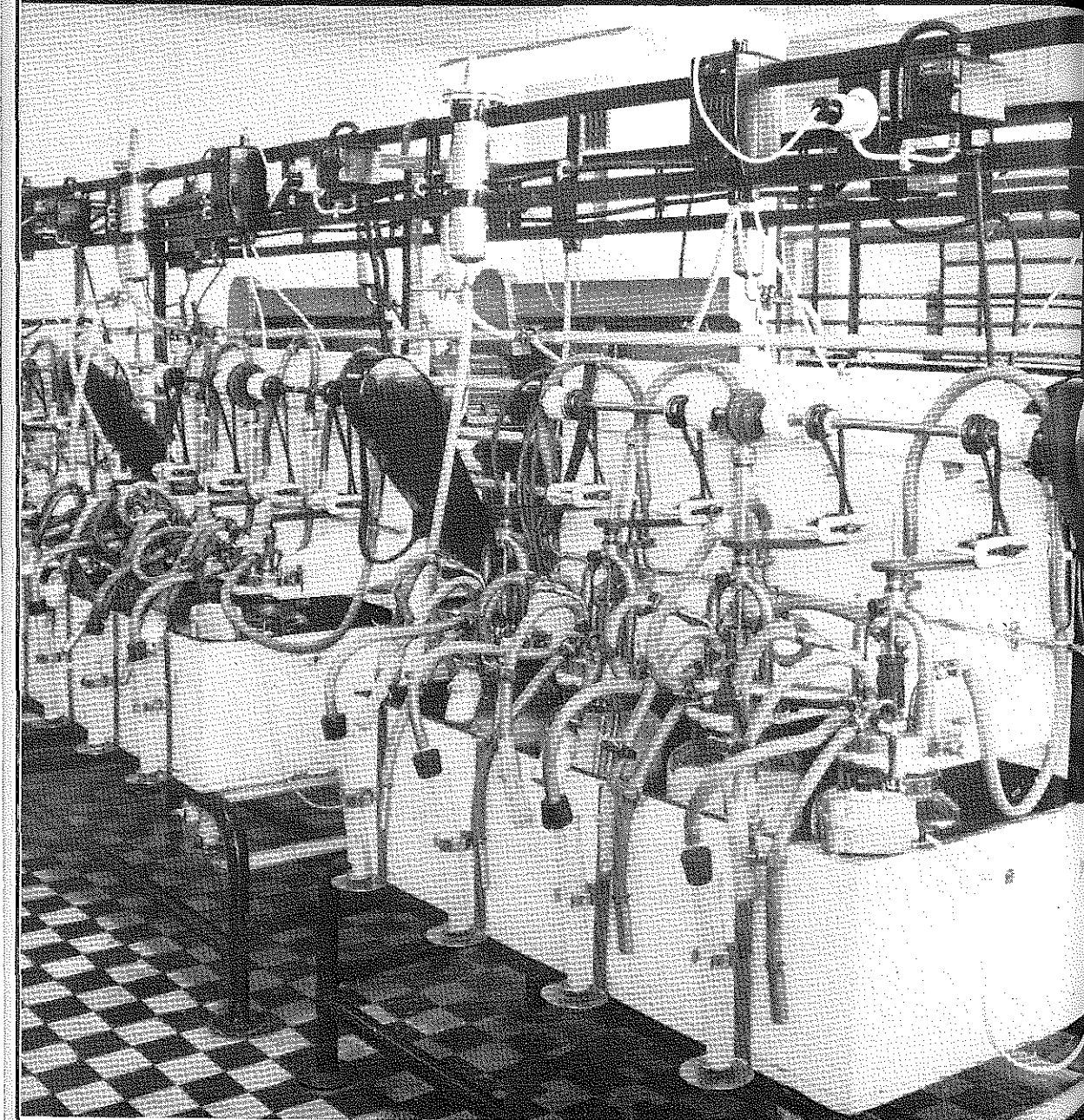


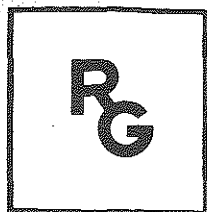
The Works were founded in 1902 by G. Richter a pharmacist, originally in the laboratory premises of a pharmacy. Because of rapidly growing demands, the laboratory proved to be small and Richter was compelled in 1907 to set up a small factory in an industrial district of Budapest.

The management of the factory followed with particular attention the rapid progress of medicine about the turn of the century and strongly impressed by the vital importance of hormones realized at that time, the small factory devoted its activity to this line. Richter succeeded to release in short intervals organotherapeutic preparations prepared from animal organs, as hypophysis, ovarium, testis, thymus and pancreas extracts.

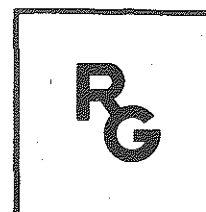
At that time the pharmaceutical market was dominated by botanical drugs. Richter Ltd. was undertaking a pioneering work in the development of preparations containing digitalis and ergot alkaloids respectively.

In addition to the wide range of products of animal and plant origin, efforts were made also to prepare modern synthetic drugs. Some of the new analgesics, local and general anaesthetics included in the programme, substantially helped





the factory and the broad network of its subsidiaries in establishing its international reputation and its rapidly growing turnover business. World War II caused a marked decline because of transient loss of export markets but after the nationalization in 1948 the introduction of planned economy, the establishing of new programmes in national economy and public health imparted a new impetus to research and production. Relying on the traditions revived research included organotherapy, medicinal plants and synthetic substances. From a single research laboratory special chemical, biochemical, phytochemical and pilot plant laboratories were developed. Quality control was reorganized, new up-to-date analytical methods were adopted. The growing demands prompted the factory to expand steadily. New modernly equipped high-capacity plants were installed and manufacturing processes modernized. Processing and packaging departments were supplied with automatic and semi-automatic equipment.



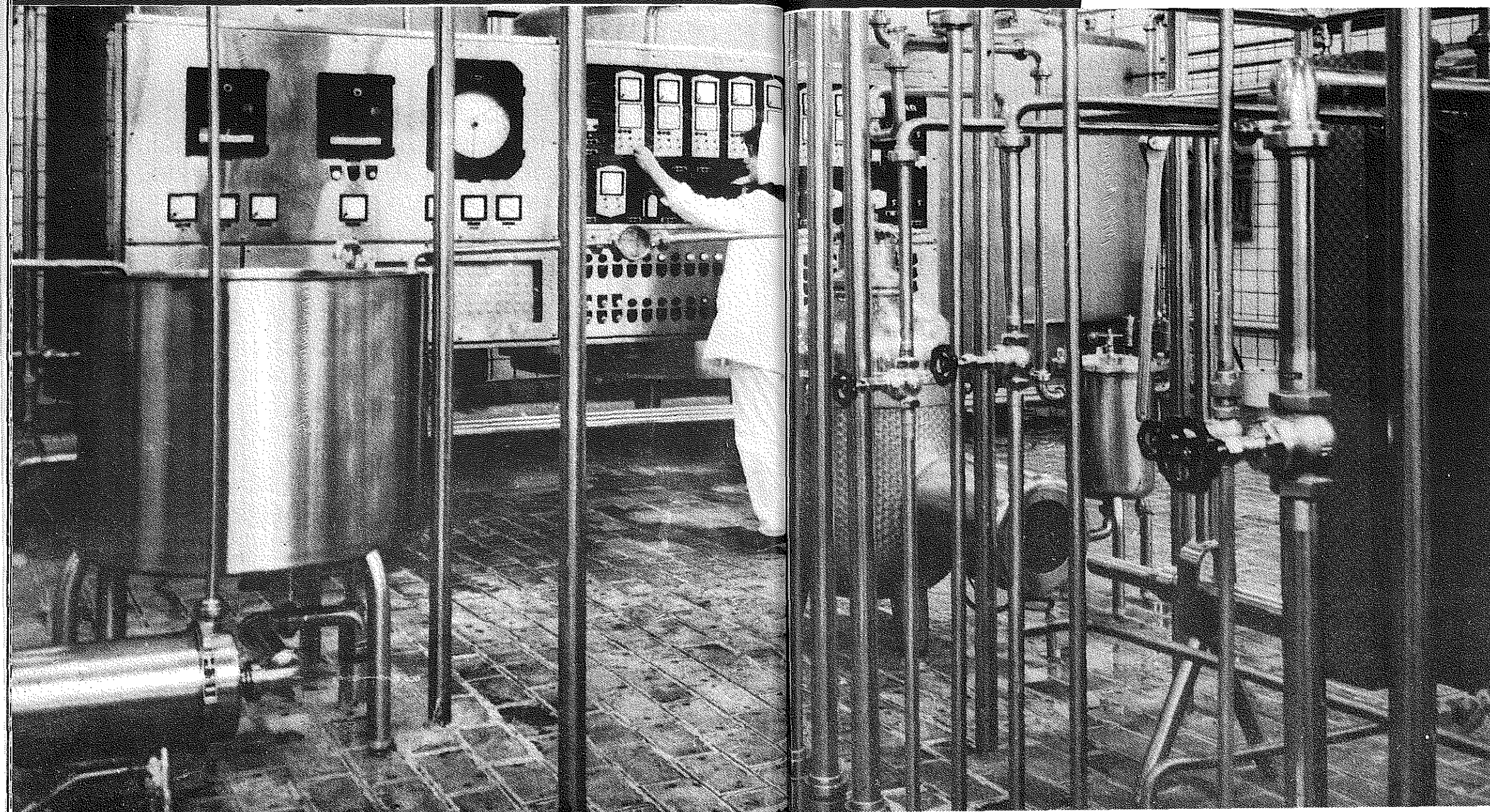
As a result of development the present production range includes 300 active substances and intermediates and about 200 specialities against the figure of 20–25 active substances and 80–100 specialities of the early years. A new trend in production is represented by bioactive cosmetics produced under the brand name Fabulon.

EGYT PHARMACOCHEMICAL WORKS

(former: UNITED WORKS
OF PHARMACEUTICAL AND DIETETIC
PRODUCTS)

Egyt

The third Hungarian pharmaceutical factory was founded in 1913 at the site of its present headquarters, mainly with foreign capital, as the Hungarian subsidiary of the Swiss undertaking Wander Co. At the beginning the programme consisted mainly of dietetics.

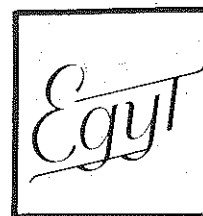




but from the 1920s onwards, the production of medicinal specialities was gradually built up. Many of the drugs introduced at that time are still in current use. In the early 1930s a research laboratory was set up and the production of different pharmaceutical substances had been worked out. 70% of the substances and dosage forms currently used were developed during the last ten years.

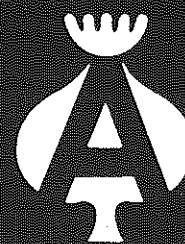
The further development is warranted by important new investments. Continuous processing methods have been introduced in the plants for manufacturing and finishing. Half-automatic machine stocks and high-standard equipment provide for the effectiveness of production.

In the frame of an overall investment programme a new plant of high capacity for the production of dietetics started operation in 1973 in Körmend (Western Hungary). As a consequence of large-scale processes at present about 80% of the production are exported to about 80 countries.



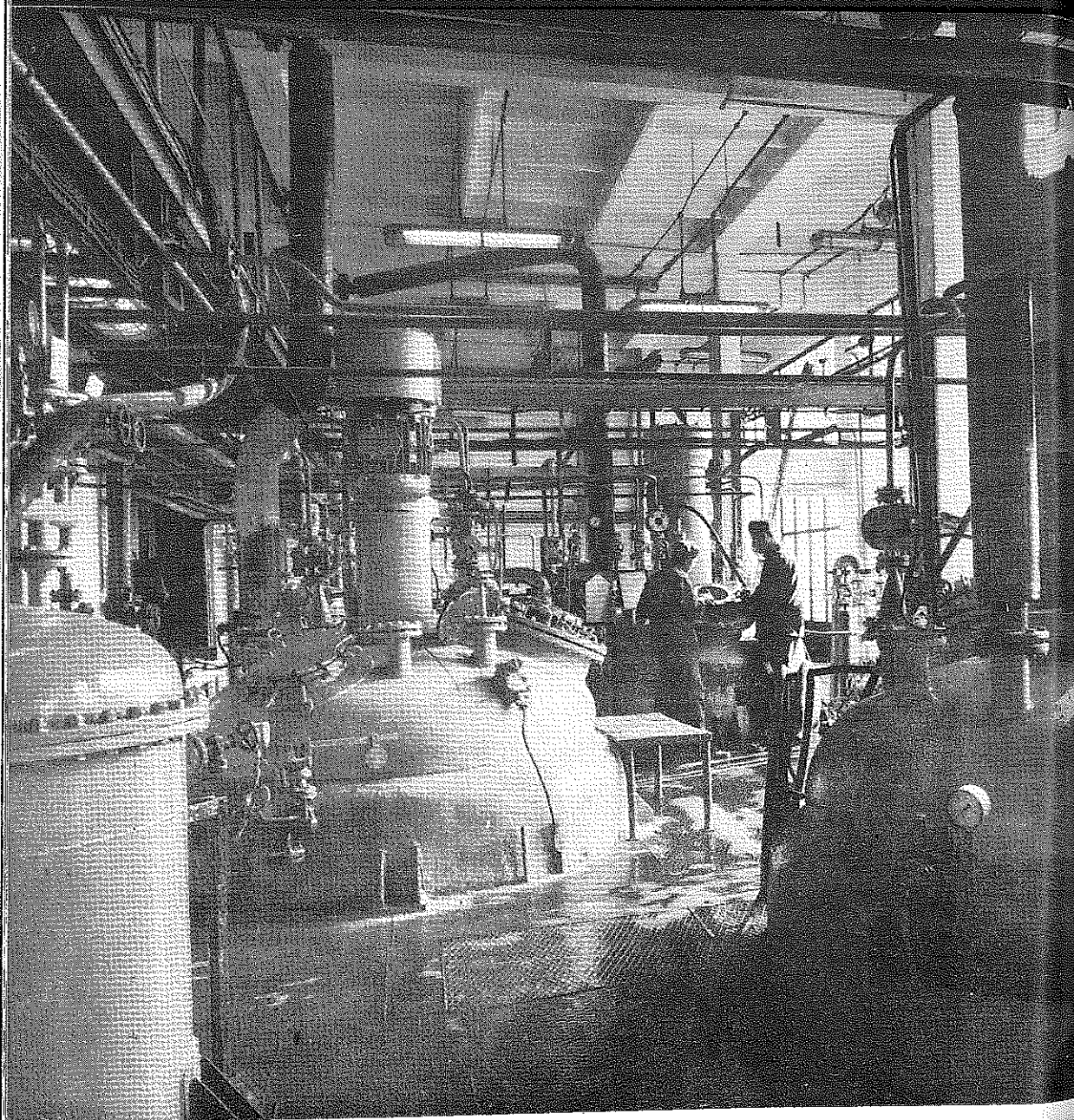
The production of chloramphenicol and its intermediates is highly important on a world scale, but the following substances are also exported in considerable quantities: Thiamphe-nicol, α -methyldopa, L-Dopa, trimethoprim, diethylcarbamazine, imipramine, trimetozine, bencyclane, etc.

ALKALOIDA CHEMICAL FACTORY

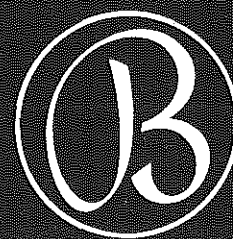


The factory was founded in 1928 in Tiszavasvári for the exploitation of J. Kabay's method to produce morphine by extraction from dry poppy-head. The invention of revolutionary importance from technological and economical point of view made it possible to

Alkaloida to produce and export opium-alkaloids in quantities which represent a considerable part of the world demand (this applies for semi-synthetic morphine-derivatives as well). From 1965 on the production of synthetic pharmaceutical active substances received a great emphasis in the programme. Plants for production of tablets and injections have been equipped with up-to-date machineries. The number of finished pharmaceuticals has reached 60.



BIOGAL PHARMACEUTICAL WORKS

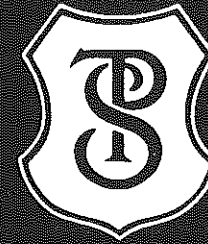


The company was founded in 1951 as the Hajdúság Pharmaceutical Works. At the beginning it produced exclusively biosynthetic products, first of all penicillin, from 1957 on oxy-tetracycline and from 1968 on neomycin. In 1960 the Debrecen Pharmaceutical

Works concerned with galenic operations, merged into it and the name was changed into Biogal. The present trends of production comprise: antibiotics, enzymes, synthetic substances, clinical diagnostics, galenics, veterinary feedstuffs and feed additives. As a recent addition to the programme, sales of human and veterinary specialities were started and a new orientation of research in this direction (e.g. antimetabolites) takes shape. Research is partly done by the own research department, partly in co-operation with outside research facilities.



PHYLAXIA VETERINARY BIOLOGICALS AND FEEDSTUFFS LTD.



The State Serum Institute Phylaxia is concerned with the preparation of vaccines, diagnostics, serobacteriological products, feed supplements and medicines. It was established in 1912, under very modest conditions. During its existence of more than sixty years the activ-

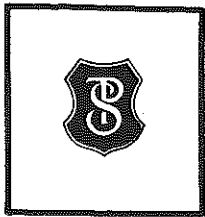
ities of Phylaxia were guided by two principles, i.e. to keep pace with international scientific progress and to adapt production to the changing demands of the market.

During the last years Phylaxia has made remarkable progress. Matters of agriculture and particularly animal health protection became the special domain of the Institute. In order to satisfy the special demands of stock-breeding, in addition to the production of vaccines, the Institute established a new research programme. As a result, a noticeable progress became manifest in the production of premixes and feedstuffs and new veterinary specialities have been introduced.

The programme of vaccine production is substantially influenced by the epizootic state of the country.

Some infection diseases which had caused heavy losses in the past, as swine pest, ceased; other diseases decreased to a minimum extent.



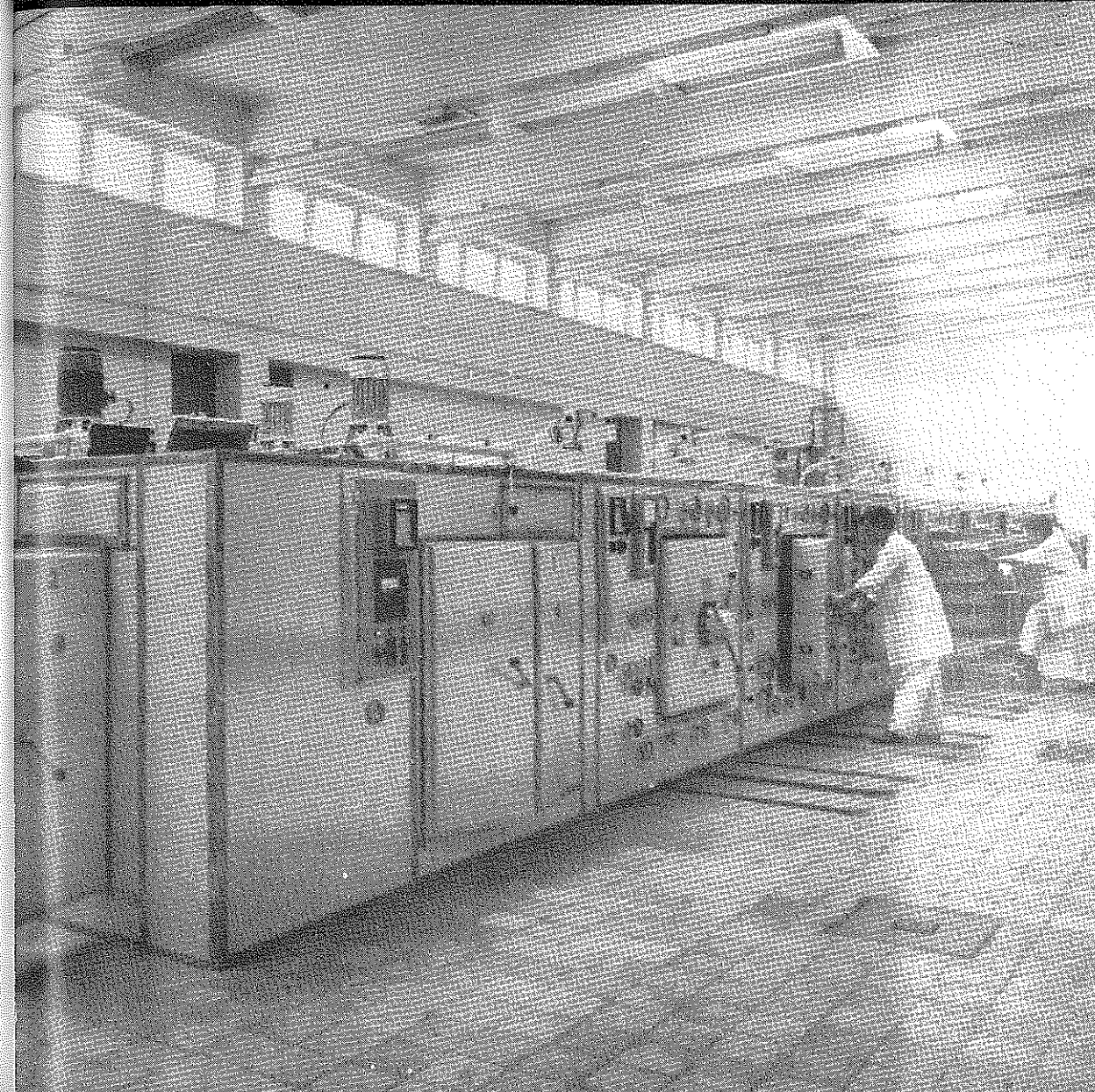


The wide-ranged programme of stock-breeding and animal health protection raised further problems and the occurrence of new diseases necessitated the elaboration of new vaccines.

During the last ten years 43 new products were launched. The range of biological products was added to by various blood preparations.

The basic substances of premixes and animal feeds are partly prepared by fermentation. The export activities of the Institute have made for the last ten years a substantial progress. Its products have been exported in 1972 to 23 countries in steadily increasing amounts. From the products first of all the antiserum for swine fever, for goose influenza and the Aujeszky's disease antiserum and the vaccine have found international recognition. A first major international co-operation activity is represented by the erection of a large-scale biological plant in Mongolia. The most important task of the new plant is to provide a basic protein resource for Hungary.

HUMAN INSTITUTE FOR SERO- BACTERIOLOGICAL PRODUCTION AND RESEARCH





The Institute for Serobacteriological Production and Research "HUMAN" celebrates the 160th anniversary of its existence in 1974 on the basis of legal continuity. This 160 years of existence can be justified by taking over the activities of the former Institute for Protection against small-pox, founded in 1814. Another predecessor to the Institute was the State Institute for Production of Diphtheria Antiserum, founded in 1896.

Its present scope of activity was worked out in 1954, when—after the nationalization of the institute for vaccine production—the preparation of vaccines for human use came under the supervision of the Ministry of Health.

During the past 20 years Hungarian public health has succeeded in eradicating—with the aid of vaccines produced by the Institute—the most important bacterial infections, as typhoid fever, diphtheria, pertussis and with the immunized age groups, tetanus as well.

Relying on the research and development activities of the Institute, it was a pioneering achievement of Hungarian public health on world scale to introduce compulsory vaccination with polyvalent vaccines as early as in 1952.

The scope of the Institute includes preparation of active vaccines, therapeutic and diagnostic sera, blood preparations, plasma-expanders, infusion solutions and modern diagnostics for immunology and immuno-chemistry. In the organization of the Institute the unity of production and of research and development activities has been accomplished.

Development activities are well illustrated by the fact that yearly 5–10 new products are introduced which are partly proper novelties or improvements.

All the products are subjected, before their release, to a triple control. The first full-scale control is carried out by the Production Department, the second one by the competent Biological Control Department of the Institute. A full control is accomplished before the putting into circulation of each product by the Department for Vaccine Control of the National Institute of Public Hygiene. The Institute was entrusted by the World Health Organisation in 1973 to set up a proper reference standard centre for bacterial vaccines as an International Reference Standard Centre of the World Health Organisation.

TESTING OF PHARMACEUTICAL PRODUCTS

The quality control of Hungarian pharmaceutical products is a responsibility of the National Institute for Pharmacy which is under the supervision

and direction of the Ministry of Health.

The National Institute for Pharmacy is concerned with the encouragement of pharmaceutical sciences, the putting of scientific achievements into practice, the control and authorization activities preceding the introduction of new medicines (registration), quality control of industrial drug production, as well as the professional supervision of regional drug control laboratories and of pharmacies. This supervision is exercised partly through a nation-wide network of pharmacy inspectors, with about fifty professional experts and partly through the Institute's staff. Supervision includes quality control of medicines prepared or stored in the pharmacy. The Institute is entitled to withdraw preparations of unsatisfactory quality.

The supervision of drug manufacture is exercised through the inspection of industrial drug control departments. Inspections on the spot belong to routine measures of the Institute. Drug Control Departments of the factories have to control basic materials, intermediates, ingredients and the end-products in each stage of processing.

PRODUCTION OF PHARMACEUTICAL SPECIALITIES AND ACTIVE SUBSTANCES

(BIOLOGICALS NOT INCLUDED)

Year	%
1949	100
1950	144
1955	473
1965	4,520
1967	5,929
1969	6,765
1970	8,110
1971	9,701
1972	10,104

DOMESTIC DRUG SUPPLY

The production and storage of pharmaceutical preparations is based on national economic planning. In view of possible occasional, unpredictable increase in consumption as well as in consideration of new products, for which no experience to assess demands is available, adequate reserve supplies have to be provided for at each level of production and supply.

In Hungary medicines are dispensed only in pharmacies. The number of pharmacies is rather high as compared with other countries (1 pharmacy for about 6,700 inhabitants). There are about 1,400 public pharmacies and about 60 institute pharmacies, most of them attached to hospitals. For the distribution of certain necessary medicines in areas provided with district

doctors, but without pharmacies, some 600 drug supply units were set up. These are operated by the doctor and supplied by a neighbouring pharmacy.

In Hungary pharmacies are institutions of public health and their scope of sales is confined—according to the traditional Central European interpretation of a pharmacy's operation—to medicines, medicated dietetic products, surgical dressing, mineral waters and certain medicated cosmetics.

The National Health Scheme covers practically 100% of the population and prescriptions are made up for insured patients against 15% of the price. Medicines for certain infectious and endemic diseases are available without any charge (e.g. insulin, medicated dietetics for babies, drugs against tuberculosis and venereal diseases).

Drug consumption—as everywhere in the world—shows a continuously increasing tendency. The per capita consumption in 1958 was 136 Forints, in 1964, 270 Forints, in 1972, 466 Forints. There is a remarkable decline in the proportion of extemporaneously made up medi-

cines from 30–40% to 10%. This is in conformity with the world trend towards the increased number of industry-made drugs which have the advantage of a more favourable shelf-life and of having been thoroughly tested as compared with drugs prepared within the limited facilities of a pharmacy.

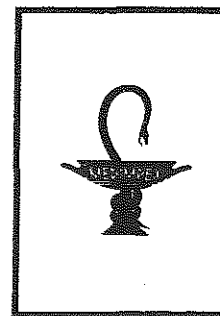
DEVELOPMENT OF DRUG EXPORT

(VACCINES AND ANTI-SERA NOT
INCLUDED)

Year	%
1955	241
1960	666
1965	2,045
1970	3,399
1971	4,021
1972	4,789



MEDIMEX
HUNGARIAN
TRADING COMPANY
FOR PHARMACEUTICAL
PRODUCTS



The Hungarian pharmaceutical industry has its fine traditions on the international market. Already immediately after World War I the pharmaceutical industry made a lot of efforts by establishing a network of subsidiaries and agencies abroad to explore foreign markets for their products. The early international recognition was clearly demonstrated by the increasing export figures. Specialities both for human and veterinary use, basic materials, biologicals and medicinal herbs were exported in considerable quantities.

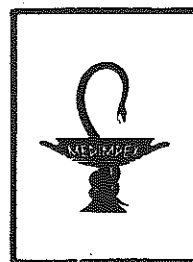
As a part of fundamental reorganization of foreign trade after the end of World War II, Medimpex Hungarian Trading Company for Pharmaceutical Products was founded in 1949, as the sole exporter and importer of pharmaceuticals. The reorganization of Hungarian drug foreign trade took place in a time, when drug industry did not yet recover from the heavy losses caused by World War II. Through the centralization of foreign trade operation it was possible to grant it all the advantages which have been the privilege only of financially well-established international big enterprises. (Unified market and price policy, adjustment of export and import activities.)



In addition to the products manufactured by the pharmaceutical industry Medimpex deals with medicinal herbs, volatile oils, mineral waters, laboratory fine chemicals, radioactive isotopes and radioactive labelled compounds.

In the course of Medimpex's 25-year activities the growth in exports has been unprecedented. Now about 75% of the production of drug industry are exported as against 28–30% in 1938. In terms of the exported volume Hungary is now the world's 7–8 largest exporter of pharmaceuticals. Medimpex delivers its goods to 90 countries of the world and in addition to it, it has also established new types of business relations in the form of international co-operation.

Since nearly 100% of domestic requirements are covered by finished drugs produced in Hungary, the figures of importation of finished products do not run parallel with exports, import activities are mainly confined to active substances, intermediates and auxiliaries.



The present Twenty-Year Plan of the pharmaceutical industry (1960–1980) envisages an even greater expansion of the industry by means of increased investments and other possibilities.

The perspective programme, besides full satisfaction of domestic requirements, devotes maximum attention to the special aspects of foreign trade.