HISTORY AND HIGHLIGHTS OF PHARMACOLOGY IN HUNGARY

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In the Middle Ages universities were already established in Hungary. The first record of the teaching of medicine in Hungary is to be found in the papal bull of Boniface IX (1399), which referred to the medical course at the high school of Esztergom, a town in northern Hungary. The occupation of Hungary by the Turks (1526–1676), however, devastated the country and paralyzed its universities.

In 1635 Péter Pázmány, the famous polemist of the Hungarian Counter-Reformation, a professor at the University of Graz for ten years, and archbishop of Esztergom from 1616, founded a new university in Nagyszombat (now Trnava in Czechoslovakia). This university, which was named after its founder, was completed with a medical faculty in 1769. In 1777 it was moved to Buda and then in 1789 to Pest (the two cities united in 1872). In 1951 the medical faculty had been divided into faculties of general medicine, dentistry, and pharmacy and became the independent University of Medicine of Budapest. In 1969 at the bicentennial of the founding of the faculty of medicine it was named Semmelweis University of Medicine.

I. P. Semmelweis (1818–1865), whose research activity belongs to the history of pharmacology, was professor of gynecology at this university. He was one of the most outstanding personalities of the history of general medicine and has been called the "Savior of mothers" (1). In his work at the first obstetrical clinic of Vienna following his graduation he noticed the high incidence of puerperal fever in the obstetrical ward, which was visited by medical students. In 1847 he analyzed this problem and concluded that "... das Kindbettfieber ist eine von einer kranken Wöchnerin auf eine gesunde Wöchnerin übertragbare Krankheit durch Vermittlung eines zersetzten thierisch-organischen Stoffes" (2, p. 108). He realized that the mothers were infected by medical students coming from the autopsy room to the labor ward who after dissecting corpses had their hands contaminated with cadaveric toxins ("disintegrative bioorganic material"). He suggested that pus might also cause infection and performed animal experiments to prove this hypothesis. In May 1847 in order to inactivate the "disintegrative bioorganic material" he initiated the use of "chlorina liquida." He decreased the incidence of puerperal fever in the

obstetrical ward of the Allgemeines Krankenhaus of Vienna from 11.4 to 1.27% by having the medical students wash their hands thoroughly in chlorinated lime before examining patients. This discovery of Semmelweiss was first mentioned in a paper by Hebra (one of the founders of dermatology) in April 1848, and then in 1849 by the famous Skoda in his report to the Academy of Sciences in Vienna

> Ich glaube, dass ich der sehr geehrten Abteilung eine der wichtigsten Entdeckungen auf dem Gebiet der medizinischen Wissenschaft zu kenntniss bringe, wenn ich die Entdeckung von Doctor Semmelweis, dem früheren Assistenten der hiesigen Geburtshilflichen Klinik, mitteile, die sich auf die Ursache der in diesem Institut mit ungewöhnlicher Häufigkeit auftretenden Kindesbetterkrankungen und auf das Mittel bezieht, mit dem diese Krankheit auf das normale Mass herabgedrückt werden kann (cf 1).

Semmelweis was a modest man. At the beginning of his career he wrote letters to professors of gynecology and published his discovery first in 1858 in Hungarian, while at the University of Pest. In 1861 his famous book was edited in German in Pest under the title *Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfibers* (2). According to the data and conclusions of this monograph Semmelweis can be regarded as the discoverer of the principles of asepsis and antisepsis.

In 1872 the first edition of *Pharmacopoea Hungarica* was published. Before that the *Pharmacopoea Austriaca* (Editions IV and V) were used in Hungary. The second edition followed in 1888, the third in 1909, the fourth in 1933, the fifth in 1954, and the sixth (three volumes, 1564 pages) in 1967.

In 1872 the first independent department of pharmacology in Hungary was established in Budapest, headed by K. Balogh. Balogh was followed in 1890 by Bókay, whose successor was Vámossy in 1920; Issekutz took the chair in 1939 and was succeeded in 1962 by Knoll.

Hungary has four medical universities: Budapest, Szeged, Debrecen, and Pécs. The Universities of Szeged and Debrecen were founded in 1921, and the one at Pécs in 1923. Their medical faculties became independent universities of medicine in 1951.

Besides the university departments of pharmacology, the Drug Research Institute, the Medical Research Institute of the Hungarian Academy of Sciences, and pharmaceutical firms (Chinoin, Gedeon Richter, and EGYT) have important divisions of experimental pharmacology.

A network devoted to clinical pharmacological research was established in 1967. At present 21 units of this network, distributed mainly in different clinical departments of the medical universities, work in close collaboration with the pharmacological research laboratories.

As in other countries, pharmacologists of Hungary are members of their national physiological society. The Hungarian Pharmacological Society (HPS) was founded in 1962. It supported the activities of the Section of Pharmacology (SEPHAR) of the International Physiological Society and as one of the members participated in the foundation of the International Union of Pharmacology (IUPHAR).

The 289 members of the HPS work in five areas: experimental pharmacology, clinical pharmacology, biochemical pharmacology, medicinal chemistry, and che-

motherapy. The society organizes congresses with international participation triannually in Budapest. The first was held in 1971 with 313 Hungarian participants and 187 guests from 25 countries. Pharmacological agents and biogenic amines in the central nervous system (3), drugs and heart metabolism (4), pharmacology of analgetics (5), pharmacology of learning and retention (6), drug-induced metabolic changes (7), and the pharmacology of gastrin and its antagonists (8) were the selected topics for the symposia. The second congress in 1974 had 510 active participants (192 guests from 24 countries) presenting 301 papers. Again six symposia were organized; the six volumes are now in press.

The HPS collaborates with other pharmacological societies. Reciprocal joint symposia were organized with the pharmacological societies of the Soviet Union, Czechoslovakia, and Italy. According to a recent agreement between the Hungarian and Polish pharmacological societies, starting in 1976 joint symposia will be organized biannually. In 1974 a joint meeting of the German, Hungarian, Portuguese, and Yugoslav pharmacological societies, organized by Professor F. Lembeck, was held in Graz, Austria. Hungarian pharmacologists (9) presented 51 papers at the meeting.

Pharmacological research in Hungary produced its first results by the end of the 19th century. In 1886 Jendrassik (10, 11) analyzed the diuretic effect of calomel and demonstrated its high efficiency when combined with opium. In 1885 Bókay demonstrated the antagonism between picrotoxin and paraldehyde (cf 1), and the studies of Kossa (12) and Köppen (13) in 1892 revealed the analeptic effect of picrotoxin. In 1897 Vámossy described the local anesthetic effect of trichloroisobutyl alcohol (14). In 1902 he analyzed the toxicity of phenolphthalein in animals for the Hungarian government in order to determine the safety of this compound, which was to be used as a means of identifying artificial wines. When he learned that it was nontoxic in animals he took one gram and discovered its strong cathartic effect (15). Tablets (Purgo) were soon marketed by a small pharmaceutical enterprise in Hungary, and because of its lack of untoward systemic effects in children, phenolphthalein is still widely employed as a cathartic all over the world.

Issekutz demonstrated in 1917 that the quaternary ammonium bases of atropine and homatropine are strong parasympatholytics with low central effects and proposed their combination with papaverine (16, 17). Homatropine methylbromide (novatropine) is still used in Hungary. Issekutz's structure-activity relationship studies led to the synthesis of useful spasmolytics at Chinoin (Perparin®, 18; No-Spa®, 19) and different curare-like tropeine-derivatives (20). As founder and head of the pharmacology laboratory of the Medical Research Institute of the Hungarian Academy of Sciences Issekutz catalyzed detailed studies in the field of central and peripheral cholinolytics. Between 1955 and 1960 Nádor, his pupil, synthesized a series of new tropeine derivatives, whose pharmacology in relation to their steric structure was studied by Gyermek (21), leading to the introduction of xentropinium-bromid (Gastripon®) into therapy. Further structure-activity relationship studies by György et al (22) resulted in the use of tropinium-xanthene-9-carboniacidmethylbromide (Gastrixon®), and potent central cholinolytics were found among tertiary tropanes (23, 24). It has been shown recently in this laboratory

that the chloroethylamino derivative of oxotremorine is irreversibly bound to central M-cholinoreceptors (25).

Using the isolated perfused liver Issekutz found in 1924 that glycogenolysis is inhibited by insulin (26) and in 1937 analyzed the effects of thyroxin on the central nervous system (27).

Between 1927 and 1932 Jancsó, a pupil of Issekutz, developed new histochemical methods (28) for research in chemotherapy, demonstrated that trypaflavine and Solganal® find entrance into trypanosomes and *Borrelia recurrentis* (29), and also discovered the storage of Neo-Salvarsan® in the reticuloendothelial system (28).

Issekutz (30) and Jancsó (31–33) proved in 1933–1935 that suramin acts on specific enzyme systems of the trypanosomes by lowering their oxygen and glucose consumption. From these experiments Jancsó thought that hypoglycemic compounds that deprive the protozoons of their main nutriment might be potent trypanocides. In 1935 he and his wife succeeded in demonstrating that Synthalin®, a guanidine derivative with hypoglycemic effect, is a potent trypanocidal agent (34). It was soon demonstrated by Yorke (35) that Synthalin was actively trypanocidal in vitro, i.e. this action proved to be entirely unrelated to the hypoglycemic effect. The discovery of the trypanocidal effect of Synthalin, however, became of practical importance initiating the structure-activity relationship studies of King et al (36) which led to the development of useful protoacidal guanidine derivatives.

Jancsó, a professor of pharmacology in Szeged from 1940 until his death in 1966, was a splendid scientist, rich in new ideas. He described histamine in 1947 as a physiological activator of the reticuloendothelial system (37) and using new techniques with Jancsó-Gábor analyzed the storage mechanism in the organism (38–42). He summarized his results and ideas in his important monograph "Speicherung. Stoffanreicherung im Retikuloendothel und in der Niere" in 1955 (43). In his last research period he became involved in the mechanism of neurogenic inflammatory responses (44) and with his co-workers analyzed the pharmacology of capsaicin (45–47). He demonstrated that capsaicin selectively and irreversibly inactivates the receptors of chemical pain as well as the peripheral and hypothalamic thermodetectors (44, 48). He concluded that chemical and physical pain are mediated by different receptors and that stimulation of the receptors of chemical pain leads to the release of a mediator that increases permeability ("neurogenic inflammation") (49).

Szent-Györgyi, one of the founders of biochemistry, was professor of this subject in Szeged. It was for his work at Szeged that he won his Nobel prize in 1937. Many of his works can be regarded as highly important contributions to pharmacology. Through his study of the oxidizing mechanism of the adrenal cortex in 1928 he isolated from the adrenals a powerful reducing agent in crystalline form, believing it to be hexuronic acid. In 1932 King & Waugh isolated a crystalline compound from lemon juice, identified it as hexuronic acid, and demonstrated its potent antiscorbutic effect (50). At the same time Svirbely and Szent-Györgyi announced the isolation of hexuronic acid from adrenal glands, cabbages, and oranges (51, 52). In 1932 Szent-Györgyi discovered the presence of the substance in the paprika that was cultivated extensively near Szeged and soon extracted a few kilograms of the substance in his department. The Hungarian pharmaceutical firm, Chinoin, became

the first en masse producer of vitamin C from paprika. Chemists soon identified vitamin C as ascorbic acid and revealed it as an endogenous oxidation-reduction system, as proposed by Szent-Györgyi.

In 1929 Drury & Szent-Györgyi noted the coronary artery dilating effect of adenosine and adenylic acid (53).

Szent-Györgyi & Rusznyák (professor of medicine in Szeged and later in Budapest and president of the Hungarian Academy of Sciences between 1949 and 1970) noticed that crude preparations of ascorbic acid obtained from natural sources were more effective in alleviating the capillary lesions and prolonging the life of scorbutic animals than was purified vitamin C. In 1936 they isolated an unknown substance from lemon, called *citrin* or *vitamin P* (Permeability vitamin), which protected the capillaries (54–56). Bruckner & Szent-Györgyi demonstrated in 1936 that eriodictyol and hesperidin are the joint components of citrin (57). It became evident that a variety of naturally occurring flavone derivatives possess vitamin P activity. The chemical structure of sophorabioside, an isoflavine glycoside isolated from the fruits of *Sophora japonica* L., was described by Zemplén & Bognár in 1942 (58). Zemplén et al (59) clarified the precise structure also of sophoricoside, whose capillary resistance–elevating and estrogenic effects were demonstrated by Gábor and Kiss in 1953 (cf 60).

Hungary received international recognition for the work of Kabay who developed a method still used throughout the world for obtaining industrial quantities of opium alkaloids from the poppy head and straw (cf 1).

After World War II many young, mainly medical, students worked in the Department of Pharmacology headed by Issekutz. Many of them were to become professors of pharmacology, physiology, biochemistry, or medicinal chemistry in Hungary and abroad (e.g. K. Nádor, J. Knoll, I. Horváth, K. Kelemen in Budapest; J. Pórszász in Pécs; J. Szegi in Debrecen; J. Szerb in Halifax, Canada; I. Bonta in Rotterdam) and leaders of research laboratories (e.g. E. Komlós, F. Herr, G. Wix, I. Pataki, K. Pfeifer, L. Gyermek, G. Fekete, L. Tardos, L. György, J. Borsy, B. Knoll). Between 1946 and 1960 structure-activity relationship studies and methodological problems were the main interest of this department. Komlós, Pórszász & Knoll studied the mechanism of the potentiation of the effects of narcotic analgesics by parasympathomimetics (61–67). Pataki, Pfeifer, and co-workers analyzed (68–70) the creatine-creatinine metabolism of the central nervous system and described the early inhibitory effects of thyroxine on convulsive thresholds as a consequence of a shift in this metabolism; later Pfeifer studied the role of catecholamines in the regulation of convulsive threshold (71). J. Knoll & B. Knoll developed new methods in psychopharmacology (72–78) and they studied with Kelemen drive-motivated behavior (79–87) and J. Knoll proposed a new psychophysiological theory in his monograph "Theory of Active Reflexes" (88). These works initiated structure-activity relationship studies in the field of psychopharmacology.

In 1961 new aminoketones with a major tranquilizing effect synthesized by Nádor, were described (89). After the finding of Knoll (cf 3, pp 13–36) that amphetamine and in smaller doses methamphetamine enhance performance of rats in behavioral tests by increasing the catcholaminergic tone and that higher doses are

inhibitory because of activation of the 5-hydroxytryptamine (5-HT) system, the goal of synthesizing new phenylalkylamines with only stimulatory or only inhibitory effects in the tests was set. Methamphetamine was the starting substance. At Chinoin Ecsery synthesized a series of new derivatives and the goal was reached by appropriate substitutions at the para position. Parabromomethamphetamine (V-111) was found to be a derivative which in small and large doses exerted only inhibitory effects, while N_1-O-carboxyphenyl-N_2 2,2-methylaminopropyl-1-phenylacetamidine (I-1703) exerted only stimulatory effects. In contrast to the acute central effects of V-111 the chronic administration of the compound was found to facilitate the learning performance of the rats because it diminished the 5-HT content of the brain and exerted a long-lasting inhibitory effect on the intraneuronal uptake of 5-HT and dopamine (90–105).

One of the practical fruits resulting from the structure-activity relationship studies with the newly synthesized metamphetamine derivatives was the discovery of the first and up to now the only selective B-type monoamine oxidase (MAO) inhibitor, l-deprenyl. The pharmacology of deprenyl (under the code name E-250) was described by Knoll et al in 1965 as a new spectrum psychic energizer, which in contrast to other MAO inhibitors did not potentiate the effect of tyramine. Its high selectivity in inhibiting the oxidation of benzylamine (a substrate of the B-type of MAO) was demonstrated by Knoll and Magyar in 1971. The pharmacology of selective MAO inhibitors was summarized in 1975 (106–110). The antidepressant effect of deprenyl in man was demonstrated by Varga et al (111) in 1967 and l-deprenyl was recently described as an excellent drug for preventing the potentiation of the anti-akinetic effect after L-dopa treatment and for the off-phenomena in parkinsonian patients (112).

Knoll et al developed a new family of non-narcotic analgesics containing the 1,5-diazanaphthalene ring system (113–116) synthesized by Mészáros et al at Chinoin (117). Probon®, the first marketed drug of this family, which potentiates the analgesic and antagonizes the respiratory depressant effect of narcotic analgesics, proved to be a useful analgesic in man (118).

Knoll et al (119–127) demonstrated the peculiar spectrum of activity of the 6-azido-7,8-dihydroisomorphine (azidomorphine) derivatives synthesized by Bognár & Makleit (128). They proved to be the most potent of all semisynthetic analgesics and antitussives containing the morphine structure. Azidomorphine showed an unusually great dissociation between analgesic activity and tolerance and dependence capacity in both animals (119–127) and man (129–131), and in combination with Probon® it proved to exert much less untoward central and peripheral effects in man than either morphine or pentazocine (129–131).

Knoll observed in 1951 the existence of an unknown cardiotonic substance in the perfusate of the frog liver. This substance was described in 1952 and 1955 (132–136). He discovered in 1956 that the isolated frog heart arrested by 16- to 45-fold potassium excess that cannot be antagonized by known cardiotonics, like β-receptor stimulants, cardiac glycosides, or calcium, starts beating again in the course of time. The auricle proved to be the determinant in the adaptation of the frog heart to the high potassium milieu. Ventricles isolated from their auricles were found to be

unable to adapt themselves, but when an isolated ventricle was in touch with the bathing fluid of an intact heart it regularly gained, sometimes even earlier than the intact heart, the ability to work in presence of the high potassium concentration. This showed that an unknown substance is produced by the auricle that enables the frog heart to work under unfavorable circumstances. This endogeneous substance was named *celluline* by Knoll, who soon demonstrated that different organ extracts exert celluline-like activity. To rule out the effect of known substances with cardiotonic effect the biological titration of celluline-like activity was based on the observation that it is unique in making the frog or mammalian heart contract in the presence of the combination of high potassium concentrations, tetrodotoxin and propranolol. Celluline-A, prepared from frog skin, was purified by gel chromatographic procedure. The unknown structure seems to be an organic Ca complex in which "salt" is produced by fatty acids and phenylalkylcarbonic acids which is surrounded by phenylalkylamines (phenylethylamine and tyramine) as ligands. Celluline-A was also found to antagonize the effect of tetrodotoxin in the guinea pig vas deferens (137–142).

Kelemen, Kecskeméti & Knoll demonstrated that celluline—A is the only substance that markedly increases at an unchanged resting potential the overshoot and rate of depolarization of the transmembrane action potential of heart cells and that under voltage clamp conditions it increases the inward sodium current. Analysis of the electrophysiological effects of PGE_1 and PGE_2 suggested the possibility of the release or activation of celluline by prostaglandins in the heart (143–148).

Vizi & Knoll presented evidence that in Auerbach's plexus the acetylcholine output per stimulus depends on the frequency and length of stimulation applied and demonstrated that the inhibition of the release of acetylcholine by the adrenergic transmitter is mediated via α-adrenoceptors situated presynaptically. It was found that the release of acetylcholine by gastrointestinal hormones can be inhibited by the stimulation of opiates and α-adrenoceptors of Auerbach's plexus. It has also been shown that the inhibitory effect of the presynaptic α-adrenoceptor stimulation on the noradrenergic transmission depends on the frequency of stimulation (149–154). Similar interaction was found for PGE_1 on guinea pig vas deferens, and it was further demonstrated that PGE_2 markedly retards the onset and depresses the velocity of mechanical responses to continous sympathetic stimulation in the guinea pig vas deferens (155). PGE_1 was found to reduce vagal bradycardia by antagonizing the effect of acetylcholine on the atrial cells (156). Vizi demonstrated (157) the stimulation by inhibition of $(Na^+\text{-}K^+\text{-}Mg^{2+})$-activated adenosine triphosphatase (ATPase) of acetylcholine release in cortical slices from rat brain. Fürst (158) proved that the intraventricular administration of naloxone increased the output of acetylcholine into perfused lateral cerebral ventricle in cats.

Szekeres, who first worked in the Department of Pharmacology in Pécs and who in 1967 succeeded Jancsó at Szeged, concentrated with his group on problems of the cardiovascular system, in particular on the pathomechanism and drug therapy of cardiac arrhythmias. The results of this work were summarized by Szekeres in 1966 (159) and by Szekeres & Papp in 1968 (160) and 1971 (161). Their studies revealed that increased excitation of the autonomic nervous centers makes the heart

more susceptible to external arrhythmogenic stimuli in the initial, moderately severe phase of hypoxia and hypothermia (162–165). Stimulation of the adrenergic β-receptors was found to promote the appearance of arrhythmias. Failure of mainly the α-receptor stimulators (phenylephrine, synephrine, and methoxamine) to decrease electrical fibrilloflutter threshold has been demonstrated, as well as the biphasic action of epinephrine and norepinephrine, which stimulates both α- and β-receptors. In dopamine- and L-dopa-induced arrhythmia, shortening of repolarization can be prevented by β-blockade. Analysis of the role of hormones and metabolites in the pathomechanism of cardiac arrhythmias has revealed that arrhythmia-producing and cardiotoxic effects of ouabain increased in experimental hyperthyroidism. In other experiments increased susceptibility of the failing heart to the arrhythmogenic action of acute stretch by sudden overloading has been observed (166–168).

Studies of the role of local myocardial ischemia in the genesis of early arrhythmias appearing after coronary occlusion revealed that appearance of arrhythmias depends on (*a*) the extent of inhomogeneity of the electrophysiological parameters between the noninfarcted myocardium and the ischemic area and (*b*) the asynchrony of conduction and inequality of repolarization within the ischemic area and the noninfarcted myocardium, respectively. Also transient metabolic alterations appeared after coronary occlusion in the noninfarcted myocardium. Pharmacological interventions protecting against early postocclusion arrhythmias such as infusion of nitroglycerine or lidocaine and especially chemical denervation (atropine with practolol or pindolol) prevented shortening of the refractory period and reduced asynchrony in recovery of excitability at nearby sites in the nonischemic myocardium.

A rational screening program for the assay of antiarrhythmic and antianginal drugs was recommended (169–171). A new type of electrode for continuous recording of monophasic action potentials from the heart in situ has been introduced (172). Alkylamine-substituted phthalimide derivatives with antiarrhythmic activity and new isoquinoline derivatives possessing marked and long-lasting antianginal action were described (173).

At Szeged Minker & Koltai studied the modulation of the receptor function of the synapses and smooth muscle under the influence of transmitters, enzymes, hormones, and peptides (174–178). It has been shown on rats that some nucleic acid and protein synthesis inhibitors inhibit the inflammatory response induced by dextran (179) and that the insulin-induced sensitization of anaphylactoid reaction is due to a release of a factor derived from lymphocytes (180). The effects of various irritants were prevented by agents producing hyperlipemia and by interferon inducers (181–183).

In the Department of Pharmacology of the Medical University of Pécs the late J. Pórszász, who was head of the department, and his group studied physiological problems of pharmacological interest, such as the effects of blood pressure changes on single-unit activity in the bulbar reticular formation, the physiological properties of tonic exspiratory vagal afferent fibers from the pulmonary stretch receptors, and the dynamics of the somatic and visceral sympathoinhibitory reflexes (184–186).

Pórszász was earlier engaged in structure-activity relationship studies mainly with aminoketones of nicotinic and antinicotinic activity, synthesized by Nádor, which led to the introduction of spiractin, a new respiratory stimulant compound, and mydetone, a new interneurone-blocking compound possessing potent peripherial vasodilator activity (187–195). In the same department Varga, who became chairman after the death of Pórszász, by studying the intestinal absorption of chloroquine presented an interesting example of an effect of a drug on the body, which in turn modifies the pharmacokinetics of the drug itself (196). Decsi studied the biochemical effects of psychopharmacological agents (197–199) and the subcortical organization of the chemically evoked rage reaction on the freely moving cat (200, 201).

The Department of Pharmacology at the University of Debrecen became independent in 1948. The late Vályi-Nagy, who was head of the department, and his co-workers isolated primycin, a new antibacterial antibiotic (202), and flavofungin and desertomycin, new antifungal antibiotics (203, 204). Between 1963 and 1971 he and his co-workers studied the mode of antitumor action of cytotoxic hexits. These compounds, in contrast to the biological alkylating agents, do not affect thermodenaturation of DNA. According to these studies the indicator of the anticarcinogenic effect is the increased RNA synthesis in the sensitive tumor cells. Based on the observations that under the effect of Dibrombulcit® cytotoxic hexits inhibited the development of the nucleohistone complex, it was suggested that by the abolishment of histone function a depression of DNA occurs and results in an increased RNA synthesis. It has not been settled whether increased RNA synthesis is only a side product of the impairment of chromatic substance or whether the increasing synthesis of RNA has a decisive role in the proliferation of tumor cells (205–211).

In the Department of Pharmacology at Debrecen, Hernádi et al analyzed the mechanism of the metabolic radioprotective effect of cysteine on *Escherichia coli* and on primordial hemopoietic germ cells of the mouse. Inhibition of the biosynthesis of amino acids, primarily the blockade of the homoserindehydrogenase and hydroxyacetic acid synthetase, was thought to be responsible for the reversible inhibition of the division of *E. coli* cells. Cysteine was found to inhibit cell division also in the primordial hemopoietic germ cell population of the mice (212–219). Kelentey et al studied the passage of drugs into and out of the central nervous system (220, 221). Hepatoendocrine regulations and sex differences in the sensitivity for different drugs were studied by Kulcsár & Kulcsár-Gergely (222–229). Szegi et al analyzed the isoproterenol-induced myocardial necrosis. (230).

In 1950 the nationalized pharmaceutical firms of the country decided to promote and intensify drug research and started a far-reaching program with a goal toward the development of their own firm base for experimental research. In the spirit of these decisions the biggest firms (Chinoin, Gedeon Richter, EGYT) successfully established new laboratories, and the Drug Research Institute, which numbers 170 research workers, was founded in Budapest in 1950. One of its departments, headed by J. Borsy, is engaged in experimental pharmacology and toxicology.

The Drug Research Institute developed a number of therapeutically useful cytostatics. The first of these, mannomustine (Degranol,® 1,6-bis (2-chloroethylamino)-1,6-dideoxy-D-mannitol) synthesized by Vargha in 1955 (231), was found more

potent and less toxic than nitrogen mustard (232). Degranol was followed by a number of new cytostatics. Mitobronitol (Myleobromol®, 1,6-dibromo-1,6-dideoxy-mannitol) was found to be effective in several forms of hemopoietic diseases and tumors (233–235a). Mannosulfan, (Zitostop®, D-mannitol-1,2,5,6-tetrabis-methanesulphonate), a new compound with a better safety margin proved to produce some delay in the development of pulmonary tumors (236), while licurim [1,4-di(2-methylsulphonooxyethylamino)-1,4-dideoxy-*m*-eritritdimethylsulphonate] is useful in lymphopoietic disorders (237, 238).

In the field of chemotherapy, the Institute solved practical problems. In collaboration with the pharmaceutical firms, workers at the institute developed procedures for producing known antibacterial and antifungal antibiotics. Penicillin, streptomycin, oxytetracycline, 6-aminopenicillanic acid, neomycin, paromomycin, gentamycin C, erythromycin, viomycin, polymyxin B and D, actinomycin D, mitramycin, nigericin, antimycin, nystatin, candicydin, nyfimycin, and mykoheptin were produced by fermentation, and among others, chloramphenicol, cycloserine, and trimethoprim were synthesized. They also worked out an efficient method for the isolation of soil actinomycetes (239) and isolated in pure form 60 antibiotics of which 50 were identified as earlier known ones; oleficin (240), desoxinigericin (241), mannosidehydroxystreptomycin, citotetrin, cinerubin C, griseofagin, new macrolids (10-desoximetimicin and 12-desoxi-4-dehydropicromycin), parvulin, krotocin (242), heptafungin A (243), and pentafungin (244) proved to be new. Pirazocillin [1-(2,6-dihydrophenyl)-4-methyl-5-pyrazolilpenicillin Na], a new semisynthetic penicillin derivative (245), was found to be of practical value.

In the domain of steroid research Krámli & Horváth (246) and Wix et al (247–249) made important observations regarding the microbiological transformation of steroids.

Structure-activity relationship studies by Borsy in the field of psychopharmacology led to the introduction of trimetozine (Trioxazin®) a useful antianxiety agent (250,251) and metofenazate (Frenolon®) a potent neuroleptic drug, synthesized by Toldy (252, 253).

In 1966 a research group of the Institute led by Bajusz in collaboration with Medzihradszky working in the Department of Organic Chemistry of the Eötvös Lóránd University in Budapest (headed by Professor Bruckner) synthesized human corticotropin according to sequences described in the literature (254, 255). This synthetic human ACTH showed an activity of 120–130 unit/mg, and clinical studies revealed that it was tolerated also in patients hypersensitive to highly purified pig corticotropin (256). Analytic studies in the institute in 1971 by Gráf et al (257, 258) revealed that the structure of pig and human corticotropins given in the literature are incorrect, because they contain at position 25–27 aspartic acid-alanine-glycine instead of the described asparagine-glycine-alanine, and at position 30, glutaminic acid instead of glutamine. The synthesis of the human ACTH with the correct structure was performed in collaboration with Gedeon Richter Co. and described by Kisfaludy et al (259).

Headed by G. Fekete the research laboratories of Gedeon Richter have made detailed studies into the effects of glucocorticoids on the adrenal cortex (260–268),

a pharmacological analysis of newly synthesized ACTH fragments of different sequences (269), and studies into the testing problem and mechanism of inflammation (270–275).

As fruits of drug research, a water-soluble glucocorticoid preparation (275), a new neuromuscular blocking agent among nitrogen-containing steroids (276), and coronary and peripheric vasodilators (277) were produced. Economical methods for the isolation of the natural alkaloids of Vinca minor L and series of half synthetic and synthetic derivatives of vincamine were developed and detailed pharmacological studies with the alkaloids were performed (278–282).

Drug research is now one of the very few fields which, in recognition of scientific accomplishments, enjoy special governmental care and support in Hungary. The history of pharmacology in this country which dates back more than a century makes, I hope, this honorable distinction understandable.

Literature Cited

1. Issekutz, B. 1971. *Die Geschichte der Arzneimittel forschung.* Budapest: Akad. Kiadó. 651 pp.
2. Semmelweis, I. P. 1861. *Die Aetiologie, der Begriff und die Prophilaxis des Kindbettfibers.* Pest, Wien & Leipzig: Hartleben's Verlags-Expedition. 543 pp.
3. Knoll, J., Magyar, K., eds. 1973. *Symp. Pharmacol. Agents Biogenic Amines Central Nervous System.* Budapest: Akad. Kiadó. 274 pp.
4. Knoll, J., Szekeres, L., Papp, J. Gy., eds. 1973. *Symp. Drugs Heart Metab.* Budapest: Akad. Kiadó. 369 pp.
5. Knoll, J., Vizi, E. S., eds. 1974. *Symp. Curr. Probl. Pharmacol. Analgetics.* Budapest: Akad. Kiadó. 183 pp.
6. Knoll, J., Knoll, B. eds. 1974. *Symp. Pharmacol. Learn. Retention.* Budapest: Akad. Kiadó. 103 pp.
7. Knoll, J., Jávor, T., Gógl, A., eds. 1974. *Symp. Drug-Induced Metabolic Changes.* Budapest: Akad. Kiadó. 253 pp.
8. Knoll, J., Borsy, J., Mózsik, Gy. eds. 1973. *Symp. Gastrin and its Antagonists.* Budapest: Akad. Kiadó. 153 pp.
9. Abstr. Pharmacol. Meet. Graz. Sept. 2–5, 1974. *Arch. Pharmacol,* Suppl. to Vol 285
10. Jendrassik, E. 1886. *Dtsch. Arch. Klin Med.* 38:499–524
11. Jendrassik, E. 1891. *Dtsch. Arch. Klin. Med.* 47:226–88
12. Kossa, Gy. 1892. *Magy. Orv. Arch.* 1:469–91
13. Köppen, L. 1892. *Arch. Exp. Pathol. Pharmakol.* 29:327–52
14. Vámossy, Z. 1897. *Dtsch. Med. Wochenschr. Ther. Beil.* 23:457–61
15. Vámossy, Z. 1902. *Ther. Ggw.* 43:201
16. Issekutz, B. 1916. *Orv. Hetil.* 60:485–87
17. Issekutz, B. 1917. *Z. Exp. Pathol. Ther.* 19:99
18. Issekutz, B., Leinzinger, M., Dirner, Z. 1932. *Arch. Exp. Pathol. Pharmakol.* 164:158–72
19. Issekutz, B. 1964. *Ther. Hung.* 12:3–9
20. Issekutz, B. 1952. *Arch. Exp. Pathol. Pharmakol.* 215:283–98
21. Gyermek, L., Nádor, K. 1957. *J. Pharm. Pharmacol.* 9:209–29
22. György, L., Dóda, M., Nádor, K. 1961. *Arzneim. Forsch.* 11:444–50
23. György, L. et al 1968. *Arzneim. Forsch.* 18:517–24
24. György, L. et al 1970. *Acta Physiol. Acad. Sci. Hung.* 37:313–18
25. György, L. et al 1971. *Acta Physiol. Acad. Sci. Hung.* 40:373–79
26. Issekutz, B. 1924. *Biochem. Z.* 147: 264–74
27. Issekutz, B. et al 1937. *Arch. Exp. Pathol. Pharmakol.* 185:673–84
28. Jancsó, N. 1928–1929. *Z. Exp. Med.* 61:63, 64:256, 65:98
29. Jancsó, N. 1931–1932. *Zentralb. Bacteriol.* 122:388, 393; 123:129; 124:167
30. Issekutz, B. 1933. *Arch. Exp. Pathol. Pharmakol.* 173:479–98
31. Jancsó, N., Jancsó, H. 1934. *Ann. Trop. Med. Parasitol.* 28:419–38
32. Jancsó, N., Jancsó, H. 1935. *Ann. Trop. Med. Parasitol.* 29:95–109
33. Jancsó, N., Jancsó, H. 1935. *Z. Immunitaetsforsch.* 84:471–504
34. Jancsó, N., Jancsó, H. 1935. *Z. Immunitaetsforsch.* 86:1–30

35. Yorke, W. 1940. *Trans. R. Soc. Trop. Med. Hyg.* 33:463–82
36. King, H., Lourie, E. M., Yorke, W. 1938. *Ann. Trop. Med. Parasitol.* 32: 177–92
37. Jancsó, N. 1947. *Nature London* 160: 227–28
38. Jancsó, N., Jancsó-Gábor, A. 1952. *Experientia* 8:465–67
39. Jancsó, N., Jancsó-Gábor, A. 1952. *Nature London* 170:567–68, 568–69
40. Jancsó, N., Jancsó-Gábor, A. 1952. *Acta Physiol. Acad. Sci. Hung.* 3:537–554, 555–62
41. Jancsó, N., Jancsó-Gábor, A. 1954. *Experientia* 10:256–57
42. Jancsó, N. 1955. *Acta Med. Acad. Sci. Hung.* 7:173–210
43. Jancsó, N. 1955. *Speicherung. Stoffanreicherung im Retikuloendothel und in der Niere.* Budapest. Akad. Kiadó. 468 pp.
44. Jancsó, N. 1962. *J. Pharm. Pharmacol.* 13:577–94
45. Jancsó, N. et al 1967. *Br. J. Pharmacol. Chemother.* 31:138–51
46. Jancsó, N. et al 1968. *Br. J. Pharmacol. Chemother.* 33:32–41
47. Pórszász, J., Jancsó, N. 1959. *Acta Physiol. Acad. Sci. Hung.* 16:299–306
48. Jancsó, N., Jancsó-Gábor, A. 1965. *Arch. Exp. Pathol. Pharmakol.* 251: 136–37
49. Jancsó, N. 1965. *Orv. Hetil.* 106:289–96
50. King, C. G., Waugh, W. A. 1932. *Science* 75:357–58
51. Svirbely, J. L., Szent-Györgyi, A. 1932. *Biochem. J.* 26:865–70
52. Svirbely, J. L., Szent-Györgyi, A. 1932. *Nature London* 129:576
53. Drury, A. N., Szent-Györgyi, A. 1929. *J. Physiol.* 68:213–37
54. Rusznyák, I. Szent-Györgyi, A. 1936. *Nature London* 138:27
55. Armentano, L. et al 1936. *Dtsch. Med. Wochenschr.* 62:1325–28
56. Bentsáth, A., Rusznyák, I., Szent-Györgyi, A. 1936. *Nature London* 138:798
57. Bruckner, V., Szent-Györgyi, A. 1936. *Nature London* 138:1057
58. Zemplén, G., Bognár, R., Farkas, L., 1943. *Ber. Dtsch. Chem. Ges.* 76:267
59. Zemplén, G., Bognár, R., Farkas, L. 1943. *Ber. Dtsch. Chem. Ges.* 76:267
60. Gábor, M. 1974. *Pathophysiology and Pharmacology of Capillary Resistance.* Budapest: Akad. Kiadó. 235 pp.
61. Komlós, E., Pórszász, J., Knoll J. 1950. *Acta Physiol. Acad. Sci. Hung.* 1:77–90
62. Knoll, J., Komlós, E. 1951. *Acta Physiol. Acad. Sci. Hung.* 2:57–69
63. Pórszász, J., Knoll, J., Komlós, E. 1951. *Acta Physiol. Acad. Sci. Hung.* 2:469–77
64. Knoll, J., Komlós, E. Pórszász, J. 1951. *Acta Physiol. Acad. Sci. Hung.* 2:479–91
65. Komlós, E., Knoll J. 1952. *Acta Physiol. Acad. Sci. Hung.* 3:123–26
66. Knoll, J., Komlós, E. 1952. *Acta Physiol. Acad. Sci. Hung.* 3:127–36
67. Knoll, J., Komlós, E., Tardos, L. 1953. *Acta Physiol. Acad. Sci. Hung.* 4:131–40
68. Pataki, I. et al 1948. *Arch. Int. Pharmacodyn. Ther.* 77:17–22, 204–11
69. Pataki, I. et al 1951. *Acta Physiol. Acad. Sci. Hung.* 2:71–76, 199–205
70. Pfeifer, A. K. et al 1952. *Acta Physiol. Acad. Sci. Hung.* 3:153–64
71. Pfeifer, A. K. et al 1967. *Arch. Int. Pharmacodyn. Ther.* 165:201–11, *J. Pharm. Pharmacol.* 19:400–402
72. Knoll, J., Knoll, B. 1958. *Arzneim. Forsch.* 8:330–33
73. Knoll, J., Knoll, B. 1959. *Arzneim. Forsch.* 9:633–36
74. Knoll, J. 1961. *Arch. Int. Pharmacodyn. Ther.* 130:141–54
75. Knoll, J., Knoll, B. 1961. *Arch. Int. Pharmacodyn. Ther.* 133:310–26
76. Knoll, J., Knoll, B. 1964. *Arch. Int. Pharmacodyn. Ther.* 148:200–216
77. Knoll, J. 1961. *Acta Biol. Med. Ger. Suppl.* 1:9–45
78. Knoll, J. 1959. In *Neuropsychopharmacology,* ed. P. B. Bradley, 1:334–37. Amsterdam:Elsevier
79. Knoll, J., Kelemen, K., Knoll, B. 1955. *Acta Physiol. Acad. Sci. Hung.* 8:327–45
80. Knoll, J., Kelemen, K., Knoll, B. 1955. *Acta Physiol. Acad. Sci. Hung.* 8:347–67
81. Knoll, J., Kelemen, K., Knoll, B. 1955. *Acta Physiol. Acad. Sci. Hung* 8:369–88
82. Knoll, J., Kelemen, K., Knoll, B. 1956. *Acta Physiol. Acad. Sci. Hung.* 9:99–109
83. Knoll, J. 1956. *Acta Physiol. Acad. Sci. Hung.* 10:89–100
84. Knoll, J. 1957. *Acta Physiol. Acad. Sci. Hung.* 12:65–92
85. Kelemen, K., Bovet, D. 1961. *Acta Physiol. Acad. Sci. Hung.* 19:143–54
86. Kelemen, K. et al 1961. *Electroencephalogr. Clin. Neurophysiol.* 13:745–51
87. Knoll, B. 1961. *Acta Physiol. Acad. Sci. Hung.* 20:265–75
88. Knoll, J. 1969. *The Theory of Active Reflexes. An Analysis of Some Fundamental Mechanisms of Higher Nervous Activity.* Budapest: Akad. Kiadó. 131 pp.

89. Knoll, J. et al 1961. *Arch. Int. Pharmacodyn. Ther.* 130:155–69
90. Knoll, J., Vizi, E. S., Ecseri, Z. 1964. *Magy. Tud. Akad. V. Oszt. Közl.* 15:413–20
91. Knoll, J. 1965. In *Pharmacology of Conditioning, Learning and Retention,* ed. M. J. Michelson, 221–30. London: Pergamon
92. Knoll, J., Vizi, E. S., Ecseri, Z. 1966. *Arch. Int. Pharmacodyn. Ther.* 159: 442–51
93. Knoll, J. 1967. In *Recent Developments of Neurobiology in Hungary,* ed. K. Lissák, 72–97. Budapest: Akad. Kiadó
94. Knoll, J. 1967. In *Animal and Clinical Pharmacologic Techniques in Drug Evaluation,* ed. P. E. Siegler, 305–21. Chicago: Yearb. Med.
95. Vizi, E. S., Knoll, B., Knoll, J. 1968. *Int. J. Neuropharmacol.* 7:503–50
96. Knoll, J. 1970. In *Amphetamines and Related Compounds,* ed. E. Costa, S. Garattini, 761–80. New York: Raven
97. Knoll, J., Vizi, E. S. 1970. *Pharmacol. Res. Commun.* 2:67–70
98. Knoll, J., Vizi, E. S. 1970. *Pharmacology* 4:278–86
99. Knoll, J., Vizi, E. S., Knoll, B. 1970. *Acta Physiol. Acad. Sci. Hung.* 37: 151–70
100. Knoll, J., Vizi, E. S., Knoll, B. 1970. *Excerpta Med. Int. Congr. Ser.* 220: 50–55
101. Knoll, B., Held, K., Knoll, J. 1971. In *Symp. Pharmacol. Learn. and Retention,* ed. J. Knoll, B. Knoll, pp. 43–47. Budapest: Akad. Kiadó
102. Knoll, J., Kelemen, K., Knoll, B. 1971. In *Biology of Memory,* ed. G. Ádám, 247–53. Budapest: Akad. Kiadó
103. Knoll, J. 1973. In *Proc. 5th Int. Congr. Pharmacol.* ed. F. E. Bloom, G. H. Acheson, 4:55–68. Basel: Karger
104. Magyar, K. et al 1972. *Acta Physiol. Acad. Sci. Hung.* 41:356
105. Knoll, J., Knoll, B. 1975. *Int. J. Neurol.* 10:198–221
106. Knoll, J. et al 1965. *Arch. Int. Pharmacodyn. Ther.* 155:154–64
107. Magyar, K. et al 1967. *Acta Physiol. Acad. Sci. Hung.* 32:377–87
108. Knoll, J. et al 1968. *Arzneim. Forsch.* 18:109–12
109. Knoll, J., Magyar, K. 1972. *Adv. Biochem. Psychopharmacol.* 5:393–408
110. Knoll, J. 1976. *CIBA Symp.* In press
111. Varga, E., Tringer, L. 1967. *Acta Med. Acad. Sci. Hung.* 23:289–95
112. Birkmayer, W. et al 1975. *J. Neural Transm.* 36:303–26
113. Knoll, J. et al 1971. *Arzneim. Forsch.* 21:717–19
114. Knoll, J., Fürst, Zs., Mészáros, Z. 1971. *Arzneim. Forsch.* 21:719–27
115. Knoll, J., Fürst, Zs., Mészáros, Z. 1971. *Arzneim. Forsch.* 21:727–33
116. Knoll, J., Magyar, K., Bánfi, D. 1971. *Arzneim. Forsch.* 21:733–38
117. Mészáros, Z. et al 1972. *Arzneim. Forsch.* 22:815–29
118. Gráber, H. 1972. *Int. J. Clin. Pharmacol.* 6:354–57
119. Knoll, J., Fürst, Zs., Kelemen, K. 1971. *Orvostudomány* 22:265–84
120. Knoll, J. et al 1975. *Orvostudomány* 26:89–95; 96–102; 103–10; 111–27
121. Knoll, J., Fürst, Zs., Vizi, E. S. 1973. *Pharmacology* 10:354–62
122. Knoll, J. et al 1974. *Pharmacology* 12:283–89
123. Knoll, J. 1973. *Pharmacol. Res. Commun.* 5:175–91
124. Knoll, J., Fürst, Zs., Kelemen, K. 1973. *J. Pharm. Pharmacol.* 25:929–39
125. Knoll, J., Fürst, Zs., Makleit, S. 1975. *J. Pharm. Pharmacol.* 27:99–105
126. Knoll, J. et al 1974. *Arch. Int. Pharmacodyn.* 210:241–49
127. Knoll, J., Zsilla, G. 1974. *Biochem. Pharmacol.* 23:745–50
128. Bognár, R., Makleit, S. 1968. *Acta Chim. Acad. Sci. Hung.* 58:203–5
129. Rétsági, Gy., Schwarzmann, É. 1973. *Orvostudomány* 24:359–69
130. Rétsági, Gy. et al 1973. *Orvostudomány* 24:371–78
131. Rétsági, Gy. et al 1974. *Orvostudomány* 25:83–90
132. Knoll, J., Komlós, E., Tardos, L. 1952. *Orv. Hetil.* 93:757–58
133. Knoll, J. et al 1955. *Acta Physiol. Acad. Sci. Hung.* 8:173–86
134. Knoll, J. et al 1955. *Acta Physiol. Acad. Sci. Hung.* 8:187–208
135. Knoll, J. et al 1957. *Acta Physiol. Acad. Sci. Hung.* 12:183–87
136. Knoll, J. 1958. *Klin, Wochenschr.* 36:141
137. Knoll, J. 1956. *Experientia* 12:262
138. Knoll, J., Kelemen, K., Knoll, B. 1958. *Pfluegers Arch. Gesamte Physiol. Menschen Tiere* 267:150–57
139. Knoll, J. 1965. *Magy. Tud. Akad. V. Oszt. Közl.* 16:311–26
140. Knoll, J., Kelemen, K., Knoll, B. 1965 *Magy. Tud. Akad. V. Oszt. Közl.* 16:327–38
141. Knoll, J. et al 1965. *Magy. Tud. Akad. V. Oszt. Közl.* 16:339–49
142. Knoll, J. 1970. *Orvostudomány* 21:271–324

143. Kelemen, K., Kecskeméti, V., Knoll, J. 1965. *Magy. Tud. Akad. V. Oszt. Közl.* 16:351–58
144. Kelemen, K. 1967. *Magy. Tud. Akad. V. Oszt. Közl.* 18:305–22
145. Kelemen, K. et al 1968. *Acta Physiol. Acad. Sci. Hung.* 33:269–84
146. Kelemen, K., Kecskeméti, V., Knoll. J. 1972. *Orvostudomány* 23:231–41
147. Kelemen, K., Skolnik, J., Knoll, J. 1972. *Orvostudomány* 23:391–402
148. Kecskeméti, V., Kelemen, K., Knoll, J. 1973. *Eur. J. Pharmacol.* 24:289–95
149. Vizi, E. S., Knoll, J. 1971. *J. Pharm. Pharmacol.* 23:918–25
150. Knoll, J., Vizi, E. S. 1971. *Br. J. Pharmacol.* 41:263–72
151. Vizi, E. S. 1973. *Br. J. Pharmacol.* 47:765–77
152. Vizi, E. S. et al 1972. *Eur. J. Pharmacol.* 17:175–78
153. Vizi, E. S. et al 1973. *Gastroenterology* 64:286–97
154. Vizi, E. S. et al 1973. *Arch. Pharmakol.* 280:79–91
155. Illés, P. et al 1973. *Eur. J. Pharmacol.* 24:29–36
155a. Knoll, J., Illés, P., Torma, Z. 1975. *Neuropharmacology* 14:317–24
156. Hadházy, P., Illés, P., Knoll, J. 1973. *Eur. J. Pharmacol.* 23:251–55
157. Vizi, E. S. 1973. *J. Physiol. London* 226:95–117
158. Fürst, Zs. et al 1975. *Sixth Int. Congr. Pharmacol.*, p. 179 (Abstr.)
159. Szekeres, L. 1966. *Actual. Pharmacol.* XIX:149–86
160. Szekeres, L., Papp, J. Gy. 1968. *Fortschr. Arzneimittelforsch.* 12:292–369
161. Szekeres, L., Papp, J. Gy. 1971. *Experimental Cardiac Arrhythmias and Anti-Arrhythmic Drugs.* Budapest: Akad. Kiadó. 374 pp.
162. Szekeres, L., Méhes, J., Papp, J. Gy. 1961. *Br. J. Pharmacol.* 17:167–75
163. Szekeres, L., Papp, J. Gy., Förster, W. 1965. *Experientia* 21:720–22
164. Szekeres, L., Papp, J. Gy. 1965. *Acta Physiol. Acad. Sci. Hung.* 26:277–86
165. Szekeres, L., Papp, J. Gy. 1967. *Acta Physiol. Acad. Sci. Hung.* 32:143–62
166. Papp, J. Gy., Szekeres, L. 1968. *Eur. J. Pharmacol.* 3:4–14
167. Papp, J. Gy., Szekeres, L. 1968. *Eur. J. Pharmacol.* 3:15–26
168. Papp, J. Gy., Szekeres, L. 1967. *Acta Physiol. Acad. Sci. Hung.* 32:163–74
169. Szekeres, L. 1971. *Methods Pharmacol.* I: 151–82
170. Szekeres, L., Papp, J. Gy. 1973. *Herzrhythmusstörungen. 2nd Wiener Symp.*, ed. H. Antoni. Stuttgart & New York: Schattauer Verlag
171. Szekeres, L., Papp, J. Gy. 1976. In *Handbuch für Experimentelle Pharmakologie.* Berlin:Springer. In press
172. Szekeres, L., Szurgent, J. 1974. *Cardiovasc. Res.* 8:132–37
173. Szekeres, L. et al 1965. *Acta Physiol. Acad. Sci. Hung.* 26:287–95
174. Minker, E., Koltai, M. 1962. *Acta Physiol. Acad. Sci. Hung.* 22:99–109
175. Minker, E., Koltai, M. 1964. *Acta Physiol. Acad. Sci. Hung.* 24:365–71
176. Koltai, M., Minker, E. 1966. *Acta Physiol. Acad. Sci. Hung.* 29:410
177. Minker, E., Koltai, M. 1967. *Acta Physiol. Acad. Sci. Hung.* 31:167–76
178. Minker, E., Koltai, M. 1965. *Naturwissenschaften* 52:189
179. Koltai, M., Minker, E. 1969. *Eur. J. Pharmacol.* 6:175
180. Koltai, M., Minker, E., Ottlecz, A. 1971. *Life Sci.* 10:315–20
181. Koltai, M., Minker, E., Ottlecz, A. 1972. *Experientia* 28:302–3
182. Ottlecz, A. et al 1974. *Pharmacology* 11:346–49
183. Koltai, M., Mécs, E. 1973. *Nature London* 242:525–26
184. Pórszász, J., Barankay, T., Pórszász-Gibiszer, K. 1965. *Acta Physiol. Acad. Sci. Hung.* 27:119–24
185. Pórszász, J., Pórszász-Gibiszer, K. 1968. *Acta Physiol. Acad. Sci. Hung* 34:249–58
186. Pórszász, J., Such, G., Pórszász-Gibiszer, K. 1972. *Acta Physiol. Acad. Sci. Hung.* 42:387–402
187. Herr, F., Pórszász, J. 1951. *Acta Physiol. Acad. Sci. Hung.* 2:17
188. Pórszász, J., Nádor, K., Pórszász-Gibiszer, K., Bacsó, I. 1957. *Acta Physiol. Acad. Sci. Hung.* 11:95–108
189. Pórszász, J. et al 1975. *Acta Physiol. Acad. Sci. Hung.* 11:211–24
190. Pórszász, J. 1958. *Acta Physiol. Acad. Sci. Hung.* 14:375–90
191. Pórszász, J., Nádor, K., Pórszász-Gibiszer, K. 1958. *Acta Physiol. Acad. Sci. Hung.* 14:403–9
192. Pórszász, J. et al 1960. *Acta Physiol. Acad. Sci. Hung.* 18:149–70
193. Nádor, K., Pórszász, J. 1956. *Arzneim. Forsch.* 6:696–98
194. Nádor, K., Pórszász, J. 1958. *Arzneim. Forsch.* 8:313–15
195. Pórszász, J. et al 1961. *Arzneim. Forsch.* 11:257–60

196. Varga, F. 1966. *Arch. Int. Pharmacodyn. Ther.* 163:38–46
197. Decsi, L. 1960. *Arzneim. Forsch.* 10: 432–34
198. Decsi, L. 1961. *Psychopharmacologia* 2:224–42
199. Decsi, L. 1964. *Fortschr. Arzneimittelforsch.* 8:53–194
200. Decsi, L. 1974. *Pharmacol. Biochem. Behav.* 2:141–43
201. Decsi, L., Nagy, J. 1974. *Neuropharmacology* 13:1153–62
202. Vályi-Nagy, T., Uri, J., Szilágyi, I. 1954. *Nature London* 1974:1105
203. Uri, J., Békési, I. 1958. *Nature London* 181:908
204. Uri, J. et al 1958. *Nature London* 182:401
205. Jeney, A. et al 1968. *Neoplasma* 15: 237–40
206. Jeney, A., Szabó, J., Vályi-Nagy, T. 1968. *Neoplasma* 15:231–36
207. Jeney, A. et al 1969. *Neoplasma* 16: 151–60
208. Zsindely, A. et al 1972. *Neoplasma* 19: 89–94
209. Szabó, J. et al 1973. *Neoplasma* 20: 13–25
210. Vályi-Nagy, T. et al 1969. *Eur. J. Cancer* 5:403
211. Jeney, A., Szabó, I., Vályi-Nagy, T. 1970. *Eur. J. Cancer* 6:297
212. Hernádi, F. et al 1962. *Radiat. Res.* 16:464
213. Nagy, Zs. et al 1968. *Radiat. Res.* 35:652–60
214. Kovács, P. et al 1968. *Radiat. Res.* 36:217–24
215. Nagy, Zs. et al 1968. *Biochem. Pharmacol.* 17:861–66
216. Kari, Cs., Nagy, Zs., Hernádi, F. 1971. *Biochem. Pharmacol.* 20:975–78
217. Kovács, P., Daróczy, A., Hernádi, F. 1971. *Stud. Biophys.* 26:13
218. Kovács, P., Hernádi, F. 1971. *Stud. Biophys.* 27:149
219. Hernádi, F., Kari, Cs. 1972. *Experientia* 28:155
220. Kelentey, B. et al 1961. *Acta Physiol. Acad. Sci. Hung.* 20:81–88
221. Kelentey, B. et al 1964. *Arch. Int. Pharmacodyn. Ther.* 150:363–72
222. Kulcsár-Gergely, J., Kulcsár, A. 1960. *J. Pharm. Pharmacol.* 12:313–16
223. Kulcsár, A., Kulcsár-Gergely, J. 1960. *Naturwissenschaften* 47:183
224. Kulcsár, A., Kulcsár-Gergely, J. 1966. *Tohoku J. Exp. Med.* 89:315–20
225. Kulcsár-Gergely, J., Kulcsár, A. 1964. *Naturwissenschaften* 51:390–91
226. Kulcsár, A., Kulcsár-Gergely, J. 1970. *Tohoku J. Exp. Med.* 101:251–56
227. Kulcsár, A. et al 1969. *Rev. Int. Hepatol.* 19:359–64
228. Kulcsár-Gergely, J., Kulcsár, A. 1973. *Toxicology* 288:125–30
229. Kulcsár-Gergely, J., Kulcsár, A. 1974. *Arzneim. Forsch.* 24:1772–74
230. Csáky, L., Szabó, J., Szegi, J. 1974. *Experientia* 30:428
231. Vargha, L. 1955. *Naturwissenschaften* 42:582
232. Kellner, B., Németh, L., Sellei, C. 1955. *Naturwissenschaften* 42:582–83
233. Institoris, L., Horváth, I. P. 1964. *Arzneim. Forsch.* 14:668–70
234. Csányi, E., Horváth, P., Institoris, L. 1964. *Arzneim. Forsch.* 14:670–73
235. Csányi, E. 1965. *Arzneim. Forsch.* 15: 198
235a. Institoris, L., Horváth, I. P., Csányi, E. 1967. *Arzneim. Forsch.* 17:145–49
236. Szentkláray, I., Sellei, C. 1967. *Neoplasma* 14:83–90
237. Csányi, E., Elekes, I. 1972. *Neoplasma* 19:189–95
238. Börzsönyi, M. et al 1967. *Arzneim. Forsch.* 17:1596–98
239. Horváth, I., Lovrekovich, I., Magyar, K. 1964. *Z. Allg. Mikrobiol.* 4:225
240. Gyimesi, J. et al 1971. *J. Antibiot.* 24:277
241. Gyimesi, J., Horváth, I., Szentirmai, A. 1964. *Z. Allg. Mikrobiol.* 4:269
242. Gláz, E. T. et al 1959. *Nature London* 184:908
243. Kalász, H. et al 1972. *Acta Microbiol. Acad. Sci. Hung.* 19:111–20
244. Bérdy, I., Horváth, I. 1965. *Z. Allg. Mikrobiol.* 5:345
245. Gadó, I. et al 1961. *Acta Microbiol. Acad. Sci. Hung.* 8:291–302
246. Krámli, A., Horváth, J. 1948. *Nature London* 162:619
247. Wix, Gy. et al 1959. *Nature London* 183:1279
248. Wix, Gy. et al 1961. *Acta Microbiol. Acad. Sci. Hung.* 8:339
249. Wix, Gy. et al 1968. *Steroids* 11:401
250. Borsy, J. et al 1959. *Acta Physiol. Acad. Sci. Hung.* 15:107–17
251. Vargha, L. et al 1962. *Biochem. Pharmacol.* 11:639–49
252. Toldy, L. et al 1964. *Acta Chim. Acad. Sci. Hung.* 42:351–58
253. Borsy, J., Toldy, L., Dumbovics, B. 1965. *Acta Physiol. Acad. Sci. Hung.* 27:65–80
254. Bajusz, S. et al 1967. *Acta Chim. Acad. Sci. Hung.* 52:335

255. Bajusz, S. et al 1968. In *Peptides,* ed. E. Brices, p. 237. Amsterdam: North-Holland
256. Kovács, K. et al 1968. Lancet. 1:698
257. Gráf, L. et al 1971. *Acta Biochim. Biophys. Hung.* 6:415
258. Gráf, L. et al 1972. *Acta Biochim. Biophys. Hung.* 7:293
259. Kisfaludy, L. et al 1972. In *Chemistry and Biology of Peptides,* ed. J. Meienhofer, p. 299. Ann Arbor, Mich.: Ann Arbor Sci.
260. Fekete, Gy. 1962. *Acta Physiol. Acad. Sci. Hung.* 21:77–82
261. Fekete, G., Görög, P. 1962. *Acta Physiol. Acad. Sci. Hung.* 21:83–86
262. Fekete, Gy., Görög, P. 1963. *J. Endocrinol.* 27:123
263. Fekete, Gy. et al 1964. *Steroids* 3:163
263a. Fekete, Gy. et al 1966. *Steroids* 6:159
264. Fekete, Gy., Szeberényi, Sz. 1965. *Endokrinologie* 49:23
265. Fekete, Gy., Szeberenyi, Sz. 1968. *Arzneim. Forsch.* 18:451–52
266. Szeberényi, Sz. et al 1964. *Steroids* 4:587
267. Szeberényi, Sz. et al 1966. *Acta Physiol. Acad. Sci. Hung.* 30:328
268. Szeberényi, Sz. et al 1966. *J. Endocrinol.* 35:323
269. Szporny, L. et al 1968. *Nature London* 218:1169
270. Szporny, L., Fekete, Gy. 1960. *Arch. Exp. Pathol. Pharmakol.* 238:233–34
271. Tóth, E., Szporny, L., Görög, P. 1965. *Arch. Exp. Pathol. Pharmakol.* 250: 265–66
272. Görög P. et al 1968. *Arzneim. Forsch.* 18:227–30
273. Görög P. et al 1962. *Arch. Int. Pharmacodyn.* 136:165
274. Görög, P., Szporny, L. 1965. *Biochem. Pharmacol.* 14:1673–77
275. Görög, P., Szporny, L. 1965. *J. Pharm. Pharmacol.* 7:250–51
276. Szporny, L., Biro, H. K., Kárpáti, E. 1974. *Arch. Exp. Pathol. Pharmacol.* 285:80
277. Kárpáti, E. et al 1968. *J. Pharm. Pharmacol.* 20:735–36
278. Kárpáti, E., Dömök, L., Szporny, L. 1969. *Arzneim. Forsch.* 19:1011–1115
279. Szporny, L. et al 1958. *Acta Physiol. Acad. Sci. Hung.* 14:46
280. Molnár, J., Szporny, L. 1962. *Acta Physiol. Acad. Sci. Hung.* 21:169–75
281. Szporny, L., Görög, P. 1962. *Arch. Int. Pharmacodyn. Ther.* 138:451–61
282. Szporny, L. et al 1962. *Biochem. Pharmacol.* 8:259–62