HISTORY AND HIGHLIGHTS OF FINNISH PHARMACOLOGY

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In 1640, when Finland was part of the Kingdom of Sweden, a university was founded in the city of Turku, then the capital of Finland. After Czar Alexander I of Russia, acting on his pact with Napoleon, had seized the country in 1808–09 and annexed it as an autonomous grand duchy to the Russian empire, he moved the capital of Finland to Helsinki in 1812. A devastating fire in Turku in 1827 prompted the transfer of Finland's only university to Helsinki. Other universities were founded after Finland had declared itself an independent state on December 6, 1917.

In 1844 a professorship in pharmacy and pharmacology was established in the faculty of medicine of the University of Helsinki. The first holder of the chair, F. J. von Becker, M.D., was appointed in 1854. He had studied pharmacy and pharmacology in Göttingen, Leipzig, and Vienna, and his research work covered, among other subjects, the metabolism of carbohydrates and the physiology of digestion, and also the structure, function, and diseases of the eye and their treatment. Dr. von Becker studied surgery and ophthalmology in Germany and France, and under his influence a professorship in ophthalmology was founded in the University of Helsinki in 1871. He held the chair from its founding up to his retirement in 1885.

As his successor in the professorship, which by that time had been changed to that of physiological chemistry and pharmacology, was appointed E. E. Sundvik, M.D., who had carried on further studies in Strassburg and Berlin. Sundvik's research work dealt with, among other subjects, conjugation processes, uric acid metabolism, and many other problems in the physiological chemistry of the living organism. He also was the head of the pharmaceutical laboratory, gave instruction both to students of pharmacy and to those of medicine, and was the principal collaborator in the preparation of Pharmacopoea Fennica IV.

Finland's autonomy included also its own pharmacopeia. The first edition, Pharmacopoea Fennica, had been published in 1819, edition II in 1850, III in 1863, and IV in 1885. The later editions V, VI and VII appeared in 1914, 1937, and 1956, respectively. A joint Scandinavian Pharmacopeia Council was formed in 1948 by Denmark, Finland, Iceland, Norway, and Sweden, and through its instrumentality the Pharmacopoea Nordica was

completed in 1964 and taken into use in the five nordic countries at the same time. Sundvik performed also the routine examinations in forensic chemistry. After Sundvik's retirement the professorship was divided into two, one of pharmacology and the other of medical chemistry.

Y. E. Airila, M.D., was appointed the first professor of the now independent pharmacology in 1924. Since 1916 Airila had been assistant professor of experimental pharmacology. He received his scientific training in the department of physiology of the University of Helsinki headed by Robert Tigerstedt, the discoverer of renin (1), and had supplemented his training in Vienna at the pharmacological department of H. H. Meyer, and in Berlin under P. Rona and L. Michaelis. Hypnotics were one of Airila's research subjects and he published an extensive study of the pharmacology of bromisovalum (Bromural) and carbromal (Adalin) (2). Of his papers on the pharmacology of the blood circulation should be mentioned a comparative study of ether and chloroform (3) and the papers on the effects of pituitrin (4) and on anaphylactic shock (5). Airila, who died in 1949, was the pioneer of modern pharmacology in Finland.

Airila's successor was A. V. Vartiainen, M.D., who had been assistant professor of pharmacology since 1931 and professor of pharmacology since 1945. He had supplemented his pharmacological training in Vienna in the department of pharmacology of the University of Vienna (E. P. Pick) in 1925 and in London in 1930 and 1933–34 in the National Institute for Medical Research headed by Sir Henry Dale. In connection with the research then in progress on the chemical transmission of nerve impulses, W. Feldberg & A. Vartiainen (6) studied the responses of a perfused sympathetic ganglion to small and large doses of acetylcholine, nicotine, and arecoline and to preganglionic stimuli, and the part played by weak and strong concentrations of eserine in these responses. They also calculated that the quantity of acetylcholine appearing in the venous effluent from the ganglion, in response to a single maximal preganglionic volley, was of the order of 10^{-15} g per synapse, whether or not the cell was paralyzed by nicotine.

Upon the retirement of Vartiainen the chair of pharmacology passed in 1966 to M. K. Paasonen, M.D., previously assistant professor and at that time associate professor of pharmacology. His training in pharmacology he had augmented by carrying out research studies during a total of nearly four years at the department of pharmacology in the universities of Edinburgh (John Gaddum), Yale (Arnold D. Welch) and Harvard (Otto Krayer) and in Basel (A. Pletscher).

During the first decades the activity of the department of pharmacology at the University of Helsinki—then the only one in this country—was not very extensive. During and after World War II the greatly increasing need of medical doctors made it necessary to expand the faculty of medicine and its departments in Helsinki, to increase their staffs, and to create new medical faculties in the Universities of Turku and Oulu. The work of the department of pharmacology at the University of Helsinki was greatly re-

stricted not only by the inadequacy of the staff but also by a lack of space in the limited premises of an old and inefficient building. When the department was able, in 1961, to move into new premises designed specifically for its purposes and to obtain additional staff, its working facilities were greatly improved. In this connection it may be mentioned that some fifteen members of the department's staff have done or are at present doing research work, usually for one or two years, in well-known departments of pharmacology in other countries. The associate professor in the department of pharmacology is at the present time M. J. Mattila, M.D., former assistant professor of the department. In addition, the University of Helsinki now has eight assistant professors in pharmacology. Of the previous assistant professors may be mentioned J. G. Grönberg, M.D., (1922–29) who originally had a pharmacist's education. The major part of his research work was concerned with the biological standardization of certain drugs (e.g. digitalis leaves and oleoresin of filix mas). He is the author of the chapter "Die biologische Vorprüfung unbekannter Arzneimittel" in Abderhalden's "Handbuch der biologischen Arbeitsmethoden" (7).

As the first professor for the department of clinical pharmacology established in the faculty of medicine of the University of Helsinki P. J. Peltola, M.D. was appointed in 1971. Until then he had been assistant professor of internal medicine.

The department of pharmacy at the University of Helsinki also has a division of pharmacology and biological standardization of drugs. Since 1969 its chief has been M. M. Airaksinen, M.D., previously assistant professor of pharmacology in the medical faculty.

The University of Turku, founded in 1922, obtained its faculty of medicine in 1943. The first professor of pharmacology, appointed in 1952, was A. I. Pekkarinen, M.D., who had been assistant professor of medical chemistry at the University of Helsinki. He has supplemented his pharmacological education at the department of pharmacology of the University of Pennsylvania (Carl F. Schmidt and George B. Koelle) in 1952–53 and 1960–61. The associate professor's chair was occupied from 1963 to 1970 by V. J. Uuspää, M.D., previously assistant professor of pharmacology. Since 1970 the associate professor has been E. I. Iisalo, M.D.

When the University of Oulu was founded in 1958 a faculty of medicine was also included, and in 1965 N. T. Kärki, M.D., assistant professor of pharmacology at the University of Helsinki, was appointed its first professor of pharmacology. The pharmacological education he obtained in Finland was supplemented at the department of pharmacology in Oxford (J. H. Burn) in 1956–57 and at the department of chemical pharmacology of the National Institutes of Health, Bethesda, Md. (B. B. Brodie) in 1959–60.

Finland's fourth faculty of medicine and the chairs of pharmacology and clinical pharmacology will be located in the University of Kuopio, which is scheduled to open in 1972.

In the College of Veterinary Medicine, established in Helsinki in 1945,

H. W. Westermarck, V.M.D., became in 1954 its first professor of pharmacology and toxicology.

Up to the 1940s the pharmacologists in the nordic countries were members of the Scandinavian Physiological Society. As a result of the vigorous expansion of pharmacology a Scandinavian Pharmacological Society was formed in 1946 to act as the uniting organ of the pharmacological societies to be organized in the individual countries. The Finnish Pharmacological Society began its activity in 1948. The annual meetings of the Scandinavian Pharmacological Society are held alternately in each of the member countries, in some years jointly with the pharmacological society of some other European country. The Scandinavian Pharmacological Society has published since 1945 the journal Acta Pharmacologica et Toxicologica.

When the International Union of Pharmacology (IUPHAR) was incorporated in 1966 it was joined by the Finnish Pharmacological Society as well as by the societies in the other nordic countries. In 1967, at the invitation of the Pharmacological Society of Leningrad and its chairman Professor S. V. Anichkov, the Finnish Pharmacological Society took part in a joint scientific meeting in Leningrad. To reciprocate, a joint meeting of the two societies was held the following year in Helsinki. In 1970 a number of members of the Finnish Pharmacological Society attended by invitation the ceremonies and meeting in Tartu (Dorpat), Estonian S.S.R., commemorating the 150th anniversary of the birth of Rudolf Buchheim, professor of pharmacology of the University of Tartu and the founder of experimental pharmacology. Lectures have been given at meetings of the Finnish Pharmacological Society by some twenty prominent representatives of pharmacology in other countries, among whom I shall mention only the honorary members Otto Krayer and S. V. Anichkov.

Among the research programs carried out in the department of pharmacology of the University of Helsinki at the end of the 1940s and in the 1950s there is reason to mention especially those concerning biogenic amines, acetylcholine, cholinesterases, and nicotine, as well as anthelminthics and the physiology of tapeworm. Of the investigations in the first group, reference should be made to the study by Eckert, Paasonen & Vartiainen (8) demonstrating that the gnat (*Culex pipiens*) contains, especially in its head, significant amounts of histamine, which, after the insect has punctured the skin of human subjects, is greatly decreased. Unspää (9) showed that the sweat excreted on the skin in the Finnish steam bath (sauna) contains small amounts of biologically active histamine. Peltola (10) performed a quantitative study demonstrating that after oral administration of powdered thyroid gland the mouse became sensitized to the action of epinephrine, the lethal dose consequently being reduced. The new biological method of standardization of powdered thyroid gland based on this observation was compared by Peltola & Vartiainen (11) with methods previously in use. Paasonen (12) showed in an extensive study that some antihistaminics, such as

chlorpheniramine, increase the action of epinephrine in various tests. As a possible mechanism of this potentiation, an inhibition of the amine uptake has recently been suggested.

In 1954 Paasonen began his pioneer work on 5-hydroxytryptamine (5HT). At the early stages of the 5HT era he and Gaddum, employing molluscan hearts, developed sensitive methods for estimation of this amine (13). Then, with Vogt, he demonstrated the release of 5HT by reserpine and amphetamine from various parts of mammalian brain (14), and with Krayer he showed the release of catecholamines from dog and cat hearts by a number of rauwolfia alkaloids (15). An interesting observation was that some rauwolfia alkaloids caused noradrenaline depletion from the brain and typical sedative symptoms without a decrease in the brain 5HT (16).

An extensive series of Paasonen's publications deals with the blood platelets, which he has used as a model system in uptake, storage, and release studies of 5HT and other amines (for ref. see 17–19). After finding, with Kärki, that raunescine increases the plasma 5HT in rats in vivo, he demonstrated, with Pletscher, that 5HT is inactivated during its release from platelets in vitro. He then provided evidence that this inactivation was due to monoamine oxidase present in the mitochondria of platelets of some animals, including man. The metabolism of platelet 5HT to 5HIAA in the presence of red cells as a source of aldehyde dehydrogenase, or to 5-hydroxytryptophole without red cells, was shown by him and Airaksinen. Platelets also inactivate epinephrine but they do not contain catechol-O-methyltransferase. Platelets were found to accumulate chlorpromazine and other phenothiazine derivatives in vitro, and, on the other hand, these compounds released 5HT and some other constituents from the platelets. At the same time structural damage was caused, as Paasonen demonstrated by using electron microscopy in co-operation with Solatunturi, who has done most of the intracellular distribution studies on platelets. Ahtee has also been a coauthor in many of the platelet studies. She has studied extensively the metabolic and cellular changes in platelets and red cells caused by various phenothiazines and related agents. The structural alterations did not similarly change the abilities of these drugs to release 5HT from platelets, to inhibit the uptake of 5HT by platelets, or to cause hemolysis of red cells (20, 21). The hemolytic activity paralleled to some degree the tranquilizing effects. Recently Ahtee & Saarnivaara (22) found also in platelets a dissociation in the orders of potencies of several antidepressive and analgesic drugs to inhibit the uptake of 5HT and a norepinephrine analog, metaraminol. Tuomisto, in a series of publications, has described the uptake and storage of histamine by rabbit platelets. Most quantitative differences between this amine and 5HT could be explained by the difficulty of histamine to penetrate the platelet membrane. Histamine has also been used to show the point of action of some uptake inhibitors. Because it is not metabolized in platelets, histamine is accumulated in the cytoplasm if the inhibitor acts on the granule,

but not if it acts on the cellular membrane (23, 24). The latest review article by Paasonen and coworkers (19) emphasizes the usefulness of platelets as a model especially for the 5HT neurones.

The development of 5HT-ergic mechanisms in mammals has been widely studied since the late 1950s by Tissari. Her initial work covered the maturation of 5HT, 5HTP decarboxylase, and monoamine oxidase activities during ontogenesis in the guinea pig (25). The maturation of 5HT-ergic parameters of brain in different mammalian species has been further examined, including the development of 5HT and 5HIAA levels, turnover and intracellular storage of 5HT, and mechanisms eliminating 5HIAA. Also synaptosomes (isolated nerve endings) from developing brain have been employed to study the maturation of transport and storage functions of 5HT (26), a preparation in which the mechanisms of biogenic amine transport and storage have earlier been investigated (27).

In studying 5HT metabolism and the effect of the mode of administration upon it, Airaksinen (28) observed that glucuronidation is the main metabolic pathway when 5HT is administered per os, whereas oxidation to 5HIAA is more dominant after intravenous administration and still greater after subcutaneous administration. 5HT metabolism in experimental liver cirrhosis was studied by Pentikäinen and associates (29) and the effect of 5HT on morphine analgesia in the rabbit by Saarnivaara (30).

Biogenic amine contents in different organs of the hedgehog, during hibernation and in active state, were examined by Uuspää, who found, among other observations, that the epinephrine content of the adrenals increased and the norepinephrine content decreased considerably during hibernation, reverting to normal values when the animal awakened (31). The brain 5HT content of the hibernating hedgehog was markedly higher (32) and the norepinephrine content lower than in the waking animal (33).

The toxicity of 5HT is increased 200- to 600-fold in rats during moderate surgical anesthesia with ether, halothane, or pentobarbital (Tammisto, 34). Death is due to respiratory failure and preventable by intermittent positive pressure ventilation. Later Tammisto, together with Ylitalo (35), demonstrated a similar increase of toxicity during hypoxia, but not during hypoglycemia. The peripheral vascular- and respiration-impairing properties of 5HT do not seem to be responsible for this high toxicity.

The pharmacology, physiology, and histochemistry of the male external reproductive organs have been the object of considerable interest. The content of acetylcholine and biogenic amines in penile erectile tissue of the bull and the rabbit, and the activity of enzymes involved in the metabolism of these substances, has been studied by Penttilä (36, 37), and some of the factors influencing the tone of the bull retractor penis muscle have been analyzed by Klinge (38). It has been suggested that the relaxed state of the penis is maintained by continuous adrenergic activity and that penile erection occurs at interruption of this activity by cholinergic impulses from the pelvic nerves (38, 39).

Direct histochemical evidence for the sympathetic adrenergic innervation of human dental pulps has been obtained by Pohto & Antila (40). The vasoconstrictor component of the autonomic nervous system is present in the dental pulps of several mammalian species. Acetylcholinesterase-positive nerve fibers are found in the pulps of various animals and man, but the enzyme activity does not correspond to that of accepted cholinergic fibers in other tissues (41). It is possible that active dilator responses of pulpal blood vessels are not mediated by neural mechanisms. Some support for vascular non-mast cell histamine in pulps has been presented (42, 43). There may be many connections between the release of nervous transmitters or vasoactive substances and the sensory mechanisms of the teeth. Pohto has also demonstrated a strong β-adrenergic effect of sympathomimetics, norepinephrine included, on the rat submandibular salivary gland (44).

According to the studies of Vapaatalo (45) chlorpromazine releases catecholamines from the adrenal medulla in vitro and in vivo, chiefly from the so-called free pool. The release is dependent on Ca^{++} and K^{+} ions and it is inhibited by parasympatholytics, substances stabilizing the cell membrane, and guanethidine. Prolonged intraperitoneal administration of chlorpromazine to rats leads to development of megacolon (46).

Pinealectomy in rats produces hypertension, in the development of which the renin-angiotensin-aldosterone system plays a part (47). In nephrogenic hypertension there occurs a decrease in the norepinephrine content of the heart and arteries and a lowered blood pressure response to norepinephrine (48).

Torsti observed in the rabbit heart in experimental heart failure a decreased acetylcholine content and an increased nonspecific cholinesterase activity. Both were normalized by ouabain treatment (49). The epinephrine content of the insufficient rabbit heart was increased but the norepinephrine content was decreased (50). Hydrochlorothiazide raises and ethacrynic acid lowers the epinephrine level in the heart, and the former inhibits the depleting action of reserpine on amines in the heart (51).

Tyramine has generally been regarded as the cause of the sometimes fatal hypertensive response after ingestion of cheese and certain other foods during therapy with monoamine oxidase inhibitors (MAOI). Airaksinen and associates (52) demonstrated in rabbits that the effects of phenethylamine are, after the administration of pargyline, several times more potent than those of tyramine. Other amines in cheese may also have a role in the "cheese reactions", among them possibly histamine, which Uuspää & Torsti (53) found to be present in large amounts in various types of cheese. Increase in the toxicity of certain analgesics, especially of pethidine, during MAOI therapy was studied by Jounela (54).

The distribution and elimination of ^{3}H-noscapine in mice and rats has been studied by Idänpään-Heikkilä (55).

Mattila & A. Vartiainen (56) and Mattila (57) in studying the effects of certain pyrrolidine-*N* substituted derivatives of nornicotine, found the

methyl derivative (nicotine) to be the most effective; the ethyl and allyl derivatives were weaker, and acetylnornicotine caused muscarine-like effects. None of the derivatives studied antagonized the effects of nicotine. Continued studies by Mattila with certain other synthetic compounds related to nicotine demonstrated that these also could not inhibit the nicotine effect. In large doses nicotine produces in mice an analgesic-sedative effect comparable to that of chlorpromazine (58). Using a radioactive technique, Mansner (59) has investigated the dependence of nicotine effects on the central nervous system upon nicotine levels in the brain.

Infestation with *Diphyllobothrium latum* was very common in Finland up to the 1960s. In this country rich in lakes, sweet-water fish, often infested with live plerocercoids, is a general item of food; in particular raw fish that has been mildly salted for one or two days is considered a delicacy. Clinically it has been found that at least 2 percent of the tapeworm carriers have megaloblastic anemia, which requires no further treatment than an anthelmintic. The cause of tapeworm anemia was demonstrated by Nyberg (60) to be the absorption of large amounts of vitamin B_{12} by the parasite. *Diphyllobothrium latum* absorbs vitamin B_{12} 50 times more than *Taenia saginata,* which never causes anemia. Almost exclusively the oleoresins of *Dryopteris filix mas* and *Dryopteris austriaca* were used earlier for expulsion of tapeworms. Since especially the oleoresin of *Dryopteris austriaca* was the cause of numerous deaths in Finland in the 1940s, attempts have been made to clarify the causes of intoxication and to study the possibilities of finding less harmful anthelmintics. Among the investigators should be mentioned in particular Huhtala (61), who endeavored to find methods for the biological standardization of oleoresins of *Dryopteris,* and O. Vartiainen (62), who examined both pharmacologically and clinically the effectiveness of thymol and of the closely related p-cymene as an anthelmintic. Pylkkö (63) observed that *Diphyllobothrium latum* and *Taenia saginata* contain small amounts of acetylcholine and acetylcholinesterase as well as of a benzoylcholine-splitting enzyme. Eränkö and associates (64) have demonstrated histochemically and biochemically that the cholinesterase of cat tapeworm is distinct from mammalian acetylcholinesterase and nonspecific cholinesterase. Mattila & Takki (65) have shown that the nontoxic residue of *Dryopteris* oleoresins increases the toxicity of phloroglucinol derivatives of the fern by promoting their absorption.

Research work carried out in Helsinki in the field of clinical and anesthesiological pharmacology includes that of Turpeinen (66), who explored the part of premedication in ether anesthesia, Aro (67) who studied the pharmacokinetics and toxicity of procaine both in sheep and in man, and Heinonen (68, 69) who clarified changes produced in the metabolism and toxicity of lidocaine and mepivacaine by the action of certain drugs. Östling (70) has demonstrated that administration of k-strophanthin to patients with congestive cardiac failure by venous infusion during one or two hours will

give a more potent effect than the same dose administered intravenously. A similar observation was made in guinea pigs concerning the lethal dose (71).

Mattila and associates have studied the pharmacokinetics of antituberculosis drugs, particularly the factors influencing the metabolism of isoniazid, e.g. in psychiatric patients (72) and mongoloids (73). Among diabetics they found a larger number of rapid inactivators of isoniazid than among nondiabetics (74). In asthmatics they have performed clinical trials on the effectiveness of bronchodilator drugs and their combinations (75, 76). Mustala & Toivonen (77) have shown that the diabetogenic properties of furosemide are weaker than those of chlorothiazide. Studies especially on diuretics have been carried out by Peltola (78), who suggests that an important factor in the electrolyte disturbance caused by saluretics in congestive cardiac patients, as well as the failure of diuretic therapy, is hyperaldosteronism caused by saluretics.

A positive 1-nitroso-2-naphthol reaction misled in one case to a wrong carcinoid tumor diagnosis and even to an unnecessary operation. Mustala (79) found that the reaction was caused not by 5HIAA but by glyceryl-guaiacolate administered to the patient. A number of other commonly used drugs produced a similar reaction.

In his extensive research series Peltola (80) has shown that in certain endemic goiter areas in Finland the cause of goiter is not iodine deficiency alone, but that the goitrogen L-vinyl-2-thio-oxazolidone secreted into cow's milk from a cruciferous plant prevalent in pastures may contribute to it.

Suxamethonium, especially when given intermittently, can cause muscular pain. Airaksinen & Tammisto (81, 82) found increased activity of some muscular enzymes, e.g. creatine phosphokinase, in plasma after intermittent suxamethonium administration during halothane anesthesia. This and myoglobinuria found in some patients was considered by them to indicate a muscle injury. Reduction of the strength of suxamethonium-fasciculations by propanidid, thiopental, or d-tubocurarine impeded this injury (83). The large individual variations indicated the importance of constitutional factors, and the incidence of rhabdomyolysis after this form of anesthesia seemed to be higher in patients with strabismus than in other patients (84). They suggested that the above muscular injury and malignant hyperpyrexia during anesthesia might be related phenomena.

When studying the probable role of halothane in the "suxamethonium reaction" a considerable toxicity of trifluoroethanol, a metabolite of furoxene and halothane, was seen (85). The toxicity seemed to be due to the corresponding aldehyde, which blocked anaerobic glycolysis, the hexose monophosphate pathway, the activity of creatine phosphokinase, etc., probably through SH-inhibition (86–88). It was considered that the metabolites of halothane are responsible for the liver injury sometimes seen in patients after an anesthesia.

The research work of Pekkarinen and associates in the department of pharmacology of the University of Turku has been centered upon the sympathetic nervous system and catecholamines, as well as on corticotropin and adrenocortical hormones. Kärki (89) investigated the diurnal rhythm of urinary excretion of norepinephrine and epinephrine at different ages and during heavy muscular work. Castrén (90) studied the excretion of these substances in late normal and toxemic pregnancy, and Iisalo (91) studied the enzymatic inactivation of epinephrine and norepinephrine in various bovine and guinea pig tissues. Suramo and associates found the norepinephrine content of rabbit heart and spleen greatly decreased after experimental hemorrhagic shock (92) and the norepinephrine content of rat heart in experimental heart failure decreased to a third (93). Recently Manninen (94) showed the inhibitory action of a number of drugs on epinephrine excretion in rats during insulin shock. Pekkarinen and associates (95–97) have also investigated the excretion of vanilmandelic acid in many physiological and disease states, including physical and psychic stress. In 50 schizophrenic patients they observed that nialamide therapy during five weeks decreased the urinary excretion of vanilmandelic acid to ⅓–¼ of normal. Six months later it had not yet reverted to the normal level (98).

Iisalo and associates demonstrated that propranolol inhibited the increase of heart rate in the high temperature conditions of the Finnish sauna bath (99) and that ambulatory patients receiving alprenolon had significantly less need of nitroglycerin than those on placebo (100).

Aho and associates (101) produced experimental hypertension in rats by injections of epinephrine and the addition of 1–2 per cent of sodium chloride to the drinking water. Instead of epinephrine, Linna and associates (102) used norepinephrine. Hypertension was also produced with sodium chloride administration combined with cortisone or desoxycorticosterone treatment (Pekkarinen and associates, 103). Pekkarinen & Sundqvist (104) proved that reserpine or diuretics, e.g. hydrochlorothiazide or furosemide, added to the drinking water prevented development of hypertension. The experimental hypertension could also be reduced with other antihypertensive drugs. The most difficult to prevent was the rapid and intensive development of desoxycorticosterone-sodium chloride hypertension. It was inhibited effectively, however, by a combined saluretic α-sympatholytic therapy.

The secretory function of the adrenal cortex and its diurnal rhythm in man has been studied in, e.g., various diseases, surgical operations, normal and toxemic pregnancy after intake of different oral contraceptive drugs (105), and during antipsychotic and antidepressive therapy. This research includes also comparisons of the effect of different doses of various long-acting corticotropin products on the urinary excretion of corticosteroids (106). Pekkarinen (107) has also developed a guinea pig method for the biological standardization of natural corticotropins and synthetic corticotropin peptides.

The University of Oulu is located in one of the most northern inhabited areas in the world. Perhaps therefore much of the research done by Kärki and coworkers in the department of pharmacology has been focused upon the effects of environmental factors (108), pathological conditions, and drugs and other foreign substances on the human physiological functions and particularly on drug metabolism. Thus experiments with guinea pigs in vivo have shown that a low as well as an elevated environmental temperature retards pentobarbital elimination. The induction of drug-metabolizing enzymes is also significantly above normal in animals kept at a low temperature (109).

Acute intestinal obstruction was found to retard progressively the metabolism of three commonly used drugs in rats. However, complete restitution occurred within a few days after removal of the obstruction (110). Experimental damage to the rat liver by chemicals was found to affect readily the hydroxylation and demethylation as well as the amount of cytochrome P-450, whereas nitroreduction and glucuronidation are partly functional in patients with even severe cirrhosis of the liver. It was possible to improve the activity of metabolizing enzymes with phenemal induction at any stage of the experiment (111, 112). The results of animal experiments have generally led to the conclusion that there is very slight, if any, metabolism of foreign substances during fetal life. Pelkonen and associates have shown, however, that the drug metabolizing activity of the human liver in parti
early stage the liver of the human fetus contains cytochrome P-450, the presence of which is considered to be additional evidence that drug metabolism actually does occur (113, 114).

The research work performed in the department of pharmacology and toxicology of the College of Veterinary Medicine has to a great degree been on the role of deficiency of macro- and microminerals in the etiology of diseases of domestic animals, and on therapy for compensation of the deficiencies. Zinc deficiency has frequently been observed in cattle, as also has been a deficiency of selenium, which leads to sterility (115). The pharmacodynamic effect of digitalis administered orally to sheep has been shown to change according to the activity of the rumen microflora (116). The use of l-adamantanamine for the treatment of avian leukosis has also been investigated (117).

The pharmaceutical industry carries out pharmacological research work which is of interest to it, partly in its own research laboratories and partly in collaboration with the departments of pharmacology. Likewise it has had research work carried out in clinical pharmacology in cooperation with various clinics. Östling (118) made an extensive field study of nearly 2400 cases to clarify the anthelmintic effectiveness and side effects of desaspidin, a phloroglucinol derivative. Runeberg has demonstrated the uncoupling effect of some fern phloroglucinols on the oxidative phosphorylation (119).

The studies of Neuvonen and associates (120) have demonstrated that ferrous sulfate administered together with tetracyclines will seriously impair the absorption of these antibiotics in man. To avoid such an interaction a time interval of about 3 hours between ingestion of iron and tetracyclines is necessary (121). Alberty (122, 123) has explored the mechanisms of anaphylactic and allergic reactions in different organs, the role of released histamine in these mechanisms, and the inhibition of its effect. The work of Mäenpää, Raivio and associates (124, 125) has explained the dose-dependence and specificity of the D-fructose-induced depletion of liver adenine nucleotides. Konttinen (126) has performed extensive studies covering the field of fibrinolysis.

The physiological department of the alcohol research laboratories of the State alcohol monopoly (Oy Alko Ab) in Helsinki carries on research work concerning the biochemistry and pharmacology of alcohol. In this laboratory Eriksson has raised two strains of rats that differ greatly in their alcohol consumption. Ahtee has studied the metabolism of 5HT in the brain of these rats. The experiments indicate that there is a higher turnover of 5HT in the brain of ethanol selecting rats and that chronic ethanol drinking affects the metabolism of 5HT differently in the brain of water and ethanol selecting rats (127).

Research work in pharmacology or allied to pharmacology has been done also in some other departments. A subject of extensive study in the department of anatomy of the University of Helsinki (O. Eränkö) is the histochemistry of nervous tissues, catecholamines, and cholinesterases. A review of this subject by Eränkö (128) was published in the *Annual Review of Pharmacology* in 1967.

The research at the department of physiology of the University of Turku (K. Hartiala) has been devoted also to the role of the intestinal mucosa in drug metabolism. The glucuronide synthesis and its regulation have been given special attention. The rate of glucuronide synthesis is highest at the oral end of the small intestine, decreasing toward the aboral end and the large intestine (129, 130) parallel to the activity of the respective enzymes needed. Studies on the metabolism of steroid hormones have revealed very extensive biotransformation during the passage through the mucosa in different animals under in vivo and in vitro conditions (131). Another line of investigations relating to the mechanisms of chemical ulcerogens, with special reference to the effects on the gastric wall mucopolysaccharides, has been worked out (132).

At the department of medical chemistry of the University of Turku (E. Kulonen) it has been demonstrated that corticosteroid therapy changes the total distribution of hyaluronic acid molecules in synovial fluid so that the pathologically small hyaluronic acid molecule occurring in rheumatic disease disappears as the condition of the joint is normalized (133–135). In lathyrism (β-amino-propionitrile poisoning) the conversion of the soluble

form of collagen to the insoluble form has been found to be disturbed (136).

It is to be hoped that I have been able to give some kind of account of pharmacology in Finland. I regard it as an acknowledgement of our efforts that *Annual Review of Pharmacology* has been eager to publish information on the pharmacology of a relatively small country with a population somewhat less than five million. I also consider it an acknowledgement that IUPHAR has decided to hold the sixth international congress on pharmacology in 1975 in Helsinki.

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