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PHARMACOLOGY AT THE JAGIELLONIAN UNIVERSITY IN KRAKOW, SHORT REVIEW OF CONTRIBUTION TO GLOBAL SCIENCE AND CARDIOVASCULAR RESEARCH THROUGH 400 YEARS OF HISTORY

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Pharmacology at the Jagiellonian University was taught since the foundation of the University in 1364 under then used names of medical botany and pharmacognosy. The first in Poland Division of Pharmacology and Pharmacognosy was created in 1857. Modern era in the history of pharmacology in Krakow starts in 1929 when Prof. Janusz Supniewski became the Head of the Department. He was the relentless researcher whose scientific interests were as diverse as ranging from anticancer chemotherapeutics, antibiotics, and oral hypoglycemic drugs to lipid-lowering agents. Skills of organic chemistry synthesis were of paramount importance for the scientific achievements. Prof. Supniewski died in 1964, leaving the Department well equipped in instruments. He raised in his laboratory many eminent scientists who later beacame heads of pharmacology departments throughout Poland.
In 1964, the Head of the Department of Pharmacology became Prof. Ryszard Gryglewski. Under his leadership the Department focused scientific efforts on various aspects of cardiovascular pharmacology. Prof. Gryglewski established collaborations with many of the best pharmacology researchers in the world, including Sir John Vane, Nobel Prize laureate. Prof. Gryglewski's assistants had ample opportunity to train in these laboratories and to bring these skills back to Krakow. Prof. Gryglewski and his team published many articles in the most prestigious scientific journals. The most important themes included discovery of prostacyclin, role of nitric oxide and of free radicals for vascular biology. Since 2003, when Prof. Gryglewski retired, the Department of Pharmacology has been led by Prof. Ryszard Korbut.

Key words: *pharmacology, history, Jagiellonian University, cardiovascular and atherosclerosis research , scientific achievements*

IN THE MIDDLE AGES

At times when Jagiellonian University was founded (1364) pharmacology was not the self-standing academic discipline. Lectures on therapy were covered

under general term of *Materia Medica* and based on Greek and Arab classical texts. Knowledge of therapy was based on skills of preparing herbal extracts. Therefore, the first department that can be related to nowadays pharmacology was that of medical botanic, led by prof. Joannice and founded in 1602. Several textbooks on herbal drugs were issued soon after founding of the university by Marcin z Urzedowa, Schneeberger, Syreniusz, Stanko. Not surprisingly, at these times the boundaries between pharmacology and pharmacy were blurred and both these subjects were taught in one department.

In 1857, when pharmacy teaching was temporarily suspended, the Division of Pharmacology and Pharmacognosy in Poland was created for the first time at the Medical Faculty. It was led by prof. Skobel until his death in 1876. He was a very active researcher who published many articles and started publishing the journal *Przeglad Lekarski* (Medical Review). In 1881 **prof. Lazarski** became Head of the Department of Pharmacology and he remained at this position until his death in 1924. The level of teaching of pharmacology was very good under his professorship but research activities were relatively limited. After his death, pharmacology was taught temporarily by **prof. Lobaczewski**, who was also Head of the Department of Pharmacognosy at the Pharmacy Faculty. Prof. Lobaczewski died in 1928 and in 1929 Head of the Department of Pharmacology became prof. Janusz Supniewski.

HIGHEST PRIORITY TO SCIENCE

Prof. Supniewski started a modern era of pharmacology in Krakow. After the World War I he had an opportunity to study and work at laboratories in the United States. He brought to his work at the Jagiellonian University strong belief that he should emphasize and support research activity in the Department. Probably for the first time in the history of the Department, scientific achievements were given the highest priority. However, research interests in the Department were diverse. Before the World War II, scientists at the Department worked on the hemolytic properties of saponins (1), small intestine histaminase (2), and vitamin B1 (3). Professor Supniewski devoted most of his time to study cancerogenic substances (4) and antisterilising agents (5, 6). In the same area of interest of "antisterilising agents" several articles were published on the mechanisms of action of yohimbine (7) and stilbestrol derivatives (8, 9).

After the World War II, Department gradually regained the scientific potential. Professor Supniewski, as a scientific advisor of Pharmaceutical Company in Krakow, established collaboration with goals to improve the synthesis of chemical substances with practical applications for the therapy. The period when Prof. Supniewski was the Head of the Department of Pharmacology could be sum up as the time when skills of organic chemical synthesis were of paramount importance for the research activities in the Department.

The properties of sulfonamides (10) and cancer chemotherapeutics were among the first drugs studied. Studies on cancer chemotherapeutics were continued for the years to come (11). The new area of interest were antihistaminic drugs (12), in particular benadryl (13) and cardiologic agents. Effects of constant infusion of cardiac glycosides were studied by titration in pigeons (14).

Supniewski and Bany developed method of ephedrin synthesis (15) and described new directions in the drug synthesis, especially related to steroid drugs and polypeptides (16). Influence of nicotinic acid and isonicotinic acid on bile secretion was studied (17) and tuberculostatic properties of isonicotinic acid hydrazide were described (18). Around that time professor Supniewski developed interest in the properties of antibiotic drugs and described properties of erythromycin and tetracyclines (19, 20). He also studied drugs used to treat megaloblastic anemia (21). 1954 marked the interest in diabetes. **Supniewski** and **Chrusciel** wrote an article about the role of biguanid, oral hypoglycemic agents (22) and soon later another class of oral hypoglycemic agents - sulfonylureas was described by Gryglewski (23).

In mid-50s, the new area of research on the mechanism of action of antiatherogenic drugs was opened. Chrusciel and Chrusciel published the first in the series of articles on experimental atherogenesis (24). This work was continued for the years to come; in 1956 the method of inducing atherogenesis in pigeons was described in detail (25). In the meantime, professor Supniewski was still working on chemotherapeutic agents and he published an article on tuberculostatic properties of pyridine, hydrazides and thiosemicarbazone (26) and on antineoplastic chemotherapeutic agents (27). Ryszard Gryglewski continued his work on sulfonylurea hypoglycemic agents (28).

In the second half of 1950s the interest in pharmacology of central nervous system resulted in a series of articles on various aspects of therapy, e.g. anxiolytic drugs (29) and psychotomimetic drugs (30). Soon the interests in studying of pharmacotherapy of the central nervous system led to establishment of the Institute of Pharmacology of the Polish Academy of Sciences in Krakow. This institute, initially led by prof. Supniewski, specializes until today in pharmacology of the central nervous system.

In 1960 prof. Supniewski published a series of articles on biosynthesis of cholesterol (31-33). In these articles he suggested prophetically that inhibition of cholesterol biosynthesis pathway might be an important option to prevent and treat atherosclerosis. In the same year, in a surge of interest in biogenic amines, prof. Supniewski described synthesis and biological properties of melatonin (34).

In 1963, the article by Gryglewski on bioassay of factor I in the rat brain (35) heralded a paradigm shift in the way pharmacology was studied. Gradually, studying the mechanisms of action of the drugs *in vivo* or in isolated organs became more important than chemical synthesis of substances.

Professor Janusz Supniewski died in 1964. His legacy was the whole school of pharmacology teaching and research in Poland. Many of his former assistants

became heads of pharmacology departments throughout the country: e.g. prof. **Jozef Hano** in Wroclaw, prof. **Wojciech Dymek** at the Faculty of Pharmacy in Krakow, prof. Chrusciel in Zabrze, prof. **Andrzej Danysz** in Bialystok. **Prof. Wajdowa** became professor of Pharmacology in New York.

PHARMACOLOGY OF CIRCULATION

The Head of the Department of Pharmacology at the Jagiellonian University became prof. **Ryszard Gryglewski**. Under his leadership research interests became gradually focused on various aspects of cardiovascular pharmacology. One of them was fibrynolysis and among the first articles on this subject was the one on fibrynolitic activity of anti-inflammatory drugs and of bicarboxylic acids (36, 37). The principles of bioassay were implemented in various modifications, e.g. to study influence of peptides on isolated, perfused rabbit arteries (38). Other issues studied in the late 60-s in the Department were: micronecrosis of the myocardium (39), resistography of mesenteric arteries (40). Other bioassay models used in the Department at that time were e.g. nictitating membrane of the pithed cat (used to study the effects of phentolamine) (41) and isolated guinea-pig lung (used to study the effects of adrenergic drugs, (42). It is important to add that in 1969 the Study Guide for Students of Pharmacology was published (43).

The sixties marked an era of new international connections of the Department. **Dr. E. Mikos** became acquainted with **Dr. John Vane** from England, later known as Sir John Vane, the Nobel Prize Laureate for the year 1982. Being invited by John Vane to England she published in *Nature* (London) (44) the paper on the effect of gastrin on isolated smooth muscles. Later on, by common effort of the above team, including prof. **S. Konturek** and prof. **W. Pawlik**, the next paper came into being in Journal of Physiology (London). In 1970 Dr. John Vane's Polish Companionship was joined by Prof. Ryszard Grylewski and his young pharmacology team (45). In those days, from the very beginning, Sir John Vane collaborated with prof. Gryglewski's Group mainly on the aspects of cardiovascular pharmacology and this collaboration lasted for the next few decades, actually incessantly to Sir John dying day in 2004. Sir John Vane visited Poland for numerous Congresses and he also hosted several of Prof. Gryglewski's assistants (Ryszard Korbut, Aldona Dembinska-Kiec) in his laboratories.

In the meantime, in the Department effects of angiotensin II and methylxantines on blood vessels of anaesthetized cats were studied successfully (46) and several novel articles on the mechanisms of action of β-adrenergic receptor antagonists were published in cooperation with Department of Physiology (47, 48).

Finally, collaboration with Sir John Vane resulted in an article on *rabbit aorta contracting substance* and suggestion that this substance may be a prostaglandin precursor (49). In the following year the article by them and co-workers on the effects of anti-inflammatory drugs on prostaglandin biosynthesis was published

in *Nature* (London) (50) as well as several articles on the relationship between prostaglandins and *rabbit aorta contracting substance* (51, 52).

Further research on prostaglandin biosynthesis, being realized in friendly collaboration with prof. **Andrzej Szczeklik**, the Head Department of Internal Medicine in Medical Academy in Krakow, resulted in formulation of prostaglandin-hypothesis of asthma (53). The role of prostaglandins in aspirin-sensitive asthmatic patients was further studied by Szczeklik, Gryglewski, Czerniawska-Mysik (54).

1976 was marked by discovery of prostacyclin, initially known as prostaglandin X (55), and discovery of its vasoprotective, antithrombotic properties (56). At this time, interactions between the prostaglandin system and other endogeneously synthesized substances were studied parallel in London and in Krakow. Gryglewski's Group in Poland: **R. Korbut**, **A. Dembinska-Kiec**, **L. Grodzinska**, **J. Robak** and **B. Panczenko**, studied generation of prostagalandins and thromboxanes in the trachea in lung strips and interactions between prostaglandins and histamine and catecholamines (57, 58).

Potential clinical significance of reduced prostacyclin synthesis was studied in a rabbit model of atherosclerosis (59). For the first time influence of steroids on prostaglandin and thromboxane biosynthesis was found (60) and modifications in bioassay of biologically active substances in a cascade of isolated organs were performed by Ryszard Korbut (61). The contradictory role of thromboxane and prostacyclin in the circulation was described in an article by Gryglewski, Dembinska-Kiec and Korbut (62).

In 1978 prostacyclin research made the next step moving from the laboratory to the clinic. Just in Poland prostacyclin was administered for the first time into humans (63) and described in Nature (London) as a circulating hormone (64). Also interactions of prostacyclin with phosphodiesterase inhibitors were studied (65). In 1978, for the first time, the role of lipid peroxides as a link between the prostacyclin deficiency and atherosclerosis was suggested (66) and the role of prostaglandins in circulatory shock (67) and in endotoxin induced hyperpyrexia (68) were studied. Lipid peroxidation was also studied in the context of adjuvant-induced and carrageenin-induced inflammation (69).

Since prostacyclin showed such promise in the protection of blood vessels, it was very important to obtain stable analogs of this short-acting substance, e.g. carboprostacyclin (70). Simultaneously, substances able to release prostacyclin, both endogenously (angiotensin), (71) and exogenously (almitrine,) (72) were searched for. Also the role of LDL as a carrier of lipid peroxides and quencher of prostacyclin biosynthesis was under investigation (73).

In 1980 cytoprotective action of prostacyclin on gastric mucosa was described in collaboration with prof. **Stanislaw Konturek** and co-workers from the Department of Physiology (74). Prostacyclin was used in the therapy of peripheral arterial disease (75), in central retinal vein occlusion (76) and in stroke (77). The Division of Clinical Pharmacology that opened in the late 70-s gathered significant expertise in

pharmacological treatment of peripheral vascular disease. Drugs like bencyclan (78), beta-piridylcarbinol (79), pentoxyfilline (80), diprophyllin (81) were tested.

Since 1984 another branch of arachidonic acid metabolites - leukotrienes were studied (82). Influence of flavonoids with antiaggregatory effects on lipoxygenase and cyclooxygenase were studied by Swies et al. (83). Unsaturated fatty acids like dihomo-gamma-linolenic acid, potentially modulating platelet aggregation were tested in patients with atherosclerosis (84). Prostacyclin was used in a placebo-controlled trial in patients with gastric ulcer (85). Role of arachidonic acid metabolites in the mediation of pain was described by **Korbut** and **Radomski** (86).

In 1986 research interests shifted gradually from studying prostacyclin toward study of endothelium-derived relaxing factor (EDRF, later discovered to be identical with nitric oxide). Prostacyclin and EDRF were bioassayed concommittantly from porcine aortic endothelial cells (87). Mechanisms of action of EDRF inhibitors were searched by **Moncada** *et al*. (88) and the role of superoxide anion in breakdown of EDRF was discovered and published in a Nature article by Gryglewski, Palmer and Moncada (89).

Oxygen free radicals as quenchers of nitric oxide were studied by Gryglewski (90) and the impact of prostaglandins on function of polymorphonuclear leukocytes was tested in collaboration with the Department of Internal Medicine (91). Interactions between prostacyclin and nitric oxide in antiaggregatory properties of vascular endothelium were a recurrent theme in research for the next several years, e.g. (92). De Nucci G., Gryglewski R., Warner T. and Vane J. demonstrated that release of EDRF and prostacyclin from cultured endothelial cells is coupled (93). Robak and Gryglewski (94) demonstrated that flavonoids are scavengers of superoxide anions and this activity may explain their vasoprotective properties. Since similar, superoxide scavenging properties were demonstrated for calcium channel blockers (95), nitrendipine was used for the treatment of arteriosclerosis obliterans (96).

In the late 1980s, studies on the mechanisms of action of nitric oxide and prostacyclin were extended to cell cultures and isolated cells. Gryglewski, Trybulec, Radziszewski, Swierkosz, Dudek and Zembowicz studied production of EDRF in fresh and cultured endothelial cells (97). Isolated cells allowed studying intracellular signaling pathways. Gryglewski, Korbut, Kalecinska and Zembowicz studied the interaction between the stimulators of adenylate and guanylate cyclase (effectors of prostacyclin and nitric oxide stimulation, respectively) in human leukocytes, platelets and arteries (98). Gryglewski, Korbut, Trabka-Janik, Zembowicz and Trybulec studied interaction between NO donors and prostacyclin analog in these cells and additionally in arterial smooth muscle cells (99). Korbut, Trabka-Janik and Gryglewski demonstrated cytoprotection of polymorphonuclear leukocytes by stimulation of adenylate and guanylate cyclases (100). Nitric oxide released from neutrophils and mononuclear cells was found to inhibit platelet aggregation (101).

While interactions between nitric oxide and prostacyclin were at this time relatively well studied, demonstration of increased fibrinolytic potential of tissue plasminogen activator (t-PA) due to nitrovasodilators was a novel direction of research (102). In the early 1990s, effects of various NO-donors were studied *in vitro* and in the clinic. Dembinska-Kiec and colleagues studied the influence of SIN-1 on inflammatory cells (103). Grodzinska and colleagues used another NO-donor, molsidomine in patients with atherosclerosis obliterans of lower limbs (104). Bieron and colleagues studied synergism between prostacyclin and molsidomine in patients with peripheral arterial disease (105). In an article published in New England Journal of Medicine Korbut, Bieron and Gryglewski discussed effect of L-arginine, NO-precursor, on plasminogen-activator inhibitor (PAI-1) in hypertensive patients with hypercholesterolemia (106).

An interaction between prostanoids and other important substances secreted by endothelium - endothelins, was studied in isolated perfused rat kidney by Trybulec, Dudek and Gryglewski (107). A series of articles studied the role of endothelium in isolated perfused guinea pig hearts (Langendorff's method). Chlopicki and Gryglewski studied the role of endothelium-dependent and endothelium-independent vasodilators in the heart (108). Role of nitric oxide as a mediator of the phenomenon known as reactive hyperemia was described by Chlopicki and Gryglewski (109). Jakubowski *et al*. (110) and Chlopicki *et al*. (111) studied the pattern of purine release depending on the duration of heart ischemia and Lomnicka *et al*. studied the role of ischemic preconditioning on the preservation of function of endothelium and smooth muscle cells (112).

Mechanisms of action of hydroxy-arginine and hydroxy-guanidine, potential NO-carrier were studied in several articles by Zembowicz and colleagues (113-115). Collaboration with GEA pharmaceutical company resulted in the study on scavenging of superoxide anion by nitric oxide donors (116) and a study that described new NO-donors, mesoionic oxatriazole derivatives (117). Role of nitric oxide, derived from neutrophils on deformability of erythrocytes was studied by Korbut *et al*. (118). Dembinska-Kiec and colleagues studied the modifications exerted by iloprost and sodium nitroprusside on adhesion of platelets to neutrophils (119). An observation that hydrogen peroxide induces endothelium-dependent vasorelaxation led to a study on the role of nitric oxide in this process (120). Around that time it became evident that excessive production of nitric oxide may be harmful, e.g. in shock state, see (118, 121). This led to interest in inhibitors of nitric oxide synthase, e.g see an article on ebselen (122). Later on these studies were extended by Chlopicki *et al*. (123) on the role of N-iminoethyl-lysine and S-methylisothiourea as NOS inhibitors. To study the interactions between antithrombotic nitric oxide and prothrombotic thromboxane a new thromboxane synthase inhibitor with interesting properties - camonagrel was studied (124).

Paradoxical thrombogenesis after administration of thrombolytic drugs was summarized in articles by Gryglewski and colleagues (125-127). Changes in the structure of platelets induced by streptokinase were described by Mackiewicz and

colleagues (128). Interactions between the three major products of endothelial cells: nitric oxide, prostacyclin, and tPA were described by Gryglewski (129, 130) suggesting that in some situations they may act in alliance and sometimes they may be only neutral.

The second half of 1990s was marked by interest on the role of endothelium in endotoxic shock. Bartus, Chlopicki and Gryglewski described the effects of NO-deficiency in endotoxin-exposed rat lungs *ex vivo* (131) while Wolkow, Bartus and Gryglewski studied this effect and that of thromboxane inhibition *in vivo* (132). Starzyk, and Korbut described deformability of red blood cells in rat endotoxemia (133) and effects of NO and prostacyclin on the studied parameters (134). Gryglewski *et al*. described protective role of pulmonary nitric oxide in acute endotoxemia (135). Uracz *et al*. compared the role played by type II and type III nitric oxide synthase in the early protection against endotoxin-induced lung injury (136). Bochenski *et al*. studied the role of thromboxane and platelet activating factor in rat response to endotoxemia (137) and thienopyridines (138) were proved in a different model to be thrombolytic (139).

At Division of Clinical Pharmacology, under supervision of **prof. Kostka-Trabka**, drugs with potential to treat peripheral ischemic disease were tested, e.g. L-arginine (140), nicotiniane xanthinol (141), misoprostol (142) and bezafibrate (143).

BEGINNING OF NEW CENTURY

At the beginning of XXI century in the Department of Pharmacology cell culture and molecular biology techniques were strongly introduced to study the effects of various drugs on endothelial cells These techniques became invaluable in search of atypical properties of drugs with well established potency in a different area, e.g. antiplatelet action of losartan (144), modulation of ticlopidine induced thrombolysis by aspirin (145) and pleiotropic actions of nebivolol, ACE inhibitors, statins and bradykinin (146-148) as well as flavonoids (149) and interleukin 1-β (150). Interaction between two enzymes with critical importance for functioning of vascular endothelium: cyclooxygenase and hem-oxygenase was studied in collaboration with researchers from New York Medical College (151). In an attempt to study *in vitro* aspirin-induced asthma, an interaction between human platelets and eosinophils and epithelial cells and eosinophils were described (152, 153). These studies were later extended to probe the effects of aspirin on leukotriene production in a co-culture of eosinophils and epithelial cells (154).

In 2003 after retirement of prof. Gryglewski, Head of the Department of Pharmacology became **prof. Ryszard Korbut**. In addition to the topics already described above, an important aspect of research at the Department of Pharmacology becomes an analysis of the role of NAD(P)H oxidase and superoxide dysmutase in human vessels (155, 156). Molecular analyses in endotoxemia are continued by Gebska who studies rapid expression of nitric oxide synthase type II in the lung (157). Completely new area of research opens

Fig. 1. Professor Janusz Supniewski (1899-1964) - The Dean of Medical Faculty (1939-…1945-1948).

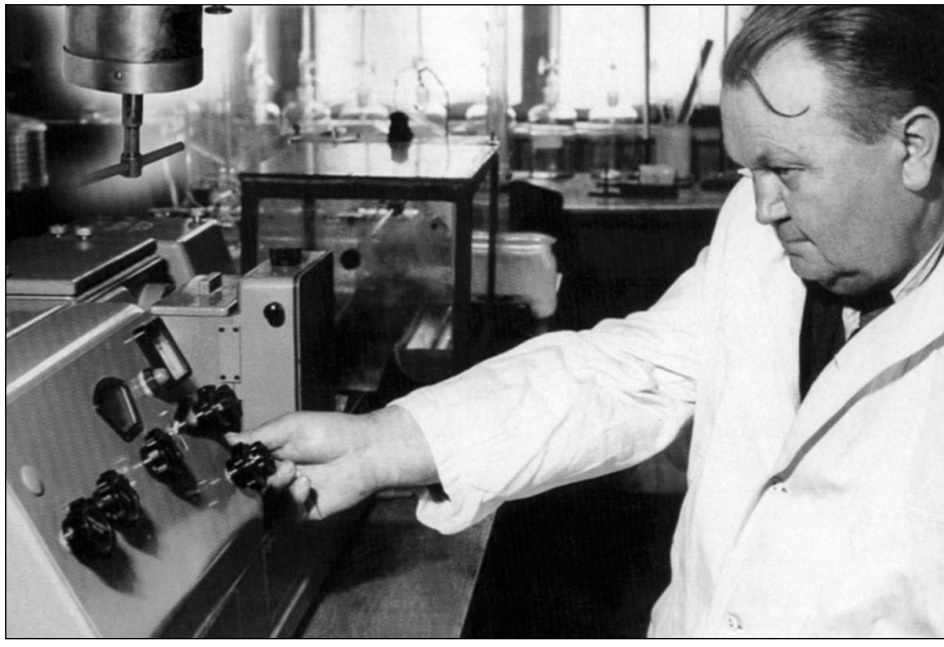

Fig. 2. Professor Janusz Supniewski at the time when "skills of organic chemical synthesis were of paramount importance for the research activities in the Department" of Pharmacology.

Fig. 3. Informal appointment with Sir John Vane (centre) in Rector's Office of Medical College of Jagiellonian University during Prof. Stanislaw Konturek's term of office 1996-1999. *From the left:* Prof. R. Korbut, Prof. J. Vetulani, Prof. A. Danysz, Prof. T. Chrusciel and his wife, Prof. S. Angielski, Sir John Vane (1927-2004)- Nobel Prize Winner, Prof. K. Ceremużyńska, Prof. R. Gryglewski, Prof. S. Konturek (The Rector), Prof. A. Szczeklik

Fig. 4. The Laboratory of Mass Spectrometry in Chair of Pharmacology (at the present).

in 2004, going into problems of etiology and prevention of atherosclerosis with the use of apoE / LDL receptor double knockout mice (158).

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