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PANCREAS; PANCREATITIS - POLISH ACCOMPLISHMENTS

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Polish accomplishments in clinical and experimental pancreatology concern acute (AP) and chronic (CP) pancreatitis. Special notice was drawn in Polish studies on hemostasis disorders in acute experimental pancreatitis (AEP), and resulting clinical implications (possibility of thrombotic-embolic complications leading to hemorrhagic defects associated with coagulation factors consumption). Studies on lysosomal hydrolases role in AEP pathogenesis were discussed. In those studies notice was drawn to initiating role of zymogen activation by lysosomal hydrolases, especially β -glucuronidase, with smaller activity of acid phosphatase and cathepsin in this process. It was stated, that also lysosomal enzymes are released from macrophages obtained from bronchoalveolar lavage fluid in AEP. It was revealed that prostacyclin (PGI_2) shows stabilizing effect on lysosomes in liver and kidneys in AEP. Platelets activating factor antagonist inhibits pulmonary lysosomal hydrolases activity in such conditions. Polish studies concerning reactive forms of oxygen role in AEP pathogenesis are one of the first in Europe. Oxidative-antioxidative balance was disturbed in acute pancreatitis course and associated multiorgan changes both under experimental conditions and in humans. Oxidative stress as an early prognostic symptom in AP in humans was also emphasized, showing correlation of oxidative stress indicators with phospholipase A serum activity and polymorphonuclear elastase in plasma of patients with different degree of this disease. In a range of clinical studies special attention should be given to studies concerning lipid disorders as an AP etiological factor in humans. Clear decrease in lipoprotein lipase activity in AP in humans was determined. Polish studies concerning importance of sphincterectomy in acute gallstone derivative pancreatitis (AGP) were presented. Polish researchers accomplishments in chronic alcoholic pancreatitis (CAP) etiopathogenesis were discussed.

Key words: *pancreas, history, polish pancreatology, pancreatitis*

Abbreviations used: acute pancreatitis - AP, acute experimental pancreatitis - AEP, chronic pancreatitis - CP, chronic alcoholic pancreatitis - CAP

INTRODUCTION

First mentions in Polish literature on pancreas and its diseases may be noted in the middle of XIXth century. M. Rozenzweig published in 1854 in few following issues of *Doctors Weekly* some lectures of prof. Oppolzer on "beside-gastric gland diseases" (1). Few years later J. Handelsman (2) in the same magazine in six following issues presented description of pancreatic disease "according to the Klessen's monograph from 1842". According to this, it is obvious, that the Polish doctors knowledge on pancreas diseases did not significantly differ from one presented at that time in other European centers. Until 1900 about 20 publications devoted to the different clinical aspects of pancreas diseases may be noted (3). Until beginning of the 30-ties of the XXth century only single studies in individual year's issues of the medical periodicals concerning pancreas physiology and pathology were published. In the first half of the XXth century internal medicine practitioners and surgeons were engaged in pancreas diseases treatment. It may be assumed, that knowledge on anatomy, physiology and clinics and pancreas disease treatment possibilities at that time corresponded with knowledge level in the major European centres.

Limited diagnostic abilities concerning only the pancreas and its diseases, mainly associated with organ structure and its anatomical location were one of the important causes of rare diagnosis of pancreas diseases in specialist departments. Beside known at that time pancreas diseases symptoms including pain, fatty diarrhea, glycemia disorders, prominences and abdominal cavity tonus and pressure painfulness in so called "Chauffard's - Rivet's pancreatic field and in Desjardins' pancreatic point" were also evaluated during physical examination. In 1935 Józef Waclaw Grott, professor at University of Łódź and after the second



Fig. 1. Józef W. Grott, professor and head of I Clinic of Internal Diseases at the Academy of Medicine in Łódź.

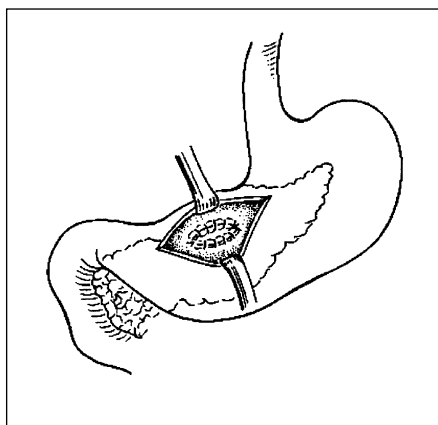


Fig. 2. The preparation of the pregastric fistula between pancreatic cyst and the stomach. (12).

world war of the Medical University of Łódź (4) described his own palpation method of so called pancreatic pressure painfulness (*Fig. 1*). Detailed technique of this examination consists in "placing the patient to lie supine with lower extremities flexed and with slightly elevated head on the pillows and superior part of trunk also elevated with little sack filled with sand of 6 cm thickness placed under lumbar part of spine or patients both hands placed in that area". Such patient setting according to J.W.Grott was supposed to decrease in abdominal cavity wall tonus and bring closer superior to anterior abdominal wall. "Slightly flexing fingers of the right hand and pressing on them fingers of the left hand did allow to penetrate right beside external margin of the left straight muscle of the abdomen deep into abdominal cavity and carefully without causing abdominal wall tension, one should bring closer right hand fingers to the spine and press pancreas body against spine". There is lack of studies at that time comparing diagnostic efficiency of this method, but with very rigorist complying with the author's hints it did create probably possibilities to evaluate some nodular changes in pancreas only using strictly palpation method. J.W.Grot expanded and compared different pancreas palpation examination methods in consecutive publications in the 50-ties of the last century (4).

In 1931 outstanding Polish surgeon, A. Jurasz professor of the University of Poznań described in 1958 an original technique of pancreatic cyst treatment by gastric anastomosis of the cyst in anterior gastric wall (5) (*Figs. 2 and 3*). W. Bross, professor of surgery at the Medical University of Wrocław described another original modification of the cystic-gastric anastomosis by anterior gastric wall, useful in such cases, when cyst convexes from minor gastric curvature into gastric cardia (6). A. Jurasz with F.Skubiszewski were authors of the pancreas diseases chapter in the surgery textbook published in 1938 (7).

At the beginning of the 50-ties of the last century, in a monumental at that time internal medicine textbook (8) Witold Orłowski, internal medicine doctor, University of Warsaw and Medical University of Warsaw professor, dedicated



Fig. 3. Antoni Jurasz, professor of surgery at the Medical University in Poznan

almost 80 pages to the pancreas diseases. It was the first extensive study describing the clinic and pancreas diseases treatment. Besides data on organ anatomy, some information on pancreas extrasecretory function, especially on carbohydrates, proteins and lipids digestion by diastase, lipase called steapsin and trypsin were discussed. All forms of proteins digestion properties were ascribed to trypsin. Acids in general, in that time for "the most powerful specific stimulus of the pancreas extrasecretory function were recognized". It was alleged, quoting Bayliss and Starling studies, that acid absorbed from the duodenum "is coating presented on its' mucous membrane prosecretin and processes it into secretin", which "circulating in the blood reaches pancreas secretory cells and stimulates them directly". However, in published almost ten years later reissue of the same part of the book we may find significantly extended information on pancreas exocrine secretion pathophysiology and clinical symptoms. W. Orłowski distinguished pancreozymin as enterohormone stimulating "thick pancreatic juice" secretion from cholecystokinin, which is supposed to cause only gall bladder constriction. In a clinical part inflammatory diseases (acute and chronic inflammations), pancreas carcinoma and pancreas cysts are being described. Auxiliary significance in acute pancreatitis diagnosis were ascribed to pancreatic amylase (diastasis) serum and urine activity, taking into consideration quick normalization of this enzyme in blood on a second day after the disease onset.

First monographic study of the pancreas diseases in Polish language was published in 1962 by T. Jankowski, professor of surgery at Medical University of Białystok (9). In this study knowledge on pancreas exocrine secretion pathophysiology was presented, secretin and pancreozymin effect and those enterohormones role in pancreas external secretion regulation were discussed.

Radiological pancreas examination methods, which might be used at this time were more extensively discussed (radiograms revealing calcifications in the pancreatic field, hypotonic duodenography, secretory cholangiography) and extrasecretory function examinations (serum enzyme concentration changes due to the influence of different secretory stimuli, e.g. prostaticin, secretin test and recently introduced secretin-pancreozymin test). So called indirect pancreatic extrasecretory function and indirect examination methods were also presented (faeces test after standard diets, lipids loss in faeces determination, ¹³¹J marked lipids absorption, starch and gelatin digestion activity). In a part devoted to clinic developmental pancreas defects and mucoviscidosis were quite extensively discussed. In a chapter discussing acute pancreatitis (AP) oedemal and hemorrhagic-necrotic forms were distinguished. In a large report author emphasized possibility of AP development in different individuals in distinct mechanisms ("aggression from pancreatic ducts, vascular aggression, toxic and metabolic aggression - including methanol, mechanical aggression, viral and bacterial aggression"), stating that often in one patient few mechanisms leading to AP occur. Worth noticing are detailed observations and descriptions of the AP clinical symptoms. Author also emphasizes, that five times increase in serum amylase activity supports AP diagnosis.

At the beginning of the 90-ties, so far the most extensive in Polish team, published interdisciplinary handbook on pancreatic diseases edited by J. Dzieniszewski, professor and head of the Gastroenterology and Metabolic Diseases Department of Food and Nutrition Institute in Warsaw and A. Gabryelewicz, professor of the Medical University of Białystok, head of the Gastroenterology Department in that university (10). Among team of individual chapters authors the most outstanding Polish experts on individual issues were accumulated. Modern review on issues associated with pancreatic extra- and secretory functions was prepared by S. Konturek, professor and head of the Clinical Physiology Department of Jagiellonian University College of Medicine, Cracow. Pancreatic diagnostic methods were presented by A. Gabryelewicz, extrasecretory pancreatic functional tests and ultrasound pancreas examination by A. Rakoczy, reader in the Food and Nutrition Institute in Warsaw, one of the pioneers of the clinical ultrasonography in Poland, radiological examinations and pancreas examination using magnetic resonance imaging by B. Pruszyński, professor of the Medical University of Warsaw, and radio-isotopic examinations in pancreatic diseases diagnostic by W. Graban and L. Królicki, professors of the Medical University of Warsaw. Chapter concerning fine-needle biopsy of the pancreas was prepared by J. Hasik, professor of the Medical University of Poznań, head of the Gastroenterology Department, and cytodiagnostic of the pancreatic diseases - S. Woyke, outstanding Polish cytologist, professor of the Pomeranian Medical University in Szczecin. Extensive discussion of the endoscopic retrograde cholangiopacreatography (ERCP) was done by A. Nowak, professor, head of the Gastroenterology Department of the Silesian Medical

University in Katowice. Clinical part was prepared by: A. Gabryelewicz (acute pancreatitis), J. Dzieniszewski (chronic pancreatitis), K. Bielecki (pancreatic cysts), S. Świtka (pancreas carcinoma), Z. Wójcik and B. Szczygieł (pancreatic trauma), J. Długosz (pancreatic endocrine tumors). Z. Puchalski, professor of the surgery in Medical Academy of Białystok, prepared surgical treatment of the pancreas diseases. J. Socha, professor in the Children's Health Center in Warsaw, prepared separate chapter concerning pancreas diseases in children.

Two monographs on pancreas surgery published in Polish should also be noted: Stanisław Ziarek (11), professor of the Silesian Medical University in Katowice and during last years more extensive review of the "Pancreas Surgery" issued by W. Kozuszek (12).

Acute Pancreatitis (AP)

Clinical and experimental studies concerning AP were conducted in Poland in few centers. But the most significant accomplishments in clinical and experimental studies concerning AP come from the Gastroenterology Department Medical University of Białystok directed by A. Gabryelewicz. Numerous papers on experimental pancreatitis have been published in center directed by S.J. Konturek of Cracow Medical College in collaboration with A. Dembiński and J. Jaworek describe the protective effects of growth factors such as EGF, calcitonin gene-related peptide (CGRP), nitric oxide, leptin and ghrelin on pancreatitis in rats. Extensive molecular biology has been carried out in these studies. These two centers published over 300 papers on that matter. At the beginning of the 60-ties of the last century Białystok team as the first one all over the world had a closer look on hemostasis disorders in acute experimental pancreatitis (AEP) (13) and on advantages from heparin use in such conditions (14). It was also shown, that positive influence of heparin depends at least partially on its' inhibiting impact on trypsinogen into trypsin conversion. Studies on hemostasis disorders in acute experimental pancreatitis (AEP) indicate two outwardly opposing phenomenon: both extensive coagulation and hemorrhagic defect caused by coagulation factors consumption may occur in this disease. In the initial phase of the AEP, disseminated intravascular coagulation (DIC) occurred in dogs, what in following stages leads to hemorrhagic defect caused by coagulation factors consumption (platelets, fibrinogen). In following years in this center studies on coagulation disorders in AEP in rats were conducted (15). Taking special notice on hemostasis disorders in AP, it has additional clinical and diagnostic aspect. Under conditions of ordinary hospital we can check platelets and fibrinogen level and also evaluate whether there are symptoms of their consumption or not. It allows to easier predicting further disadvantageous aftermaths and AP course. Confirmation of the coagulation disorders presence under experimental conditions and in humans is proving, that in AP there is significant antithrombin III decrease and in humans there are multi-organ

thrombotic complications observed (16). There was also observed, that in hemostasis disorders in AP in inflammatory changes pancreas tissue plasminogen activator presence and its' inhibitor (17) plays some role, what significantly extends this disease pathogenesis understanding.

Center in Białystok conducted wide-range studies on lysosomal hydrolases role in AEP pathogenesis. In that studies special caution was drawn to zymogen activation role initiating pancreatitis by lysosomal hydrolases, and especially β -glucuronidase, with smaller activity of acid phosphatase and cathepsin (18). Those finding continuation showed, that in AEP prostacyclin (PGI_2) has a stabilizing effect on liver and kidney lysosomes (19, 20). Further studies from this center showed those enzymes activation derived from macrophages obtained from bronchoalveolar lavage fluid show the lysosomal hydrolases role in acute experimental pancreatitis in rats (21). It was also shown, that platelets activating factor antagonist inhibits pulmonary lysosomal hydrolases activity in such conditions (22).

Studies showing homodynamic disorders in AEP with positive influence of proteases inhibitor - Gabexate Mesilate (FOY) were also conducted in Poland (23, 24).

Polish studies concerning oxygen reactive forms role in AEP etiopathogenesis are one of the first in Europe (25 - 27). Special attention was also drawn to oxidative-antioxidative balance role in AP course and accompanying multiorgan changes under experimental conditions and in humans (27). Oxidative stress role as an early prognostic symptom in AP in humans was emphasized, showing oxidative stress factors correlation with phospholipase A serum activity and polymorphonuclear elastase in plasma of patients with different stages of the disease (28). Studies on oxidative stress importance in AEP were also conducted in Gdańsk under direction of Z. Wajda, Medical University of Gdańsk surgery professor (29, 30). In this center studies on pancreatic microcirculation disorders in AEP were also conducted (31).

In the range of clinical studies notice should be taken on reports from Center in Białystok concerning multiorgan thrombotic complications in AP, confirming experimental studies (32), and lipids management disorders as the AP etiological factor in humans (33). There was also shown significant lipoprotein lipase activity decrease in AP in humans (34). Those last observations are of significant diagnostic importance and draw attention to need of lipid management testing in patients with AP, and also they may be of therapeutic and prophylactic significance through dietary recommendation modification or lipid management disorders pharmacological treatment.

B. Szczygieł, professor of surgery in Medical University of Warsaw team, leads studies concerning advantages associated with early dietary treatment introduction in severe AP (35).

Biliary sphincterectomy in acute gall pancreatitis (AGP) treatment is a significant accomplishment. In clinical studies on sphincterectomy effects in

AGP important contribution belongs to A. Nowak, professor of the Silesian Medical University in Katowice with his associates (36). As it stated, early performed endoscopic sphincterectomy brings advantages and significantly decreases mortality rate in all patients with AGP regardless of the disease stage.

In few centers in Poland studies on pancreas endocrine function behavior in patients after AP were conducted (37, 38).

In conservative and surgical AP treatment significant progress during last 20 years occurred, consisting in introduction of the intensive care rules, infections prophylaxis, dietary treatment, endoscopic sphincterectomy in AGP, more precise criteria concerning early and postpone indications for surgical intervention and progress in surgical techniques. All leading surgical centers in Poland currently do have experience in acute pancreatitis surgical treatment.

Chronic pancreatitis (CP)

In 1934 J. Węgieńko, internal medicine professor of the Warsaw University, in a chapter discussing "Dietary treatment of the pancreas diseases" (39) said, that pancreas diseases "are not seen very often". He did distinguish acute and chronic pancreatitis. In this outstanding Polish internal medicine specialist opinion, "acute pancreatitis usually proceeds very impetuously, it happens to be diagnosed with much difficulty and requires surgical treatment". Similarly, writing about CP diagnostics he said, that "this disease might be clinically symptomless and it may be accidentally diagnosed during autopsy". In 30-ties and 40-ties of the last century majority of publications concerning CP were published by J.W. Grott, mainly as a case reports. Original observation of J.W. Grott was dermal trophic changes description in CP (40). In 50-ties and 60-ties of the last century in Polish periodicals up to a dozen or so publications every year concerning casuistic case reports on pancreatic cysts, or reviews on chronic pancreatitis diagnosis and treatment were being published. Worth noting are first reports in 1964 in Polish literature about long-term results of CP treatment with surgical sphincterectomy (41).

In a first part of 70-ties retrograde cholangiopancreatography was introduced to pancreas diseases diagnostics in Poland and first Polish experience on that matter was published (42 - 44).

Polish researchers important accomplishment in chronic alcoholic pancreatitis (CAP) etiopathogenesis understanding were common studies conducted by Jan Dzieniszewski in prof. H. Sarles team in Marseilles on chronic ethanol use influence on pancreatic extrasecretory function (45, 46). In these studies it was proven, that single intravenous ethanol infusion in dogs without previous contact with alcohol (non alcoholic dogs) in the initial phase causes pancreatic secretory inhibition (up to 30%) stimulated by secretin and cholecystokinin and this phenomenon stops after about 120 minutes from ethanol administration stopping. However, single ethanol infusion in dogs receiving alcohol chronically for at least

6 weeks (alcohol feed dogs) causes different reaction. Instead of initial inhibition phase constant pancreatic juice secretion stimulation (increase in secreted water volume, increased protein and carbohydrates output), lasting for about 120 minutes from the beginning of ethanol intravenous infusion occurs. Due to chronic ethanol use pancreatic external secretion "retunation" occurs as a response to consecutive ethanol doses from inhibition to stimulation secretion of the pancreatic juice rich in enzymatic enzymes. It causes pancreatic juice density increase and enzymatic proteins precipitation, which form "protein plugs" in pancreatic juice, obliterating small pancreatic ductules. Consequence of excreting juice to obstructed pancreatic ductule is pancreatic follicles atrophy. These studies were the basis to put forward theory of small pancreatic ductules obstruction in CAP etiopathogenesis by Henri Sarles (47). These studies continuation in humans was nourishment role evaluation in CAP pathogenesis. It was observed, that large amount of lipids and proteins in diet of individuals chronically consuming alcohol may be additional factor increasing CP development risk (48). Studies on ethanol effect on pancreatic extrasecretory function were also conducted in the Center in Białystok (49). It was observed on isolated follicular rat cells, that phospholipase D may play an important role in pancreas damage due to alcohol use (49).

In a field of diagnostic, it is worth recognizing the efforts of amino acids serum level establishing use in pancreatic extrasecretory function evaluation. These studies were conducted in the Metabolic Diseases and Gastroenterology Department of the Food and Nourishment Institute in Warsaw (50). To assume that pancreatic secretion stimulation with secretin and CCK causes sudden increase in pancreatic enzymes synthesis, what should lead to decrease in serum amino acids concentrations essential to their production. High correlation between serum amino acids decrease value and pancreatic extrasecretory function efficiency determined using NBT-PABA test was stated. Similar studies were also conducted in the Centers in Białystok and Cracow (51).

Polish researchers also took part in CP ultrasound diagnostics basis development (52, 53).

Great progress which currently happened in CP diagnostics and treatment concerns especially introducing imaging procedures to the diagnostics (ultrasound, computer tomography, magnetic resonance angiography, ERCP), and surgical endoscopic methods to therapy and improving surgical treatment techniques. The vast majority of Polish clinical centers have abilities to lead complete diagnostics and endoscopic and surgical treatment of CP.

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Received: November 15, 2003

Accepted: December 15, 2003

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