

ACHIEVEMENTS OF THE MEDICAL FACULTY — VARNA IN THE FIELD OF MICROBIOLOGY, INFECTIOUS DISEASES AND EPIDEMIOLOGY

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An important part of the activity of the Chair of Microbiology and Virology over the past fifteen years since the foundation of the Medical Faculty — Varna, has been to raise the level of scientific — research work on the basis of establishing close relations between research studies and medical practice needs. The strive for integration with other chairs (infectious diseases, hygiene and occupational diseases, pediatrics, psychiatry, internal diseases, eye and ear diseases, pharmacology, pathology, HEI — Varna and other institutes), and the focusing of attention on research projects relating to the infectious pathology of the district and region, infectious diseases, epidemiologic problems of the Devnja industrial complex, and on a number of fundamental studies at molecular and submolecular level, explaining the regularities of virus-cell interaction, characterize the overall activities of the Chair.

The listed below contributions to the theory and practice of medicine are considered as more significant on a nationwide scale:

1. Having in mind the responsible and urgent task undertaken by Bulgarian medical research institutes and personnel, emanating from the decisions of the X and XI Communist Party congresses, as well as from the decisions, research concepts and plans of the Ministry of Public Health and Medical Academy, we directed the efforts of the research teams of the Chair and HEI—Varna, in collaboration with epidemiologists, infectionists, pediatricists and others, towards comprehensive, consistent research and practical investigation of the problems of influenza and other acute respiratory diseases with a view to establish and determine with precision virological, epidemiologic and clinical regularities, conditioning the widespreading of such diseases.

The first main problem along this line was the consistent and thorough study of influenza outbreaks in Varna and district, covering the period 1962—1975. The biological and antigenic properties of more than 600 influenza type A viruses isolated were investigated.

Researches conducted into some biological properties of viruses, isolated in the Varna district during 1962—1975, and more particularly, their antigenic structure warrant the assumption about the periodic variability of this important biological property under natural conditions, and the differentiation of influenza virus variants in the district A/69, AHKJ/68, A/42/72, ARC/76 etc. The consecutive study of hemagglutination, inhibitor-sensitive, hemadsorption and alkylating properties of the isolated viruses, their pathogenic, toxic, infectious and other qualities thoroughly elucidate the biological properties of influenza viruses, causing the big epidemic bursts in the district and throughout the country during the period 1962 through 1975, and the regularities deduced therefrom.

Virological, immunofluorescent and pathomorphological researches, conducted on cadaveric material from 186 death children up to 3 years of age, as well as on test animals, have yielded data on the toxicity of viruses manifested with massive diapedetic hemorrhages, hemodynamic disturbances in the pulmonary parenchyma, necrotic desquamative changes in the epithelium of trachea and bronchi. Most likely, it is a matter of toxic strains (viruses) conditioning the different clinical picture of influenza in the persons affected, the slow and prolonged course of epidemics, and the comparatively high lethality rate and incidence of complications (32).

The results of original cytologic, cytomorphologic and other studies on cell culture from adenoma of the thyroid of people infected with influenza viruses A/72, A/74 and PG₁ (Sendai) have shown that this particular cell culture, relatively lacking contaminant latent viruses might be successfully employed in experimental and virological laboratory practice (14, 15).

In the course of cytologic, cytomorphologic and cytochemical fluorescent-microscopic researches into cell cultures HEK and CEK, infected with influenza viruses A/74, AVn 75/ and ARC/73, A/69, it was found that these cells are a good model for the study of some biological properties of the viruses in question, and may be employed in experimental practice. During differential-densitometric researches into viral reproduction of HEK cell cultures, infected with virus AVn/75, definite changes in the structure of nucleus and increased nuclear area were established. Thus the recommendation of the extensive use of viral cytodiagnostics through quantitative cytologic techniques was justified (46).

The study of enzyme activity of CEK and HEK cell cultures, infected with influenza type A viruses, enabled us to establish early enzymologic changes and regularities of viral reproduction which, in constellation with cytologic, cytochemical, immunofluorescent and other techniques, might be used in virological diagnostics and experimental practice (35, 36).

Epidemiologic, clinical and serological researches into individuals immunized with Bulgarian and Soviet vaccine during the epidemic influenza outbreaks in this country in 1972 and 1974/75, enabled us to determine an index of epidemiologic activity, as well as to recommend an adequate scheme of immunization. Thus, we made our contribution to the difficult and still unsolved issue concerning prophylaxis against influenza with live influenza vaccine. Studies on the dynamics of serum immunoglobulins, following influenza immunization, are worth noting (13, 24, 28).

The presence of group correlation between influenza morbidity rate and antibody level among the population at the onset of the epidemic outbreak, has posed the question about the possibility to use immunologic indicators for the aims of epidemiologic prognostication. The results of our systematic researches into collective immunity to influenza and other respiratory viral affections gave us sufficient reason to conclude that immunological prognosis of influenza, influenza-like diseases and asymptomatic infections is by all means possible.

The results of our study on the evolutive mechanisms of influenza type A virus has an essential practical bearing on the further improvement of active immunization methods. Exhaustive information on the biological properties of the influenza causing agent, consecutive changes in its serologic variants, choice of the chief antigenic variants liable to inclusion in the com-

position of the live and inactive influenza vaccine have all contributed greatly to the availability of preparations endowed with a high degree specificity and immunogeneity.

Over the period 1969 to 1975, making use of the well equipped laboratory base of the Medical Faculty — Varna, G. Kaprelian alone, and in collaboration with a numerous team of virologists, epidemiologists, therapists, pediatricists, infectionists, pathomorphologists and HEI—Varna collaborators, conducted large scale, complex virological, serological, immunofluorescent, epidemiologic, clinical, pathomorphologic and other researches into adenoviruses, respiratory — syncytial, parainfluenza and intestinal viral infections, and infections caused by *Mycoplasma pneumoniae*, thereby succeeding in decoding the etiology of acute respiratory diseases during the various years, seasons and by regions. These studies are most valuable for the practice, and through them the Chair was recognized as playing a guiding role in the study of acute respiratory diseases nationwide.

Researches in the antigenic and biological properties of influenza type A viruses, isolated in the Varna district over the period 1962—1976, and in the etiology of acute respiratory diseases constitute a serious scientific contribution to the study of influenza and ARD not only in Bulgaria, but also on a world-wide scale (11, 12, 27, 29, 30, 34).

Etiological decoding of viral and bacterial pneumoniae is a scientific achievement of utmost interest. The attempts made at their clinical description in compliance with the viral etiology are likewise worthy of special notice. More than 1000 patients hospitalized in the clinic of the Faculty, and in the inpatient units of city hospitals were examined. A variety of virologic, serologic, immunofluorescent, clinical and paraclinical, and pathomorphological methods were employed. The role and proportion of various infectious agents are estimated, namely: influenza and parainfluenza viruses, adenoviruses, RS-virus, *Mycoplasma pneumoniae*, rickettsiae, chlamydiae, pathogenic bacteria etc (17, 18, 19, 22). The studies covered newborns, suckling age and early infancy, and grown-ups — workers from various industrial enterprises. It was established that during influenza epidemic, a considerable percentage of bronchopneumoniae were not related etiologically to influenza, but rather to other infectious agents. The study of dead children and adults has great practical implications (14, 16, 38, 47).

Similarly important for practice are the researches made by the Chair, jointly with a team under the guidance of G. Mitev, on collective immunity against poliomyelitis in Bulgaria (31, 43, 44).

Of no less interest are the data concerning the serological study on the widespreading of some rickettsiosis and ornithosis forms among animals and birds in this country. A numerous team of epidemiologists, virologists and microbiologists have carried on serological investigations on the widespreading of ornithosis among birds and human beings in Bulgaria, covering the period 1963—1966. A total of 4 286 patients with ARD and obscure febrility were investigated, and in 11.5 per cent of them antibodies against the ornithosis causing agent were proved. In health officers engaged in poultry farms this percentage amounted to 23.1, in wood pigeons — 50.5, and in some domestic animals such as hens, ducks and geese — from 15.1 to 60.3 per cent.

Our many years clinical, microbiological and immunological researches in schizophrenia and protracted schizophrenoid psychoses, under the guidance

of prof. L. Ivanova, have an essential theoretical and practical bearing. Valuable results with merits of original contributions were obtained, characterizing the etiology and clinical picture of these conditions.

Studies on the etiology, clinical course and treatment of intestinal infections with diarrhea syndrome, performed under the guidance of V. Zozikov and G. Kaprelian and co-workers, have been estimated very highly — it is a matter of a research project realized through complex, multilateral clinical, paraclinical and microbiological methods.

Researches and scientific publications dealing with the diagnosis and treatment of nongonococcal urethritis, etiology and clinical picture of acute chronic tonsillitis, etiology of viral conjunctivitis (20, 26, 37), and aphthous stomatitis (21) are likewise significant from scientific and practical viewpoint.

Particularly valuable and contributive in the field of bacterial infections are the many years investigations performed by R. Marinova on the genetic transfer of bacteria — the mechanisms of transfer and diffusion of multiple drug resistance, eventually of other plasmids too, between different bacterial groups. The studies were carried on at molecular and submolecular level, and the results obtained are estimated as most valuable in terms of clarifying the mechanism of infectious plasmids' transfer (sex factors and participation of superficial bacterial structures in the process — 33).

Also relevant for the practice are the researches performed in the Chair under the guidance of prof. Zheliazkov, jointly with clinicists, pharmacologists, etc, into the antibacterial effect of a number of Bulgarian and foreign antibiotics — gentamycin, gramicidin, piopen, oleandomycin, tetraoleane and the like.

The bacteriologic and immunologic study of streptococcus infections and various forms of rheumatic diseases, carried out by A. Panayotova over a period of six years, is particularly contributive. Investigation of the level of antistreptolysin titer in the hemagglutination reaction of Waler-Rose, determination of sialic acid serum content and serum proteins in patients with rheumatism, in persons susceptible to rheumatic affection, and in chronic tonsillitis patients have elucidated a number of regularities having an essential practical bearing on the clinical course, prophylaxis and treatment of this mass affection among children and adults. Similarly important for medical theory and practice are the consistent and comprehensive researches into listeriosis among men and some animals (L. Nicheva). Bacteriologic and serologic studies for listeriosis are performed among pregnant women with a past history of spontaneous abortions, premature births, stillbirths, as well as in patients with diagnosis epidemic meningitis, infectious mononucleosis, neurotic and mental patients etc.

The second main topic, included in the research plan of the Chair already for more than ten years, is entitled "Biochemical, cytochemical and biophysical study of virus reproduction". Investigated is the reproduction of influenza, parainfluenza, adenoviral, ECHO, coxsackie and other viruses over different cell culture models, from the human thyroid, HEK, ChEK, HeLa, Destr. 6 etc, and a number of regularities are established through cytological, cytochemical, immunofluorescent and other methods, as well as changes in the infected cell cultures with a view to establish early virological diagnosis and relationships, created upon virus reproduction within contaminated cells. Studies are carried out for total microscopic demonstration of the lysozyme complex in

tissue cultures HEK, infected with various types ECHO, adeno- and parainfluenza viruses. The study of the topography of lysozymes is essential for early and prompt demonstration of the cytopathic effect with a view to early diagnosis of viral affections. Of no less interest are the data concerning quantitatively characterized changes in various cultivated cellular systems under the influence of different types of viral agents, investigated at the level of cell genetic regulatory apparatus and enzyme biosynthesis.

The results of our researches have shown that the dynamics of the complex changes in infected cells' nuclei, the formation of intranuclear eosinophils and subsequent basophilic inclusions are dependent on the stage of reproduction, and on the amount of accumulated virus, particularly clearcut in the immunofluorescent analysis of viral reproduction. The approach described allowed us to follow the localization and dynamics of virus biosynthesis, the probable integration of the genomes of either of the systems, and the creation of a virus-cell biological complex unity (2, 23, 45).

The problems studied at the Chair, in collaboration with research teams from the Medical Faculty — Varna, and other research institutes throughout the country, attest the high theoretical-experimental level of most of the studies, the actuality of the research projects, and the extensive utilization of updated cytologic, cytochemical, biochemical and other methods in the virological and bacteriologic research. In compliance with the decisions reached at the XI Communist Party Congress, and with the Ministry of Public Health and Medical Academy programs, in the next stage, the efforts of the Chair and its research staff, in collaboration with research workers and practitioners from other chairs and health units, especially HEI—Varna, the Institute of Infectious and Parasitic Diseases and the central institutes in Sofia, ought to be directed towards a further development of fundamental and scientific-practical studies at molecular biology level and genetics with a view to attain important theoretical aims, and meet completely the needs of practical health in the strive for reducing and eliminating infectious morbidity throughout the country.

The Chair of Infectious Diseases and Epidemiology, proceeding from the practical demands of public health throughout the full period of its existence has endeavoured to adopt and develop furthermore the optimal achievements in the struggle against infectious disease. Over the period indicated above, the research activity of the Chair covers the field of the most frequently occurring and important bacterial and viral infections: bacillary dysentery, colienteritis, salmonellosis, alimentary toxic infections, viral hepatitis etc. Clinical manifestations as well as laboratory tests in the listed conditions have been thoroughly studied with a view to secure quick and exact diagnosis, differential diagnosis, prophylaxis etc (7, 8).

It should be emphasized that a very broad range of research studies have been dedicated to viral hepatitis mainly. Its early manifestations, rarely met with clinical forms (as cholangiolitic hepatitis), heavy clinical forms (dystrophic with hepatic coma), and the like are studied and described in detail. An original contribution to the problem is the study and catamnestic follow up of viral hepatitis among medical personnel groups. Since it is a matter of a condition met with much more frequently among medical workers, the special interest in the issue is fully justified. Viral hepatitis manifestations in suckling age associated with other somatic diseases (the so-called "mixed forms") are also

investigated. Problems relating to the comparative epidemiology of hepatitis virus A and hepatitis virus B are also discussed, as well as the characteristic features of hepatitis affecting holiday makers along the Black-sea coast, and the treatment of patients with hepatitis in the past history using some of the seaside factors (thalassotherapy and fangothrapy) (5, 6, 25, 39, 40, 50).

Over the past few years, the issues concerning changes in the humoral immunity of viral hepatitis and some other intestinal infections have been clarified through serum immunoglobulins' determination. The immune status established among healthy adults and children, assayed in a great number of individuals from Varna and Varna district, allows its implementation in the routine, everyday practice of other clinical disciplines (internal, children's and other diseases) for diagnosing and prophylaxis of immune, allergic, hepatic and other conditions (42, 48).

Nowadays, a possibility exists of accelerating the trend for viral hepatitis morbidity reduction through mass gamma-globulin prophylaxis and mandatory donor blood control by means of performing investigations for superficial antigen of the hepatitis B virus (Australia antigen). Since 1971, the clinic of infectious diseases in Varna, for the first time after the Chair of Forensic Medicine, has adopted the practice of performing systematic investigations of blood from viral hepatitis patients for this particular antigen (41, 49). To secure maximum efficiency of treatment the infectious clinic in Varna, since nearly ten years, applies a rational and prompt method for treating dysentery and intestinal infections. While in the other health units throughout the country dysentery patients are hospitalized and treated for 12—15 days in the average, in Varna the patients are discharged within 5—7 days, following urgent, combined antibiotic treatment for two days. Actually, this effective method of treatment is adopted and already applied in some of the neighbouring district units. The introduction of intracutaneous allergic test using the preparation dysenterin (for the first time in this country on the basis of Soviet experience) is a contribution to the diagnosis of bacillary dysentery. In the clinic of infectious diseases a systematic control of unwarranted, excessive medication administration is carried out already for many years, since not infrequently, it leads to hazardous polypragmasia which in turn reduces, and occasionally deteriorates the effect of the therapy in course. An important step ahead along this line is the creation of a unified system of examination and treatment of the basic infectious diseases in the clinic against the background of personal experience and existing methodological instructions by the Ministry of Public Health (3, 9).

Also a contribution has been made to the thorough study of the effect of some new and valuable therapeutical preparations, offered by the national pharmaceutical industry, such as gentamycin and carbenicillin.

Worthy of notice are likewise the joint research projects with the Chair of Microbiology and Virology on the diagnosis of influenza and epidemic parotitis, and on the modern clinico-laboratory picture of infectious mononucleosis and typho-paratyphoid diseases. The publications of the Chair on the mentioned issues are accepted with interest from specialists, and serve directly the diagnostic-therapeutical practice. Casuistic reports such as the description of a case with Zieve disease, allergic vasculitis with autoamputation of a lower limb etc. are also noteworthy.

The study of hepatic lesions in some viroses, epidemic parotitis in particular, are also considered as important contributions.

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ДОСТИЖЕНИЯ МЕДИЦИНСКОГО ФАКУЛЬТЕТА — ВАРНА В ОБЛАСТИ МИКРОБИОЛОГИИ, ВИРУСОЛОГИИ, ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ И ЭПИДЕМИОЛОГИИ

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РЕЗЮМЕ

Авторы прослеживают успехи обеих кафедр Медицинского факультета — Варна в области учебно-воспитательной, научно-исследовательской и лечебно-диагностической их деятельности за период 1961—1976 г.

Огромны усилия коллективов соответствующих кафедр в целях осовре- менения учебного процесса со студентами и специализантами, создания твор- ческих личностей и хороших медицинских кадров. Приводятся убедитель- ные данные о деятельности обеих кафедр в течение этих 15 лет по вопросам лечебно-диагностической и практической деятельности для преуспевания здравоохранения в Варненском округе и соседних округах. Подчеркиваются огромные успехи научно-преподавательских и других кадров при разра- ботке ряда проблем научно-исследовательской работы, в связи с эпидемио- логической, серологической, вирусологической, бактериологической и кли- нической расшифровкой ряда инфекционных болезней. Прослеживаются ре- зультаты ряда экспериментальных исследований, проведенных на молеку- лярном и субмолекулярном уровне, в целях выяснения некоторых законо- мерностей при репродукции вирусов на различных моделях.