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Cronicle

Former Institution with Traditions Who's Past Lives on in the Future

History of the Pharmacological Section at the Chemical Pharmaceutical Research Insitute (NIHFI)

The 1950s and 1960s saw a rapid growth of the chemical and pharmaceutical industry in Bulgaria. The Galenus factory in Sofia grew into a Chemical and pharmaceutical plant, with number of enterprises were established across the country: the Antibiotics plant in Razgrad, the Plant for veterinary medicinal preparations in Peshtera, cosmetics manufacturing plants in Sofia and Plovdiv, a plant in Troyan, a Chemical and pharmaceutical plant in Dupnitsa, etc. The manufacture of pharmaceuticals required full chemical, analytical and toxicological control evaluation. As laboratories of synthesis and phytochemistry developed new, original medicinal products were created, which prompted the need for speedy introduction of toxicological, pharmacological and clinical-pharmacological analysis. The centre of investigations became the Scientific Chemical and Pharmaceutical Research Institute (NIHFI), established simultaneously with the progression of this industry. The institute developed, keeping abreast with similar institutes in the countries of Central and Eastern Europe. Along with the laboratories of synthesis, biosynthesis, phytochemistry, analytical testing, organ preparations, a pharmacological unit was formed at the institute, which was later to become the Medico-biological devision. The initially created pharmacological unit of the early 1950s was headed by Al. Minchev, a graduate from the Department of Pharmacology at the Medical Academy, and by L. Daleva until it became Medico-biological devision, which was afterwards headed by M. Nikolova for 25 years (L. Daleva was Scientific Director), and in the last seven years by N. Tyutyulkova.

The purpose of the Medico-biological devision at NIHFI was to organize specialise laboratories and specialists for them for the purpose of conducting full screening and extensive pharmacological and toxicological characterization of synthesized chemical compounds and products derived from natural substances. The result of these efforts was the largest Medico-biological devision formed in Bulgaria in the 1970s and 1980s, with a staff of about 120, encompassing laboratories of pharmacology, toxicology, clinical pharmacology, pharmacokinetics, pharmacobiochemistry with an isotope laboratory, and laboratory of chemotherapy. Specialised laboratories were developed for studying the effects on the central nervous system (CNS) using EEG; the cardiovascular system; the vegetative nervous system; single organs; anti-inflammatory effect; cosmetics; dental products and toothpastes; X-ray laboratory; pharmacokinetic laboratory, pharmacobiochemical laboratory and laboratory of chemotherapy with microbiology and mycology laboratories; toxicology and pathomorphology laboratory. The availability of up-to-date equipment, including isotope and X-ray laboratories, and the skilled specialists opened the way to a wide range of modern evaluation methods of medicinal products at the large complex Medico-biological devision, at the time unique for Bulgaria. It thus became possible to carry out relatively large-scale screening of new compounds and extensive investigation of the substances with manifested effect.

The Medico-biological devision at the institute was the first to introduce systematic screening of novel substances - newly synthesised or newly isolated natural products – for neuropharmacological, cardiovascular and antispasmodic effect. Over the years, more than 5,000 original, newly synthesized and isolated natural products were subjected to trials.

Methods for the assessment of psychotropic, anti-hypoxic, anti-ischemic effects were introduced; an EEG method, methods for the assessment of the cerebral blood flow; analgesic, cardiovascular, gastrointestinal, dermatological, anti-inflammatory, antibacterial, antifungal effects. Specific methods were developed to assess the effects on neuromuscular conductivity, specific methods for evaluation the effects on blood clotting, capillary resistance, anti-atheromathosis agents, anti-inflam-

matory, etc. as well as histochemical methods.

A range of most advanced biochemical methods and approaches were adopted that helped clarify the pharmacodynamics of pharmaceutical drugs, such as: determination of the level of the biogenic amines noradrenaline, dopamine, and serotonin and their metabolites in different brain structures; radioisotope methods for determination of drug effects on specific receptors; investigation of the effect of certain drug groups on oxidative phosphorylation; determination of RNA metabolism in the brain, microsomal glycoprotein biosynthesis in the liver; studies on platelet aggregation, acetylcholinesterase activity, etc. The complexity of the Medico-biological section facilitated the implementation of all new biochemical methods on adequate pharmacological models, thus contributing to the objectivization of the results.

A significant share of the activities of the section involved comparative bioavailability studies (since 1967), the results of which were a obligatory part of the documentation for the registration of medicinal products. To determine the concentration of drugs and their metabolites in plasma and urine, modern methods, such as liquid chromatography and gas chromatography-mass spectrometry, were developed and adopted. Such studies were conducted on healthy volunteers at leading medical clinics with the authorization of the Committee for Medicinal Products.

Parallel studies were conducted on the possible toxicity – acute, sub-acute, or chronic toxicity, embryotoxicity, mutagenicity, carcinogenicity and local allergic and irritant action - using histomorphological methods.

The section was equipped with the largest vivarium in Bulgaria, with relevant breeding lines of mice, rats, rabbits, guinea pigs, hamsters, Beagle dogs, bred for experimental purposes.

Results were processed by applying contemporary statistical techniques.

All preliminary investigations were summarized at the Registration department, where a comprehensive dossier of the medicinal product was compiled, and afterwards passed on to the Clinical department for preparation for clinical trial authorisation.

Drug dossiers were submitted to the Committee for Medicinal Products for clinical investigation authorisation. The medicinal products applied in the clinical practice were both generic medicines, as well as original products created at the institute. By permission of the Committee for Medicinal Products, targeted, systemic clinical trials of Bulgarian products first began in 1962 in university clinics and hospitals across the country. The experts from the clinical department of the Medico-biological devision were involved in the development of the test methodology for a given medicinal product from a particular clinical group and directly participated in the study and analysis of the results. The cardiologists, neurologists, dermatologists and rheumatologists at the Department of Clinical Pharmacology of the Medico-biological section deserve special merit for the organization of the clinical part of the study.

The organization of experimental laboratories, the Registration and Clinical departments, and the qualification of the personnel followed the requirements for introducing new drugs to both domestic and foreign markets, especially the vast market of the USSR. Gradually, European and FDA requirements for approval of drugs were introduced.

The laboratories were headed by a multitude of highly trained professionals: doctors, dentists, veterinars, biologists, pharmacists, chemists, many of whom had specialised in renowned laboratories at home and abroad:

Doctors of Science, Senior Research Fellows (1st grade) (now full professors) with defended doctoral dissertations: Dr. L. Daleva, Dr. M. Nikolova, Dr. T. Harizanova, Dr. P. Manolov, Dr. R. Nikolov.

Doctors, Senior Research Fellows (2nd grade) with defended dissertations (now associate professors): Dr. N. Tyutyulkova, Dr. P. Arnaoudova, Dr. V. Chavdarova, Dr. J. Jordanov, Dr. N. Donev, V. Marinova (biologist), Dr. J. Illarionov, Dr. M. Taskov, Dr. Stefan Vankov, V. Ognyanova (chemist), Dr. V. Marinova, Dr. D. Stefanova, Dr. V. Dimova, A. Dryanska (chemist), Dr. S. Zarkova (vet. surgeon), Dr. O. Angelova, M. Dikova (MPharm), Dr. V. Atanasova, N. Ivanova (biologist), Dr. Z. Gendzhev (vet. surgeon).

Research Fellows: Dr. L. Petrova, St. Markova (biologist), Dr G. Tanev, Dr. O. Petkov, Dr. D. Delev (vet. surgeon), M. Deleva (biologist), Dr. R. Sheikova (stomatologist), Dr. Ivan Torlakov (vet. surgeon), Dr. P. Stefanova, Y. Gorancheva (biologist), Dr. M. Dencheva Dr. E. Kozhinkova, Dr. D. Hodzheva, Dr. S. Katsarova, I. Mihailova (chemist), R. Panikian (stomatologist), Galina Nakova (chemist), Nina Valchanova (biologist), Dr. Inna Kirkova, Dr. Julia Maslarova, S. Tuneva (biologist), Dr. Blenika Manolova, M. Vatsova (chemist), Dr. K. Bogoslovov (vet. surgeon), D. Bogoslovo-

va (MPharm), E. Kerimyan (MPharm), L. Tokuschieva (MPharm), S. Mandjukova (chemist), Julia Yaneva (biologist), Kina Konstantinova (chemist), Tsveta Potourlian (MPharm).

Specialists: L. Zankova (MPharm), Dr. G. Shumkov (vet.surgeon), St. Tsvetanov (chemist), Dr. E. Shumkova (stomatologist), Yanka Germanlieva (MPharm), Ralitsa Atanasova (MPharm), and a large number of laboratory assistants and technicians specialized in clinical laboratory, microbiology, pharmacology, zootechnicians, etc.

The specialists at NIHFI were initiators and active facilitators in organizing an extensive network of contracts with various scientific and clinical institutions for the full characterization of their medicinal products, where certain specific laboratories were created for that purpose.

Members of the Scientific Council of the Medico-biological devision were distinguished university and research experimental pharmacologists and clinicians who discussed and evaluated the results of the experimental and clinical trials characterising newly created medicines and their formulations. The Council also discussed the expediency of developing new drugs, new galenic formulations and drug combinations in order to meet the needs of clinical practice. NIHFI and the Medico-biological devision organized annual conferences and symposia to share and exchange experience with eminent specialists. For instance, a significant amount of experience was gained in the 1960s during the joint research on the possible toxicity of Metamizole – Pharmachim's analgin – with specialists from Hoehst, Germany, carried out by Bulgarian and Israeli clinical specialists. Undoubtedly, the Medico-biological devision at NIHFI contributed greatly to the inclusion of leading experts from all medical institutions in Bulgaria in the process of characterisation of the medicinal products offered by the manufacturing enterprises and Pharmachim institute, subsequently by Sopharma and Balkanpharma.

Some of the therapeutic products created at the institute, tested and introduced into practice by the Medico-biological unit were:

– Original: Nifimicin, Nivalin, Stenopril, Aescuvasin, Lonetil, Tabex, Glauvent, Tribestan and Combination Vitaton, Tempidon and its Combination Tempalgin, Dolyspan, Mukarthrin, Aligeron, Cratemon, Combinations of Piracetam - Phezam, Orocetam, Vitapiracen, Indovasin.

– Generic synthetic products: analgin, indomethacin, Feloran, acetaminophen - paracetamol now paramax - piroxicam, cimetidine, ranitidine, carsil, chlophazolin, its combination Chlophadon, captopril, nifedipine, nitrendipine, prazosin, izodinit, monizid, atenolol, Sydnopharm, antistenocardin, molsidomine, verapamil; Troxevasin, venoruton, Pyramem - cinnarizine, flunarizine, medazepam, alprazolam, vinpocetine, furantril, clenbuterol - revealed immunostimulatory effect - famotidine, ketotifen, clemastine, insulin preparations.

– Generic chemotherapeutics and antibiotics: 5-Nitrox, ciprofloxacin, gentamicin, cefalexin, ampicillin, amopen, cefamandole, cefazolin, doxycycline, tetracycline, tobramycin, tubocin.

The institute has ceased to exist since the 1990s.

Many of the well-established therapeutic products of the institute did not sink into oblivion; they are still manufactured and sold in Bulgaria and abroad, and have their role in health care. Numerous young professionals who have passed through the school of NIHFI now work in pharmaceutical enterprises, laboratories and foreign companies.

Milka Nikolova and **Nadejda Tyutyulkova**