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DEVELOPMENT OF MEDICAL GENETICS IN THE CZECH REPUBLIC

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ABSTRACT – In 1950 Lysenkoism was introduced but not accepted in medical genetics in the former Czechoslovakia. In 1962 Prof. Milan Hašek, M.D., DSc. on a plenary session of the Czech Academy of Sciences refuted it as a non-scientific theory. In 1961 he supported the creation of 1st department of medical genetics at the Faculty of Paediatrics of Charles University. In 1963 department of medical genetics was established at the Paediatric Research Institute in Brno. Lysenkoism was scientifically disproved in 1965 Brno at the international Mendel Memorial Conference, and officially eliminated de iure in 1966 in our country.
In 1966 the Czech Ministry of Health through the 1st Conception of Medical Genetics legalized medical genetics as medical specialty and fostered obligatory creation of departments of medical genetics at all medical schools and established postgraduate medical education.
In 1962 the Section of Medical Cytogenetics of the Biological Society was founded and in 1967 the Czech Society of Medical Genetics (and Genomics) of the Czech Medical Society of J. E. Purkyně was established.
By the end of 1969 four departments of medical genetics and three cytogenetic laboratories started their operation. In 1971 the first successful prenatal cytogenetic diagnosis was performed and since then prenatal prevention of chromosomal aberrations and of metabolic disorders was performed in close cooperation with Western European biochemical laboratories. Prior to 1979 all regional departments guaranteed complex genetic services, including prenatal diagnosis with ultrasound and obstetrical examination in at risk pregnancies.
In 1980 the new government Conception of Medical Genetics incorporated genetic services into the national health care system and funded their further development. First trimester prenatal diagnosis was introduced in 1985. Between 1990–2022 there has been a substantial progress in early diagnosis, prenatal screening, prevention, and treatment of genetic disorders, including development of private genetic centres. There has been extended international cooperation and support from national/European grants, broader molecular genetic examinations for individualized medical genetics diagnostics and care still fully reimbursed by the Czech health care system.

INTRODUCTION

The history of the critical years for the development of medical genetic in European countries was documented recently by Prof. Peter Harper's review (1), as well as for other European countries behind the "iron curtain" (2). The positive development after the end of the cold war and birth of European Union was reflected by the harmonisation of

training and education of medical doctors from different medical specialties with licensing the specialisation in medical genetics in all European countries (3).

The development and progress in the field of genetic counselling in our country was evaluated by Dr. Michal Šimůnek (4) and Prof. Peter Harper, M.D. published interviews with Assoc. prof. Milan Macek Sr., M.D., CSc. and Prof. Renata Laxová. M.D., DSc. (5).

The aim of this study is to document the way to clinical implementation of G. J. Mendel's laws of heredity in the country, where they were discovered, including the development of medical genetics through the critical years of Second World War, subsequent totalitarian regimes, and ideologies to the present times, as presented at Mendel Bicentennial Genetics Conference in Brno (www.mendel22.cz).

RESULTS

Period 1918 to 1945

Prof. Bohumil Sekla, M.D., DSc. (16. 5. 1901 – 7. 8. 1987; Figure1) from the Biological institute of Charles University Prague in his book Hereditary Health ("Dědičné zdraví" – 1937) proclaimed Mendelism as a basis for the development of medical genetics and condemned the misuse of eugenic strategies of Nazi "Rassenhygiene". In 1939 after Nazi occupation of Czechoslovakia all universities were closed, his Biological Institute was transformed into the Institute for Racial Hygiene until April 1945. His co-worker Assoc. Prof. Vladimír Bergauer. M.D. was executed in 1942, while Prof. Jan Bělehrádek, M.D. was jailed at the Terezin concentration camp.

Period 1946 to 1961

In 1951 Lysenkoism (promoted by Trofim Denisovich Lysenko; 1898–1976) was introduced as an official Soviet ideology, while Mendelism was declared as "reactionary" pseudoscience, that was also eliminated from regular school biology education. Nevertheless, Prof. Sekla in his lectures had been explaining Mendelism as an original scientifically verified laws of heredity as well as his colleague Assoc. Prof. Jaroslav Kříženecký, RNDr, CSc. in Brno defended Mendelism in the field of agriculture and natural sciences.

Fig. 1: Prof. Bohumil Sekla, M.D., DSc.

Fig. 2: Prof. Milan Hašek, M.D., DSc.

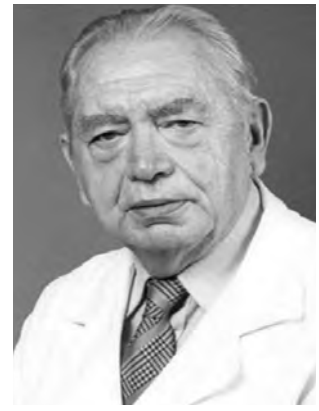

Fig. 3: Prof. Josef Houštěk M.D., DSc.

Prof. Milan Hašek, M.D., DSc (4. 10. 1925 –14. 11. 1984; (Figure 2), co-worker of Prof. Sekla initially supported Lysenkoism as a possibility to environmentally introduce new hereditary traits, because he had experimentally induced immunological tolerance by fusion of blood flows in chicken embryos. His discovery was simultaneous to that of Prof. Peter E. Medawar, later Nobel prize awardee. However, induced immune tolerance was not hereditary, therefore Lysenko's theories were not confirmed, as well as in agricultural experiments by other authors. Prof. Hašek later established a renown Immunogenetic Institute at the Czechoslovak Academy of Sciences and in 1962 initiated a plenary session of all academic and university representatives to declare that he was wrong in his initial support of Lysenkoism and asked with regrets for excuse Prof. Sekla, whom he had opposed in his defence of Mendelism. This meeting eliminated Lysenkoism *de facto*, even though it was *de iure* officially refuted only in 1965.

Nevertheless, it needs to be noted that Lysenkoism had not been accepted within the medical community from the very beginning. This period is characterized by an increasing interest in implementation of medical genetic especially in paediatrics and internal medicine.

At the Faculty of Paediatrics of Charles University at the Institute for the Child Development Research Prof. Věra Vávrová, M.D., DSc. created the laboratory for cystic fibrosis research, diagnosis and therapy. Prof. Josef Hyánek, M.D., DSc. had been introducing new detection methods of hereditary disorders of amino acid metabolism. He also organized the first targeted screening of phenylketonuria in our country, that was initiated in 1958 by available methods of that time by Assoc. Prof. Bohunka Blehová, M.D., CSc. from the Paediatric Clinic of the University Hospital of Faculty of Hygiene of Charles University.

New department for the surgery therapy of severe congenital malformations of cardiovascular system was created (Prof. Milan Šamánek, M.D., DSc). Prof. Otakar Hněvkovský, M.D., DSc. studied genetic risk of congenital hip luxation in Paediatric orthopaedic clinic.

Assoc Prof. Křížek, M.D., CSc., performed cystinuria screening for urolithiasis prevention at the Institute of Balneology in Mariánské lázně.

Prof. Josef Šobra, M.D., DSc., established the second world outpatient unit for clinical genetic examination of disorders of lipid metabolism for atherosclerosis prevention at the 3rd Internal clinic of the Faculty of General Medicine of Charles University.

Miroslav Bejšovec, M.D., achieved first successful therapy in the world of familial in utero convulsions in pyridoxin dependency 6) iSn the neurologic department of hospital in Ústí nad Labem.

Period 1961 to 1970

Prof. Josef Houštěk, M.D., DSc. (25. 7. 1913 – 22. 9. 1994; Figure 3.), dean of the former Faculty of Paediatrics of Charles University at his Institute of Child Development Research founded already in August 1961 the first official department of medical genetics in our country with Prof. Hašek's support. As Prof. Hašek's postgraduate student I was invited to fulfil this goal. Prof. Houštěk also at this time arranged for genetic education for other students of his medical faculty, such as Maria Kučerová. M.D. and Eva Seemanová, M.D., who had participated in Prof. Hašek's WHO grant for genetic load studies genetically isolated populations of Slovakia.

Since August 1961 I started to develop this department after 4-year practice in the paediatrics at a regional hospital in Ústí and Labem. First cytogenetic diagnosis of two Turner syndrome children by karyotyping of short-term cultivated bone marrow cells I presented in

November 1961 at a Paediatric society meeting. In years 1962–1963 methods of short-term blood and long-term tissue cultures *in vivo*, *post mortem*, including human tumours were developed for cytogenetic examination, biochemical diagnosis of inborn errors of metabolism, in 1970 amniocyte long-term culture methods for clinical prenatal diagnosis, were elaborated.

The genetic counselling unit at our department was developed by Prof. Eva Seemanová, M.D., DSc.

In 1963 Prof. Zdeněk Brunecký. M.D., DSc. established the Department of Medical Genetics at the Research Pediatric Institute in Brno, in 1966 Prof. Jan Žižka, M.D., DSc. established the Department of Medical Genetics at the University Hospital in Hradec Králové, in 1969 Assoc. Prof. Miloš Černý, M.D., CSc. established the Department of Medical Genetics at the Biological institute of Faculty of General Medicine of Charles University in Prague. All departments from this period combined genetic counselling and cytogenetic laboratory services.

Successful cytogenetic laboratories were developed at University Hospital of the Faculty of Hygiene of Charles University (Ivan Šubrt, M.D., CSc.), at the 3rd Internal clinic of the Faculty of General Medicine of Charles University (Radovan Chrz, M.D., CSc.) and Laboratory of the Institute of Postgraduate Medical Education in Prague (Prof. Maria Kučerová, M.D., CSc).

Organization and scientific support of medical genetic development

In 1962 Assoc. Prof. Dušan Soudek, M.D., CSc. from the Research Paediatric Institute in Brno initiated with Assoc. Prof. Milan Macek Sr., M.D., CSc. and Assoc. Prof. František Soukup, M.D., CSc. founding of the Cytogenetic Section of the Biological Society of the Czechoslovak Academy of Sciences for Czech and Slovak cytogenetic laboratories in order to improve clinical implementation of cytogenetic, oncocytogenetic and animal cytogenetic studies. This section fostered not only clinical and research cooperation within COMECON countries, but also with top European laboratories, which assured rapid transfer of new methods into clinical practice and international scientific cooperation.

In 1965 the Mendel Memorial Conference in Brno finished definitively Lysenkoism *de iure*. Therefore, in 1966 the first Conception of Medical Genetics, elaborated by Assoc. Prof. Černý from the Biological institute of Faculty of General Medicine of Charles University, was approved by the Ministry of Health. Prof. Sekla was enlisted into the Scientific Board of the Ministry of Health. Medical genetics was legalized as medical speciality within other healthcare medical services. Obligatory courses of human genetics at all medical faculties in the country and in the Institute of Postgraduate Medical Education (Prof. Kučerová) were installed. Assoc. Prof. Černý published an excellent first textbook of Medical Genetics in 1967.

In 1967 the Society of Medical Genetics of the Czech Medical Genetics Society of J. E. Purkyně (www.slg.cz) was founded thanks to the initiative of Prof. Josef Charvát, M.D., DSc., Prof. Sekla, Prof Hněvkovský , Assoc. Prof. Černý, Prof. Šobra. This society has been the partner of the Ministry of Health and guarantees implementation of medical genetics in our healthcare; supports scientific conferences and financial organization of top foreign geneticists' lectures, that contributed significantly to the successful development medical genetics, including international scientific cooperation within years 1970–1989. Before 1989 "Velvet Revolution" the Society provided legal counselling, including protection against political discrimination for its members. Prof. Otakar Štark, M.D., DSc. from the Biological Institute of the Faculty of General Medicine of Charles University became president of Czech Medical Genetics Society at this time.

Period 1971 to 1980

In 1971 in the Department of Medical Genetics of the Institute for the Child Development Research of the Paediatric Faculty of Charles University in Prague (Assoc. Prof. Macek Sr.) with his co-workers from the Clinic of Obstetrics and Gynecology (Prof. Vladimir Fuchs, M.D., DSc. and Prof. Miroslav Břešťák, M.D., DSc. and Václav Suk, M.D.) performed first successful prenatal cytogenetic diagnosis from long-term cultivated amniocytes for the prevention of translocation form of the Down syndrome, being first on continental Europe. Establishment of successful cultivation methods enabled systematic prenatal prevention of aneuploidies and prevention of severe inborn errors of metabolism for the entire country in cooperation with laboratories in Great Britain and the Netherlands. Prof. Helena Tomášová, RND., DSc, introduced amniotic fluid biochemical examination to improve prenatal diagnostic reliability.

Diagnosis of metabolic disorders was assured in the Institute of Inherited Metabolic Disorders of the Faculty of General Medicine in Prague (Prof. Hyánek, Prof. Milan Ellleder, M.D., DSc.) and at the Brno Paediatric Research Institute (Prof. Jaromír Kamarýt, DSc. and Dipl. Ing. Antonín Mrskoš, CSc.).

In this period cytogenetic laboratories gradually introduced new chromosome banding methods. Oncocytogenetic examinations were applied at university centres of oncology in Prague at the 3rd Clinic of Internal Medicine of the Faculty of General Medicine by Radovan Chrz, M.D., CSc. and Prof. Dipl. Ing. Kyra Michalová, DSc., for oncohematology in adults, at the Motol University Hospital Department of Medical Genetics by Assoc. Prof. Macek Sr. and. Assoc. Prof. Alena Petráková, M.D., CSc. for solid tumour cytogenetics, Prof. Petr Goetz, M.D. CSc. for oncohematology in children. In Brno Assoc. Prof. Lenka Foretová, PhD. developed oncogenetic examinations and studies in Masaryk Memorial Cancer Institute, Alexandra Oltová, PhD. commenced cytogenetics examinations at the Masaryk University, and in Olomouc Prof. RNDr. Marie Jarošová, CSc. for oncohematology at the Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc.

Before the end of this period departments of medical genetics were established in all regions of the country including new regions of Western Bohemia by Assoc. Prof. František Lošan, M.D., CSc. (Plzeň), Southern Bohemia by Karel Čutka, M.D. (České Budějovice), Northern Bohemia by Josef Kofer, M.D. (Ústí nad Labem), in Northern Moravia by Prof. Jiří Šantavý, M.D. DSc. (Olomouc), and in Northeastern Moravia by Melania Ševčíková, M.D., Jan Všetička, M.D. (Ostrava). Elsa Švagrová M.D., created first genetic counselling unit in our country for district town of Benešov, combined with paediatric praxis, thanks to cooperation with Prof. Seemanová.

Genetic counselling has reached European standards due to cooperation with top European university centres and thanks to work and results of Prof. Seemanová, from the Department of Medical Genetics of the Institute of Child Development Research in Prague and Prof. Renata Laxová, M.D., DSc. from the Research Paediatric Institute in Brno.

Prenatal diagnosis was performed in all regions in laboratories associated with university gynaecology-obstetrics clinics.

Period 1981 to 1990

In 1980 the second Conception of Medical Genetics of the Ministry of Health was conceived by Assoc. Prof. Macek Sr. because further progress was hindered by insufficient funding and the departments did not have their own budget. They used rather limited budgets of other health care/university facilities.

The new Conception introduced medical genetic services into the state healthcare system with their own budget, covering all the expenses of medical genetic departments and of specialized genetic institutions in order to reach optimal quality of their services, laboratory infrastructure, technical and personal equipment together with state grants. The Conception was adopted in 1980 and fulfilled without delay with all above mentioned requirements in all regional departments of medical genetics.

Therefore, since 1980 the Conception stimulated rapid establishment, growth and development of all medical genetic departments, increased diagnostic quality of genetic services and counselling, improved clinical cytogenetics, facilitated association with international progress in the field, to achieve comparable quality level with other European countries. This high standard was guaranteed by all regional departments of medical genetics and assured improvement of postgraduate education in medical genetics for university graduates and technical personnel active within those departments.

In 1985, thanks to cooperation of Department of Medical genetics (Institute for the Child Development Research (Assoc. Prof. Macek Sr.) and the Clinic of Gynaecology and Obstetrics of the Faculty of General Medicine Charles University (Prof. Zdeněk Hájek, M.D., DSc. and Eduard Kulovaný, M.D., CSc.) chorionic villus biopsy was introduced. First trimester prenatal cytogenetic and biochemical diagnosis from short and long-term cultivated chorion villi cells significantly improved diagnostic efficiency of prenatal diagnosis and prevention.

Prof. Radim Brdička, M.D., DSc. from the Department of Biology of Faculty of General Medicine of Charles University is founder of molecular genetics and molecular genetic diagnosis in our country. International cooperation with EU countries, thanks also to Charles University international cooperation agreements with European universities, in all fields of medical genetics and in molecular genetic diagnosis genetics enabled training of our co-workers and their participation in the mapping of the Huntington disease gene (Prof. Dipl. Ing. Zdeněk Sedláček, DSc.) and prenatal/ postnatal CFTR gene mutation detection (Prof. Milan Macek Jr., M.D., DSc.). These developments enabled in 1990 the establishment of the Cystic Fibrosis centre for its prenatal and postnatal diagnosis for the entire country.

The cooperation within COMECON countries increased financial support of medical genetics in participation in state priority grant "Mother and Child Health Care for Health of the Present and Next Generation", prepared and guaranteed by Prof. Houštěk.

Our country was awarded by the organization of the 5th International Congress of Early Prenatal Diagnosis, organized in the frame of the Society of Medical Genetics of Medical society of J. E. Purkyně by Assoc. Prof. Macek Sr. from the Department of Medical Genetics of the Institute of the Child Development Research of the Paediatrics faculty of Charles University.

Period 1991 to 2022

The velvet revolution opened a smooth transition to a new period of medical genetics development in our country.

Organization of medical genetic care was preserved in regional state departments of medical genetics including the professional Society. Private genetic departments and laboratories have been established.

University institutes of biology were transformed into Institutes of Biology and Medical Genetics comprising biology and genetics education at all medical schools in the country, as well as the system of postgraduate education of medical doctors/ university

specialists and of postgraduate education of technical personal, corresponding to international standards, elaborated by Prof. Kučerová, Prof. Goetz and Vladimir Gregor, M.D., pre-gradual education by Assoc. Prof. Miloslava Kohoutová, M.D, CSs. and prof Goetz.

Research grant support was extended to university grants, Ministry of Health / Ministry of Youth Education and Sports grants, Academy of Sciences. International grants became available from Norway and EU framework programs, including bilateral Czech and USA scientific cooperation.

Successful cooperation between private and state centres provided higher availability of genetic services, especially in reproductive genetics, preimplantation diagnosis, molecular genetic diagnostics, later in a non-invasive prenatal genetic testing. David Stejskal, M.D., who developed the biggest private Centre of medical genetics in our country (Genomics database https://slg.cz/pracoviste/), supported this successful development of medical genetics by sponsoring and organisation of regular scientific conferences with the participation of top foreign geneticist. He introduced in 1993 prenatal biochemical screening in the second trimester with N. Wald ALPHA computer programme for risk ascertainement in the central Bohemia regional department of medical genetics between first ones in Europe.

The first trimester biochemical screening was clinically implemented since 1999 thanks to our cooperation with H. Cuckle and his software risk evaluation, integrated with the ultrasoound examination, QFPCR rapid detection of the most frequent chromosomal aneuploidies and second trimester biochemical screening in the case of necessity.

Therefore, this development corresponded with the progress of medical genetic services in the EU and was reflected in the improvement of reliability and success in prenatal/postnatal diagnosis, prevention and therapy, by implementation of 1st and 2nd trimester prenatal biochemical screening combined with ultrasound examination, by preimplantation genetic diagnosis of monogenic diseases and of chromosomal aberrations, successful prenatal testing from peripheral blood (NIPT) and recently also by preconception screening of genetic risk families for early preimplantation/prenatal prevention, as well as neonatal screening of cystic fibrosis, thyroidal diseases for early therapy, for individualised healthcare.

This successful development induced medical genetic subspecialisations in different clinical specialties as oncogenetic, cardiogenetic, stomatognathic, ofthalmogenetic, neurogenetic, reproduction genetics, pharmacognetic and others as well as in medical genetics, in mutual interdisciplinary cooperation.

Interdisciplinary cooperation guaranteed not only successful implementation of medical genetics in all medical specialties, but also to overcome technical problems, as is documented in our own experience. We could develop and introduce prenatal diagnosis since 1971 to 1973 only thanks to possibility to use tissue culture laboratories of Prof. Vladimír Vonka, M.D., DSc. Department of Experimental Virology at the Institute of Sera and Vaccines in Prague, until our own laboratory in University Hospital Motol was finished.

In 2020–2022 rare disease-related research and diagnosis national plans and in collaboration with the national rare disease alliance has been established within Czech Rare Disease Association (Prof. Macek Jr., Renáta Gaiillyová, M.D., Markéta Havlovicová, M.D.).

The level of genetic research and services in our country was confirmed by the fact, that our country participated /coordinated EU grants (Assoc. Prof. Macek Sr.), Prof. Macek Jr was elected president of the European Society of Human Genetics

(2010–2011) and successfully implemented our experience in recognition of medical genetics as a primary specialty in the entire EU. International cooperation successfully continued with the European Society of Human Genetics which held its 2005 annual meeting in Prague (local host Prof. Macek Jr.), with the European Cystic Fibrosis society which held its 2008 annual meeting in Prague (local host Prof. Macek Jr.) and European Society of Human Reproduction and Endocrinology that held specialised courses in Prague in 2009 (local host Assoc. Prof. Milan Macek).

Radim Šrám, M.D., DSc. from the Czech Academy of Sciences proved in long-term population studies, that epigenetic risk of environmental factors has been increasing risks for genetic health of present and future generations.

Within recent years the Institute of Animal Physiology and Genetics of the Czech Academy of Sciences has been actively involved within international cooperation in the development of new methods of gene therapy to slow down neurodegeneration in Huntington disease, to reverse severe neuropathic pain, to restore hearing and vision in Usher syndrome on animal models of minipigs, elaborated by Prof. Jan Motlík, MVD., DSc.

Since the very beginning of medical genetics development in Czechoslovakia we closely cooperated with pioneers of medical genetics in Slovakia, comprising Prof. Viliam Izakovič, M.D., CSc., Prof. Štefan Sršeň, M.D., DSc., Prof. Vlado Ferák, M.D., CSc., Assoc. Prof. Michal Ondrejčák, CSc. and other Slovak colleagues in clinical genetics, cytogenetics and molecular genetic diagnosis development, in common publications, meetings, conferences, as well as after both parts or the republic were separated 30 years ago.

Finally, I allow to remember important message of Prof. Peter S. Harper (1) on human genetics in troubled times and places to avoid repetition of similar disasters in the future: „*The power of modern human genetics and genomic techniques now gives greater potential for abuse as well as for beneficial use that has ever been seen in the past*."

CONCLUSIONS

This review documents how totalitarian ideology and political system misused genetics and hindered the development of medical genetics and how we tried to overcome it.

The successful development was due to:

- the decisive role of top representants of clinical medicine and biomedical science,
- high level of clinical medicine supporting implementation of medical genetics in clinical practice,
- cooperation between genetic departments,
- interdisciplinary cooperation in clinical medicine, with research institutes of the Ministry of Health and biomedical institutes of the Czech Academy of Sciences,
- international scientific and clinical cooperation with countries before/behind the "iron curtain",
- inclusion of medical genetics in high priority research and medical care state programs,
- combination of this strategy with cooperating private genetic departments and specialized centres contributed significantly to the present high level of all available medical genetic services.

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