Medical genetics around the world

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Medical genetics in Hungary*

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The history of medical genetics in Hungary

The beginnings of medical genetics were promising in the early decades of this century.¹ The concept of hereditary degenerative diseases was established by a Hungarian neurologist, Ernő Jendrassik (1858–1921), in 1902. Another neurologist, Károly Schaffer (1864–1938), described the pathological basis of Tay-Sachs-Schaffer disease in 1905, and thus delineated the first inborn error of lipid metabolism. Károly Csörsz (1892–1935) organised the first twin and population genetic studies, and the McKusick catalogue² gives him priority in describing X linked recessive ichthyosis (30810). Unfortunately in the 1930s and early 1940s, the German influence and a drift towards fascism brought about the dominance of an unscientific applied genetics which was used to mask vile political crimes. This programme divested eugenics of its original character as envisaged by Galton. Naturally, many talented young medical doctors kept themselves aloof from medical genetics and the active, decent medical geneticists were overshadowed, for example, Kornél Kőrösy (1879–1948), who had previously written a monograph on gene linkage of great international reputation,³ or Lipót Szondi (1893–1986), who established a Genetic Registry of Handicapped Children in 1930. In the 1950s Lysenko's doctrine also made scientific studies in medical genetics impossible. The door was opened again only in the early 1960s, owing to the activities of molecular geneticists, but by that time a generation of Hungarian geneticists was missing. Human cytogenetic methods were introduced by Dezső Schuler, a paediatrician, in the early 1960s. A milestone in the revival of Hungarian medical genetics was a 'refresher course of human genetics',

organised by Gábor Szabó, a molecular geneticist and supported by the WHO and the Postgraduate Medical School, Budapest, with the help of the Dane Mogens Hauge and his coworkers in Tihany in 1965. Another important event was the establishment of the first Hungarian genetic counselling clinic in Budapest in 1963 by Georg Lenart (1896–1983), a paediatrician who was keenly interested in medical genetics. In the meantime some of us grasped opportunities to obtain short fellowships to learn about recent developments in medical genetics abroad. The first department of human genetics was set up in the National Institute of Hygiene in 1971. An International Symposium on Medical Genetics sponsored by the WHO was held in Debrecen-Hajduszoboszló in 1976.⁴ The Hungarian Ministry of Health planned to found the National Institute of Human Genetics in 1978; however, owing to financial problems it was postponed. The Hungarian Society of Human Genetics was created in 1972; at present it has about 260 members. The 18th Symposium of the European Society of Human Genetics was held in Budapest in 1985. The Department of Human Genetics and Teratology, National Institute of Hygiene, was appointed as a WHO Collaborating Centre for the Community Control of Hereditary Diseases in 1986.

A general view of the Hungarian population

Hungary has a population of 10.6 million people of European origin but more than three million Hungarians live in the surrounding countries. There is only one group in Hungary which differs from the Hungarian stock: the gypsy population of about 400 000 people. Genetic markers confirm that they originate from north-west India. Their birth prevalences of cleft palate, congenital cardiovascular malformations, and congenital talipes equinovarus exceed the usual Hungarian rate; however, the incidence of multiple sclerosis (MS) is lower. The

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increased rates are explained by the relatively high occurrence of consanguinity; the frequency of cousin marriages is between 2% and 20% in different gypsy samples, and is only 0.3% in the population at large. The low incidence of MS is explained by a peculiar HLA haplotype.

Hungarians are the descendants of a Finno-Ugrian population that settled in the Carpathian basin in the last decades of the ninth century, after mass migration from different regions of western Asia (around the Ural mountains) and eastern Europe. There was a close connection with Turkish, Iranian, and other populations during the long migration and also with some Oriental-Mongoloid and European populations that joined the original group after the establishment of the Hungarian state. These historical events may explain the intermediate position of the Hungarian population between the west European and east Oriental populations which is indicated by the distribution of blood groups (ABO, Rh, etc) and by the 37% prevalence of lactose malabsorption. After the disaster of Mohács in 1526, a fatal defeat by the Turkish army, Hungary lost its political power in Europe and a considerable part of the population was destroyed during a Turkish occupation lasting nearly 150 years. Later it provided opportunities for the different European groups to settle down in this territory. The lack of 'typical' Hungarian genetic disorders is congruent with the high rate of hybridisation.

The present demographic state of Hungary is considered to be unfavourable. Recently the rate of livebirths has dropped dramatically (figure). In 1956 the Abortion Law let women decide whether or not they wanted to have their pregnancies terminated. Subsequently the number of legally induced abortions increased continuously and peaked at 207 000 in 1969. In contrast to the international trend, this law was restricted in 1974 for social reasons, but broadened with respect to medical indications. Among the medical indications are those of a genetic-teratogenic nature. Abortion is permitted (1) before the 12th week when there is $\geq 10\%$ risk of a severe, untreatable fetal disorder which is not diagnosable prenatally; (2) before the 20th week when there is $\geq 50\%$ risk of a prenatally diagnosed fetal disorder; and (3) at any time when a lethal disorder, incompatible with postnatal life, is diagnosed prenatally. The occurrence of medically indicated induced abortions increased significantly after 1973 (figure). Fetal death, the third outcome of pregnancy, occurs relatively infrequently; the rates of recorded miscarriages and stillbirths were 13.1% and 0.8% respectively in 1975 to 1984. Infant mortality is decreasing, but even recent figures of

FIGURE Number of livebirths and induced abortions, together with the rate of recorded congenital anomalies (per 100 total births) and genetic counselees (per 100 livebirths).

about 2% considerably exceed the rates in developed countries. The first day mortality is extremely high because of the rigorous classification of infant deaths; this statement is in agreement with the relatively low rate of stillbirths and the extremely high frequency of newborns with a birth weight under 2500 g (about 10%). The mortality pattern is also disadvantageous, as indicated by the low life expectancy at birth: 65.6 years for males and 73.7 years for females in 1984.

The present situation of medical and clinical genetics

There is an adequate number of physicians in Hungary (with 34 548 in 1985, Hungary ranks fourth on the list of physicians/population rate in the world), but there are only 25 human geneticists and only five full time medical geneticists. However, of the above 25 human geneticists, 16 have science degrees in addition. The requirements for 'human genetics' as a medical specialty were regulated in 1978. The minimal requirements of qualification for human geneticists are as follows: a four year practice after graduation and recommendation of the head of the institution; curriculum vitae and a list of publications are also needed for this application. The board of the Postgraduate Medical University, Budapest, decides on recognition without any examination (the majority of other medical specialties require examination). Unfortunately, after the first year (1979), the number of physicians with the qualification of human geneticist has been very low. A postgraduate course of medical genetics has not been organised in the past 10 years. (An exception was a prenatal

diagnostic course in Debrecen in 1984.) Other postgraduate medical courses, mainly in paediatrics and gynaecology-obstetrics, have some genetic topics within their 60 hour courses. Thus, present postgraduate education is inadequate for providing training and for stimulating and supplying the necessary replacements, that is, a new generation of medical geneticists. Additionally, four medical universities have no independent institutions for human or medical genetics. The principles of molecular genetics are taught within the subject 'biology' in the first year of the six year medical curriculum. A 'clinical genetics' course of two to 24 hours is taught by the staff of biological, paediatric, or obstetric institutes in the fifth year. However, at the end of this course an examination is required only at two universities, whereas at the other two universities it is included in paediatrics. In general, this amount of education is not enough to arouse the interest of medical students in medical genetics. It explains the inadequate knowledge of medical genetics of medical graduates and the difficulty of attracting young medical doctors for genetic counselling outpatient clinics.

Clinical genetics is pursued in paediatric inpatient clinics in four medical universities (Budapest, Debrecen, Pécs, and Szeged) and some county hospitals (Győr, Szombathely) by qualified medical geneticists. Four prenatal diagnostic centres (Budapest: Postgraduate Medical School, Debrecen, Pécs, and Szeged) function within obstetric inpatient clinics. Both chorionic villus sampling and transabdominal amniocentesis are used after ultrasound scanning for this purpose. (These procedures are performed on pregnant women admitted to hospital.) The group of clinical geneticists headed by Z Papp in Debrecen has achieved a high standard of prenatal diagnosis and postgraduate teaching. The national policy on indications for prenatal diagnosis has been determined by official guidelines. The general principle is that prenatal diagnosis is reasonable in cases in which there is $\geq 2\%$ risk of severe fetal disorders that cannot be effectively treated. In general, this procedure is offered by genetic counselling clinics; however, the heads of Prenatal Diagnostic Centres consider the maternal indications for amniocentesis or chorion biopsy. Until 1984, there was a fifth Prenatal Diagnostic Centre with a high standard of cytogenetic methods; however, after the head retired it was not possible to find an adequate successor. The use of biochemical methods is limited and DNA probes have not been introduced into Hungary, though some groups are making efforts to use them in clinical practice*. There are only two

well established biochemical laboratories mainly interested in medical genetics (paediatric clinics in Pécs and Szeged).

Technical facilities, including equipment, reagents, kits, etc, have lagged behind rapid international developments. At present this gap causes serious difficulties for both medical services and research. Consequently, our strategy is to concentrate our research efforts only on certain topics with expertise and a good tradition, for example, studies on haemoglobinopathies,^{5,6} minor anomalies,⁷ and pharmacogenetics,⁸ or with special advantages from an international viewpoint, for example, population based studies that are easier to undertake in Hungary than in some developed countries.

The social appreciation of medical genetics is controversial in Hungary. The consequences of previous political events (fascist eugenics and the statement that genetics was a 'guilty' and reactionary science in the 1950s) cast a shadow of suspicion on medical genetics. The lack of appreciation or understanding of the discipline may also stem from the fact that there are no independent institutions of medical genetics in Hungary. In addition, the current leaders of the health system lack any education in medical genetics and this fact may explain why they consider genetic disorders to be rare and generally untreatable. Genetic susceptibilities to common diseases are not recognised and consequently not used in preventive programmes. Furthermore, the importance of some original approaches may not be understood, as indicated by the following example. In 1977, the PhD application of Zoltan Kazy (in Hungary this corresponds to the degree of candidate of sciences) was accepted so that he was able to undertake prenatal genetic research in Moscow. Under the direction of I S Rozovsky, he pursued studies on early pregnancy and soon established a routine method of chorion biopsy at six to 12 weeks of gestation following the ultrasonic or transcervical embryoscopic localisation of chorion frondosum. The genetic study of sex chromatin and enzymes in these fetal tissues proved to be successful in pregnant women in 1978. These results were published in Hungarian in 1979 and in English in 1982.⁹ After his return to Hungary, he received no help to continue this pioneer work and thus lost his favourable position.

Organisation and concept of genetic counselling

After some spontaneously established genetic counselling outpatient clinics, a national network was set up in 1976 as part of the National Mother and Child Care System. This network is directed by the National Institute of Gynecology and Obstetrics.

*Note added in proof. This method is available now in cystic fibrosis, Duchenne muscular dystrophy, and haemophilia A.

The choice of this base was a poor decision which has caused a decrease in the standard of genetic counselling.

On the one hand this Institute cannot provide adequate guidelines for genetic counselling because it has no experience in this field. On the other hand the financial support comes through the budget of the Family and Female Counselling Clinics and the share of Genetic Counselling Clinics is decided by gynaecologists; thus, these institutions are under-supported. Additionally, no consideration is given to case load when funds are allocated: genetic counselling clinics with 3000 or 100 new counsellees per year are given the same amount. At present there are 13 genetic counselling outpatient clinics in Hungary, six in Budapest with 2 million inhabitants and seven in the remainder of the country with 8.6 million persons. The head of each genetic counselling clinic is a medical doctor (seven paediatricians, three gynaecologists, three medical geneticists) and nearly all genetic counselling clinics have a suitable cytogenetic laboratory and clinical backup as well as auxiliary personnel. (Of 16 medical cytogenetic laboratories in Hungary, 11 work directly with or closely connected with genetic counselling clinics, three others are involved with tumour cytogenetics, one is located in a paediatric clinic in Debrecen, and another in a forensic institute in Budapest.) The genetic counselling clinics cover a defined territory. All clinics are prepared to deal with all types of genetic disorders but some also specialise in certain types of genetic diseases. As a result of exposure in the Hungarian media, medical genetics has gained high popularity in the population and explains the high participation rate in genetic counselling clinics. The number of new counsellees continues to increase; at present four consultations per 100 live-born infants are recorded yearly (figure). In addition to formal genetic counselling, advice concerning teratogens is also given by these clinics and this special group represents about 15% of counsellees. Since 1987 there has been an attempt to lower this proportion by providing a centralised telephone counselling service.

In the early 1970s, the traditional non-directive method of counselling was introduced. However, Hungarian counsellees were not satisfied with this because they expect more help from counsellors than mere information. More exactly, they asked for specific advice-guidelines to make an appropriate choice among several options. To satisfy the requirements of the counsellees so-called 'information-guidance' counselling was established.¹⁰ (This term was coined with the help of the late Professor C O Carter.) First, the nosological diagnosis must be clarified. In our clinic 60% of probands are referred

with a diagnosis, in another 20% this diagnosis is established as a result of supplementary examinations during the counselling investigations, while in the final 20% a diagnosis cannot be established. Secondly, the explanation of the so-called 'danger' or 'burden' involves (1) the severity of the expected disorder, (2) the possibilities of treatment, (3) the suitability of prenatal diagnosis, (4) the magnitude of the genetic risk, (5) the maternal risk during pregnancy, (6) the teratogenic risk of maternal disease and its treatment during pregnancy, (7) the postnatal risks connected with affected parents, for example, a schizophrenic or alcoholic mother, (8) the coping potential of the family, (9) the socio-economic situation of the family, and (10) the number of previous affected or unaffected children. Thirdly, if counsellees want our advice, we summarise it after we obtain informed consent from them to be guided about their choices in reproduction. Each genetic counselling session is individual; however, the counselling situations can be grouped into five general categories of advice (table 1). After the 'persuasive' advice of categories I, II, and III, 95% of counsellees want to have a baby. After the 'dissuasive' advice of categories IV and V, 61% of counsellees are deterred. Of course, we do our best to help the remaining 39% with no compliance. We hope that this Hungarian counselling method suits the original Galtonian idea (that the task of medical geneticists is to inform and counsel, while the decision is the right and responsibility of counsellees), the expectation of our clients based on their cultural tradition, and human rights in general. Nevertheless, the ethical issues of our practical work have been highlighted and are continuously discussed within society.¹¹

There are some serious difficulties in the practical work of genetic counselling, the majority of which

TABLE 1 *Distribution of consultands according to five categories of 'advice'.*

Category of advice	Meaning	Percent	Undeterred (%)	Proportion (%) of affected sibs (by specific and non-specific anomalies)
I	No essential problem, pregnancy recommended	20	96	3
II	Pregnancy recommended after some preparation	65	94	6
III	Pregnancy recommended with prenatal fetal examination	5	90	2
IV	There is some problem, pregnancy requires consideration	5	40	20
V	There is a serious problem, pregnancy is not recommended	5	38	44

are connected with the lack of adequate coordination of the work of counselling. The lack of clear direction explains why the criteria for qualifying those who do genetic counselling are not prescribed. Recently, medical doctors and biologists without any qualifications have been doing genetic counselling. Finally, the lack of necessary consensus in methods used in counselling has caused a decrease in counselling standards. This became obvious after assessing the extreme variation in counselling given after the Chernobyl accident and after evaluating the international variation in an international cross cultural study of ethics and human genetics.¹² The lack of independent representation of medical genetics may explain some of the ethical mistakes in official regulations, for example, a directive method of premarital counselling, the exclusion of women over 40 from heterologous artificial insemination, and the legal prohibition of sterilisation in males (in females it is allowed under certain conditions)*. The point is that Hungarian medical geneticists have to fight for some independence in their own field.

Optimal family planning programme

Parallel with the increasing popularity of genetic counselling, a growing number of couples without significant specific risk factors seek advice in genetic counselling clinics with the desire of having 'perfect' (in Hungary 'optimal') babies. On the one hand they want to do their best and to use modern methods of family planning in order to decrease the random risk. On the other hand they have not been satisfied with the obligatory premarital counselling, which seemed to be a bureaucratic procedure without any medical benefit. This frequent wish has prompted us to combine some available methods in an 'Optimal Family Planning Programme' supported by the WHO to prevent some specific disorders and to reduce random risk. This programme has three guiding principles.

I *Checking reproductive health.* This is based on seven points: (1) family history of both partners (to determine whether or not it is worthwhile visiting the genetic counselling clinic), (2) case history of the female to reduce any maternal risk, for example, diabetes mellitus or epilepsy, that may exist, (3) pregnancy fitness (special gynaecological examination for the detection of anomalies or inflammation of the reproductive organs and hormonal disturbances), (4) male procreativity fitness (sperm analysis), (5) exploration of psychosexual life (whether or not it is worth visiting a sexologist), (6) occupational history, and (7) exclusion of some specific risks, for

example, rubella seronegative females are vaccinated, toxoplasma seronegative females are followed up serologically, and anaemia is treated by multivitamins.

II *A three month preparation for conception.* Conception is prepared for by (8) protection of germ cells (advice to stop smoking, drinking alcohol, unnecessary medication, etc), (9) restoration of hormonal balance after using the contraceptive pill (the rate of use is 45%), (10) estimating two optimal days for conception by basal body temperature, (11) administration of a preconceptional multivitamin (Elevit Pronatal^R-Roche) supplement.

III *Protection of very early pregnancy.* At the end of the three month preparation period couples in general (92%) get a 'start' signal to commence conception and females are asked to visit experts immediately after the first missed menstrual period. This principle aims (12) to achieve pregnancy in the optimal days of conception, (13) to diagnose pregnancy at a very early stage by a sensitive pregnancy test (in general it is also confirmed by ultrasound scanning), (14) to exempt the fetus from hazards, for example, any previously detected occupational hazards, (15) to continue postconceptional multivitamin supplementation up to the 10th week of gestation. After the 10th week of gestation pregnant women are referred to antenatal care clinics. In the first 1000 outcomes of pregnancy, the best result was a more than 50% decrease in livebirths of low birth weight.

Public health programmes

Congenital anomalies (CA) have an increasing public health importance. In Hungary they comprise 6% of all births. CA as a group is the eighth leading cause of death and the second largest cause of infant mortality accounting for 23% in Hungary in the 1980s. Altogether they cause nearly 5000 years of lost life and about 4500 years of actually impaired life within our population each year.

The Hungarian Congenital Malformation Registry was established in 1962 based on obligatory notification of CA diagnosed in malformed index patients from birth up to the age of one year. Notification is exclusively the task of physicians: obstetricians (all deliveries take place in hospital), paediatricians (inpatient and outpatient clinics), and pathologists (necropsy is obligatory). Data are critically evaluated before registration, for example, isolated and multiple CA are separated rigorously because, in general, isolated CA entities could be considered to be nosological ones while component CA within multiple CA are of heterogeneous origin. Recently recorded total figures of CA have been

*This regulation was changed on 1 September 1987.

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near to 5% of total births (figure). Validity of diagnoses and completeness of ascertainment are checked in ad hoc epidemiological studies; thus true birth prevalences of common CA (birth prevalence ≥ 1 per 1000 births¹³) and moderately frequent CA (0.1 to 0.99 per 1000 births) are known (table 2). Since 1973 other surveillance programmes have been based on this Registry within the Centre of Congenital Anomaly Control. Here only two will be mentioned.

The national follow up programme of multiformed babies¹⁴ has three purposes. (1) To increase the rate of identified multiple CA entities (the success rate increased from 33% to 50%). (2) To attempt the delineation of further recognisable CA patterns since their identification helps to estimate the prognosis and sib occurrence. (3) To establish a special surveillance for the detection of environmental mutagens because mutant genes, owing to their pleiotropic effect, and microscopically visible chromosomal aberrations, owing to their generalised impact, in general cause multiple CA.

The purpose of the Surveillance of Indicator Conditions is to estimate the occurrence of new germinal mutations. The so-called indicator conditions in offspring are or may be distant phenotypic manifestations of altered DNA in germ cells of the parent. This surveillance involves three indicator conditions checked by personal or cytogenetic examination and completed by the family history: (1) 15 sentinel anomalies as indicators of germinal dominant gene mutations; 46 new mutations per year were detected in 1980 to 1984; (2) Down's syndrome as an indicator of germinal numerical chromosomal mutations; its birth prevalence is 1.2 per 1000 total births and 98% occurred as a de novo event; (3) pairwise analysis of component CA within unidentified multiple CA. Ten year baseline figures

of these sets were determined in 1973 to 1982 and recent annual figures are compared with them.

Multiple births in women in Budapest and its surrounding area have been recorded by the Budapest Twin Registry since 1 January 1970. Every obstetric institution is obliged to notify every multiple delivery and the completeness of notifications exceeds 90%. Placentas are collected and examined by the same pathologist. In like sexed twins with a dichorionic placenta, zygosity is determined between the ages of three and six years by examination of blood and serum protein groups. The zygosity of twins born between 1970 and 1979 was determined in 78.7% of all pairs. Congenital structural talipes equinovarus, congenital inguinal hernia, hypospadias, and undescended testes are significantly more frequent while the occurrence of congenital hypertrophic pyloric stenosis is significantly lower in twins.

There are four preventative programmes concerned with genetically determined disorders. (1) Maternal serum AFP (MS-AFP) screening is undertaken in the 16th week of gestation with ultrasound examination and, if necessary (after repeated positive MS-AFP values with negative ultrasound scanning), amniotic AFP examination. This programme became population based in 1985, but the efficacy is low. In 1984 to 1985 331 cases with isolated neural tube defects were recorded but the necessary data were only available in 279 for further analysis. Only 79 were prenatally diagnosed before the 22nd week of pregnancy and only 74 of the pregnancies were terminated. However, of the remaining 200 births, 188 were examined by MS-AFP and 161 by ultrasound. MS-AFP indicated a positive finding in 94 cases (50%) while ultrasound demonstrated a neural tube defect in 22 cases. The lack of elective abortion was explained by deviation in results of two examinations, mothers did not want to terminate their pregnancies, or examinations were performed too late. (2) Prenatal chromosome examination is undertaken in fetuses of mothers over 40 years of age. Only 23.4% of pregnant women in this category were examined in 1984 to 1985 and 16 numerical chromosome aberrations were detected (2.6% of all fetal chromosome analyses). This is far from the desired goal. (3) Newborn screening for phenylketonuria (PKU) became a population based programme in 1973. Later, galactosaemia and hypothyroidism were added to the screening. This programme seems to work well; the recorded birth prevalence of PKU is 0.09 per 1000. (4) Orthopaedic screening of newborns is undertaken which has resulted in almost total prevention of Hungary's most common CA, dislocation of the hip. The problem is that the screening has resulted in

TABLE 2 True birth prevalence and sib occurrences of 10 common congenital anomalies in Hungary.

Congenital anomaly	True birth prevalence per 1000 total births	Sib occurrence (%)
*Congenital liability for dislocation of hip (Ortolani click)	28.00 $\pm$ 0.98	14
Congenital inguinal hernia (operated)	11.04 $\pm$ 1.29	10
Undescended testes	6.7 $\pm$ 0.62	7 (in brothers)
Neural tube defects	2.80 $\pm$ 0.40	3
Hypospadias	2.2 $\pm$ 0.32	5 (in brothers)
Congenital hypertrophic pyloric stenosis	1.46 $\pm$ 0.20	6
Ventricular septal defect	1.39 $\pm$ 0.47	3
Structural talipes equinovarus	1.30 $\pm$ 0.38	6
Down's syndrome	1.2 $\pm$ 0.18	1
Cleft lip $\pm$ palate	1.03 $\pm$ 0.20	5

*See text.

overdiagnosis which has greatly increased the birth prevalence of this CA (28 per 1000 compared with the prevalence of manifest cases of about 10 per 1000 in the 1940s). At present there is an effort to make the diagnosis more reliable.

Conclusion

Two features, among others, are characteristic for medical geneticists and allied specialists in Hungary. On the one hand there is dissatisfaction with available conditions of practice in the light of the increasing opportunities provided by new developments in medical genetics. On the other hand there is optimism due to the belief that the time has come to be able to prevent severe genetic disorders showing as a precedent how an apparently fixed destiny may be overcome.

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