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Medical genetics

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Medical genetics essentially consists of the application of knowledge and methods collected and worked out in the many specialized fields of human genetics. In a multi-author review covering most of the important subspecialities it becomes a difficult task to write about 'medical genetics'. The usual way out, namely to escape into some special field, is not open to me. Instead, I shall describe some general experiences of centers dealing with 'medical genetics', and discuss current trends and the expectations we have for the future.

1. The tasks of genetic counselling services

In Switzerland, as is the case in most European countries, *genetic counselling* in diagnostically clear cases of monogenic or multifactorial disease is quite often performed by well-informed physicians in private practice and in hospitals. It is the aim of our teaching in medical schools as well as in postgraduate training to broaden this competence. Part of this uncomplicated 'conventional' genetic counselling belongs, however, to the daily duties of the specialized medical geneticist. Insecurity or lack of time on the part of general practitioners, and direct enquiries from laymen create a demand for such services. To secure a high standard in medical genetics and for the training of our younger workers it is, in my opinion, important that the public should have direct access to the genetic counselling provided in specialized institutions. Providing this direct access makes it, however, practically mandatory that the principal counsellors be medically trained persons who are in a position to obtain the necessary medical information from colleagues and from hospitals. In the not too distant future more well-trained medical geneticists will be needed to meet the challenges of the application of DNA technologies in genetic counselling, a topic that will be dealt with in more detail below.

Cytogenetic analyses are frequently performed in centers for medical genetics. Although this is often mainly for historical reasons – the centers having evolved from cytogenetic laboratories – this organizational link has proved useful. The checking of the indications for these expensive analyses by medically and cytogenetically competent supervisors diminishes the number of unnecessary tests and furthers the correct interpretation of the results as well as the follow-up of carrier families. In addition, the routine work profits from research-oriented centers where rarely used cytogenetic techniques are readily available.

The present-day work load of medical genetics centers can be illustrated by some figures from our institute. This unit – first in the Children's Hospital, later independent – has been involved in service functions for over 15 years and has a population base of about two million people in eastern Switzerland. The routine work is shared by three MD-geneticists each of whom devotes about half of his working time to it. Eight technicians are employed, mostly in cytogenetics.

The number of *counselling sessions* involving extended interviews has remained fairly constant over the last few years at around 500 a year. Qualitatively, there has been a shift to – genetically speaking – more interesting cases; interviews just providing general information about prenatal diagnosis have become rare since this has been taken over by obstetricians or is done with printed fact sheets. In addition, a similar number of telephone calls has to be answered from physicians asking for advice. The extent to which counselling visits take place in hospital wards largely depends on the presence of specialists among the staff; for example, dysmorphologists, are often called by pediatricians and neonatologists.

Despite the sinking birthrate we still notice a slow increase in the number of *karyotype studies* of patients and their relatives; in 1983 our institute dealt with 720 cases. More effort is now being devoted to the thorough diagnostic evaluation of cases of developmental or mental retardation. New cytogenetic discoveries such as the fragile X in sex-linked mental retardation play a role in the increase in the number of tests as well.

Also on the rise are karyotype studies in couples with repeated abortions. The usefulness of these studies is still a matter of debate; the percentage of couples in whom the abortions can be attributed to a balanced structural aberration is of the order of 5%. A positive finding means that 50% of future fetuses ought to be viable and normal. Only exceptionally is a result found indicating that *all* future pregnancies would also end in abortions. In modern societies increasingly fewer couples want to have children at all, but those who do are very concerned if they are faced by problems of infertility or repeated abortions.

The highest growth rate is still observed in the demand for *prenatal diagnosis,* with over 90% motivated by the problem of trisomy 21. Prenatal tests are recommended and financially supported by our unit for mothers 35 years and older and for couples with a specific risk for which a method of detection is available. For younger women the tests are also available on request; in such cases the costs for amniocentesis and laboratory work must be borne by the patients. The number of tests has consistently risen from 100 in 1974, to 300 (1977), 800 (1979), 1400 (1981) and 1700 in 1983. Details of the results in Zürich were recently presented by the author[15]. Obviously, the public acceptance of this type of preventive medicine is unusually high and this holds true for most regions of Switzerland[9]. The relevant figures show that roughly 42% of pregnant women of the age of 35

Table 1. Prenatal diagnosis in Swizerland, 1971–1983 (laboratories in Basel, Berne, Geneva, Lausanne, Locarno and Zurich, references guoted in text). In practically all cases, irrespective of indication, karyotype and AFP were determined. Pathological findings only comprise clinically severe defects, leading, with few exceptions, to termination of pregnancy. (NTD = neural tube defects, MMC = myelomeningocele)

Indications	Tests n	%	Pathological findings n	%	Details of particular interest
a) Age 35 years or older	12485	62.8	252	2.0	241 Chromosome aberrations; 125 trisomies 21; 30 trisomies 18; 11 trisomies 13; 51 sex chromosome anomalies of which 27 XXY; 7 NTD
b) De novo chromosome aberration in previous child (mostly trisomy 21)	724	3.7	12	1.7	5 Trisomies 21 2 NTD
c) Chromosome aberration in a parent (mostly translocations)	110	0.5	5	4.5	3 Unbalanced translocations
d) Metabolic diseases (parents heterozygous for a.r. disease, as a rule)	83	0.4	18	21.7	
e) X-chromosomal recessive disease (mother heterozygous for Duchenne or hemophilia	80	0.4	25	31.2	
f) Neural tube defects (usually in previous pregnancy)	431	2.2	9	2.0	5 NTD 4 Chromosome anomalies
g) 'Obstetrical' indications (fetal pathology, usually after 20 weeks of pregnancy)	483	2.4	77	15.9	26 Chromosome anomalies; 25 anencephali; 6 MMC
h) Other. Usually wish of women below 35 years of age	5225	26.3	26	0.5	7 Trisomies 21; 6 sex chromosome anomalies; 2 NTD
i) Elevated serum AFP in pregnant women	251	1.3	30	11.9	8 MMC; 6 anencephali; 7 chromosome anomalies (2 trisomies 18; 2 triploids)
Total		19872	100.0	454	2.3

and older make use of amniocentesis. It appears that in our country almost all women of that age group are informed about the increased risk of Down's syndrome and the possibility of its prevention. In my opinion two factors have been important in achieving this success; information from the press and television across European borders, and the high degree of reliability of the services offered.

By presenting table 1 I do not intend to delve deeply into the – mostly well-known – details of current prenatal diagnosis. This table, dealing with almost 20,000 amniotic fluid tests carried out in Switzerland from 1971 to 1983 may serve mainly to convey a realistic picture of proportions and priorities. These figures are a compilation of data published in the 'Informationsblatt' of the Swiss Society of Medical Genetics, for the periods 1971–1980[10] and 1981–1983[9]. The figures speak largely for themselves and need few comments. Important is a comparison of the figures in lines a) and b): 12,500 karyotype studies in the advanced maternal age group resulted in the prevention of 125 trisomies 21, whereas 5200 studies in women below 35 years (most of them between 32 and 34 years) prevented 7 trisomies 21 only. An extension of karyotype studies to women below 35 years - at *public* cost – clearly does not deserve to be given high priority. The incidence of indication d), metabolic diseases, has seen practically no rise from the early 1970s up to 1983. Indication g), 'obstetrical reasons' has decreased somewhat in importance owing to progress in ultrasound diagnosis of fetal malformations.

Prenatal diagnosis by ultrasound

Technical progress with the equipment, combined with the growing experience of specialized obstetricians, has led to great success in the early recognition of fetal structural defects. Before 20 weeks of pregnancy it has become possible to visualize the length and functioning of the extremities quite accurately. For example humero-radial synostosis was used as a diagnostic criterion in the prenatal diagnosis of a case of Antley-Bixler syndrome in this institute by Savoldelli and Schinzel[12]. In a case at risk for Jeune syndrome an affected fetus was recognized by measurements of the thorax as published by Schinzel et al.[14]. Cleft lip and palate is another example of a diagnosable malformation, as reported by Savoldelli et al.[13].

Table 2 provides a list of structures and defects which are amenable to ultrasound diagnosis. The method is most useful with a range of severe malformations of multifactorial origin but it is also of help in cases of monogenic diseases provided there are morphological symptoms to look for.

2. Impending developments

The near future of applied medical genetics will be dominated by the challenges posed by DNA technology in presymptomatic and prenatal diagnosis. Certainly the next two decades are going to be a demanding and exciting period for medical genetics.

The situation is comparable with, but considerably more complex than that a dozen years ago when prenatal chromosome analyses had to be made available to the public, and laboratories had to be equipped and staffed and new

Table 2. List of fetal defects and organ systems commonly investigated by ultrasound between 14 and 24 weeks of pregnancy

- Anencephaly, hydrocephaly, microcephaly
- Spina bifida (open or closed defects; vertebral column can best be judged between 16 and 22 weeks of pregnancy)
- Kidneys, ureters, bladder, genitalia (functionally related: amount of amniotic fluid, dilatation of ducts)
- Extremities: Absence of parts, polydactyly, syndactyly, synostoses (humerus, ulna, radius), dysproportionate dwarfism, osteogenesis imperfecta congenita
- Esophageal occlusion, duodenal atresia
- Facial clefts
- Omphaloceles, gastroschisis, teratomas, hydrops fetalis

positions created. There are good reasons to anticipate that, in the long run, no other institutions will be willing or able to carry out the new routine tasks; manufacture and sale of DNA probes and diagnostic kits is one thing, but their application in clinical cases and families is another one. Almost all the monogenic defects we are dealing with are, individually, very rare and there are many hundreds of them. Furthermore, this kind of service requires a great deal of clinical knowledge as well as experience in genetic counselling.

At first sight the situation may appear similar to the one we met with prenatal diagnosis of rare metabolic diseases. The biochemical assays and micro-assays used in the diagnosis of these disorders are usually difficult and require experience with a greater number of cases, therefore, from the early seventies on, a limited number of laboratories have become specialists in prenatal diagnosis of a small number or even single metabolic defects[5]. Amniotic fluid or cultivated cells are shipped from far away to these laboratories; in this field we have been relying and will continue to rely on international cooperation. Each metabolic disease diagnosed from enzymes or other gene products requires its own set of assays. However, this is no longer so if DNA is analyzed; here, a limited number of methods is, in principle, applicable to all mapped monogenic diseases and to the different families in which the disease occurs. There will be a lot of the same type of work and it appears inevitable that a greater number of medical genetics centers will have to share this task. In those centers a close collaboration between medical geneticists and experts in the application of DNA technology needs to be built up.

The past few years have witnessed a surprisingly fast development in the application of the new techniques for important diagnostic problems. Restriction fragment length polymorphisms (RFLPs) and the use of oligonucleotides in sequenced genes have amply proven their usefulness in diagnosis of Thalassemias and sickle cell disease[2,7]. One should, however, not overlook the exceptional positions held by these 'model' diseases; their high incidences in certain populations and the fact that the beta-globin gene was analyzed a considerable time ago. On the other hand, we have witnessed break-throughs in diseases where success seemed much less likely, for example in Huntington's chorea, where neither a gene product nor the mapping position of the gene were known[6].

For a number of important monogenic diseases, diagnostic procedures have been developed recently and may soon be ready for practical application. In particular I am thinking of socially significant diseases with a long and severe course: Steinert myotonic dystrophy, polycystic kidney disease, cystic fibrosis, Duchenne muscular dystrophy and the hemophilias.

As far as the several thousand rare and rarest monogenic defects are concerned one must consider the following points: 1) The number of mapped genes involved in these diseases is still small and progress in mapping takes time. In the catalogue by McKusick[8] the map named 'The morbid anatomy of the human genome' contains less than a hundred defects, and many assignments are still preliminary. The majority of the some 800 mapped human genes are loci for enzymes, serum constituents and DNA probes. 2) Better news is the following; once a gene is localized and a linked DNA probe is available we apparently do not have to fear a lack of restriction fragment length polymorphisms[3,11]. Inherited differences in base sequences have been demonstrated to occur in the population on the average every 100–300 base pairs. If we admit that a diagnostically useful DNA segment may be up to 5 centimorgans long this means that the piece may contain 5000 kb (a gene flanked by 2000–3000 kb of other DNA on both sides). This implies that a very high number of RFLPs is bound to be present in virtually every case. The tedious task will be to explore the individual polymorphisms that will be useful in a given family. 3) Genetic heterogeneity in many clinical entities will pose formidable problems. Heritable hearing defects may be quoted here; seemingly identical forms of congenital deafness or progressive forms of hearing loss are evidently caused by mutations in a great number of gene loci. Neuromuscular diseases are another example of a high degree of genetic heterogeneity.

In the light of the progress with DNA technologies *common multifactorial diseases* will continue to pose difficult problems in genetic counselling. At issue are mainly the following diseases: diabetes, epilepsies, schizophrenias and affective psychoses. It is not unlikely that in the future genes will be singled out which must be considered as major predisposing factors. Most of these – so far hypothetical – alleles will be found to be transmitted as dominant or codominant traits and, therefore, the number of potentially predisposed offspring will be high. From twin studies we know well enough that even in the presence of a completely identical genotype less than half of the predisposed individuals will actually manifest the disease at some time in their lives. Prenatal diagnosis becomes a very problematical choice if the empirical risk of developing a given disease is 5 or 10% but, for prevention, one would have to abort 25–50% of the fetuses.

A much more positive use of the genetic possibilities could be thought of if effective preventive therapies became available, in which case most affected families would welcome the possibility of identifying the carriers of predisposing genes preclinically. Without preventive therapy it would, however, make little sense to find out, for example, that a young child has a 20% rather than a 10% likelihood of later developing schizophrenia.

First trimester prenatal diagnosis by chorionic villi sampling

This promising development is dealt with in another chapter of this review[16]. There is little doubt that chorionic villi sampling will become the method of choice in prenatal DNA diagnosis. Collecting and cultivating the necessary amounts of amniotic fluid cells in the second trimester, together with the analytical processing, simply takes too much time. In these genetic high risk situations termination of pregnancy will usually be necessary in 25 or even 50% of the cases. Repeated terminations after 20 weeks of pregnancy are hardly acceptable for a mother and therefore, even if the risk of chorionic villi sampling should remain at a relatively high level, this would still be preferable to cell sampling by amniocentesis.

Somewhat less clear is the future role of this technique in prenatal cytogenetic studies. It may be that villi sampling combined with direct cytogenetic techniques (without cell cultivation) will become routine. Provided the obstetrical procedures become simpler and safer it is likely that prenatal karyotyping would spread to a much larger segment of pregnant women. We may end up with screening almost the entire population for chromosome aberrations. Only economic limitations would curb such a development.

3. Ethical issues

I agree with the statement of a study group[1] that hardly any other speciality requires as much ethical sensitivity as does medical genetics. Both a glance back in history and an imaginative look into the future tell us that we should give much thought to the sociological implications of what we do or intend to do.

The past few decades, with the advent of genetic screening and prenatal diagnosis, have confronted us with many new moral issues. On the whole, I believe that our professional community has mastered these problems quite well; where errors occurred they were usually corrected in due time. Fortunately, there is an almost worldwide agreement among medical geneticists that our services, designed to relieve human suffering from genetic disorders, must be limited to the offering of information to those who desire it in order to make their own medical or reproductive choices. We abhor any kind of coercion.

In the scientific press there has been no lack of contributions dealing with ethical issues. An extensive bibliography can be found, for example, in a recent paper on 'Ethics and trends in applied human genetics' by J.C. Fletcher[4]. Discussions in this field must continue and publications should be encouraged. When it comes to establishing detailed guidelines, however, we suddenly become aware of difficulties. Some of these have to do with the medical systems in different countries; it plays a role whether medicine is socialized or not and whether we are dealing with affluent or less affluent societies. A classical example is the problem of whether prenatal karyotyping should be available for young women on demand (or for 'maternal anxiety'). In a country like Switzerland this poses no major problem. Provided the woman is informed about the small magnitude of the genetic risk and also about the abortion risk of amniocentesis, she can have the test but has to pay for the costs, which, in relation to salaries here, are by no means prohibitive. In countries with bureaucratic socialized medicine such Salomonic solutions appear to be flatly impossible.

Another problem associated with too detailed guidelines is posed by fast moving technical developments. This may be illustrated by prenatal diagnosis in twin pregnancies. A few years ago most workers were inclined to keep their hands off these cases, and this attitude might well have been incorporated into a guideline. In the meantime it has become routine safely to puncture the two sacs, and if one twin is abnormal, selective feticide has become a common practice giving a fair chance of undisturbed development to the normal twin.

The more guidelines try to cope with details, the more the experienced counsellor will find exceptions to the rules, whether these concern conventional counselling, prenatal diagnosis or screening. Nevertheless, personally I support the idea that guidelines should be drafted and discussed periodically by bodies of medical geneticists.

Some of the most actively discussed issues in reproductive biology, such as test tube babies, embryo transfer and problems with AID (artificial insemination by donor) are only of borderline concern to the medical geneticist, though he should, of course, be free to express his personal opinions. The positions of 'keeping one's hands off these things' often seems to be attractive but may, however, not be wise. Since these practices will go on with or without our approval, it is better to maintain a flexible approach. By not withholding our services, where it makes sense to use them, we remain in a position to avert unnecessary harm and keep the door open for dialogue with our fellow scientists.

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