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Cases of a Genetic Counselling Clinic

By

A. Czeizel, Julia Métneki, Magda Osztovics

Department of Human Genetics, National Institute of Hygiene, Budapest

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The 1973—1978 material of the Genetic Counselling Clinic, National Institute of Hygiene in Budapest 1973—1978 consists of 3778 counselees. Based on the disorders of probands, 15 nosological categories are differentiated. The theoretical expectations based on the occurrence of monolocal, chromosomal and multifactorial disorders were compared with the observed experience. Obviously, the occurrence of abnormality is not what primarily motivates the consultation; the severity (mainly the lethality), early manifestation (e.g. of congenital abnormalities) and the preventive programs are more important factors in seeking genetic counselling.

The 1973—1978 material of the Genetic Counselling Clinic, National Institute of Hygiene in Budapest 1973—1978 consists of 3778 cases and/or families. This number represents the first presentations, i.e. the first contacts. Counselling averaged 1.8 meetings for every case, not including the patients who came for examination [5]. In addition, especially if a child was brought to the counselling, both parents and occasionally the grandmother, too, appeared at the Clinic. In such cases only one person, in general the consultand, was registered as counselee. If an abnormality is diagnosed in the proband (e.g. a structural chromosomal aberration, recessive anomaly, Huntington chorea, etc.), several family members are examined. All these are taken as one case, unless other relatives have come independently to consult the Clinic.

The present paper has three objectives. (i) To demonstrate the clinical-nosological distribution of our material which to our best knowledge is the largest one hitherto reported and may besides reveal some Hungarian peculiarities (ii) At present, no uniform recommendations are available for the grouping and classification of the counselees in genetic counselling clinics. Our system might thus serve as a tentative recommendation. (iii) The prevalence of individual abnormalities within the population, their participation in the material, and a comparison of the two features may throw light on the motives of seeking advice.

Clinical-nosological distribution of the cases

Literary reports on genetic counselling almost invariably discuss the motivation for consultation. If these data are compared to the distribution of the clinical-nosological aetiology of

TABLE I

Distribution of nosological categories in the material of the Genetic Counselling Clinic, 1973—1978

Nosological categories	Abbreviation	1973	1974	1975	1976	1977	1978	Together	
								No.	per cent
Genetic									
Mendelian (monolocal) conditions	Mo	9	25	130	113	137	168	582	15.4
Chromosomal aberrations	Kr	5	21	41	52	58	77	254	6.7
Multifactorial-congenital abnormalities	Mt-CA	3	46	96	88	95	145	473	12.5
Multifactorial-common diseases	Mt-D	0	12	33	37	25	47	154	4.1
Mutagenic noxae	Mut	0	2	11	11	10	25	59	1.6
Consanguinity	Cons	1	0	10	10	12	11	44	1.2
Together No.		18	106	321	311	337	473	1566	—
%		33.3	33.3	48.1	39.9	40.4	42.1	—	41.5
Exogenic									
Congenital abnormalities caused by teratogenic and maternal noxae	CA-Ex	3	5	13	37	20	24	102	2.7
Exogenic noxae during pregnancy	Ter	2	26	34	61	63	80	266	7.0
Together No.		5	31	47	98	83	104	368	—
%		9.3	9.8	7.0	12.5	10.0	9.2	—	9.7
Only clinical diagnoses									
Sterility	St	7	68	87	159	186	253	760	20.1
Fetal death	Fd	16	34	116	96	103	133	498	13.2
Infant death	Im	2	35	31	37	35	37	177	4.7
Defects (mental subnormality etc.)	Def	2	8	13	20	26	35	104	2.7
Congenital abnormalities of unknown origin	CA-?	4	31	29	31	21	47	163	4.3
Diseases (non-genetic)	No-gen	0	4	13	11	22	28	78	2.1
General informations	Inf	0	1	11	17	21	14	64	1.7
Together No.		31	181	300	371	414	547	1844	—
%		57.4	56.9	44.9	47.5	49.6	48.7	—	48.8
Total		54	318	668	780	834	1124	3778	100.0

our probands (Table I), striking differences can be observed. The initiative for consultation does not come from scientific literature but is based on personal problems. In this way, the category with the highest participation in our material is infertility, a complaint usually neglected in the literature. Noxae during pregnancy and fetal death also form a considerable proportion of the cases. Exogenous noxae (e.g. perinatal hypoxia) are primarily in the background of early neonatal deaths and developmental defects. Therefore, the genetic counselling clinics are rather "qualitative family planning counsellings", since their work can by no means be limited to entirely or partly defined genetic disorders. This fact involves two practical considerations. On the one hand, the physician working at a genetic counselling clinic has to adopt a wide professional view. Clinicians specialised in a certain field are often reluctant in this respect, since e.g. the paediatrician does not feel inclined to deal with problems of infertility, the gynaecologist feels helpless when confronted with cases of congenital muscular dystrophy, etc. Therefore, the international organizations advise to employ full-time medical-geneticists at the genetic counselling clinics. It is only natural that this concept requires a background with appropriate consultant clinicians and laboratories.

It has to be endeavoured that only such persons should call at the counselling clinics who can receive there efficient help. This is not what usually happens, as most of the cases present because of infertility or sexual problems. In addition, many infertile couples come to counselling without having had proper examinations (e.g. sperm tests, examination for oviduct patency). It is not the aim of the genetic counselling clinics to perform the duties of other specialities.

Interpretation of the diagnosis of the proband often raises problems. Efficient counselling can only be provided if the nosological diagnosis, the aetiology of the condition is known. Most of the probands referred to a genetic counselling clinic present with a clinical-symptomatic diagnosis. For this reason, the diagnosis had to be revised or the nosological diagnosis established in 22.8% of our material [5]. In the background of symptomatic diagnoses such as infertility or multiple congenital abnormality, clinical and laboratory examinations revealed nosological entities, e.g. the infertility was due to Klinefelter disease, the multiple abnormality proved to be autosomal recessive Meckel-Gruber syndrome, or a Becker-type of X-linked muscular dystrophy was identified.

Based on the disorders of our probands, 15 nosological categories are differentiated (Table I).

The first category includes disorders entirely or partly of genetic origin.

(1) Within the abnormalities localised to a single locus (henceforth *monolocal)*, i.e. the mendelian abnormalities, three main modes of inheritance give the possibility of subdivision. (Monolocal abnormalities were for-

TABLE II

Number of probands of autosomal dominant phenotypes in the material of the Genetic Counselling Clinic, 1973—1978

No. of entry	Phenotype	No. of cases
10010	Prune belly (absence of abdominal muscles)	1
*10080	Achondroplasia	8
*10120	Apert syndrome	3
*10540	Amyotrophic lateral sclerosis	1
*10620	Aniridia	2
*10920	Baldness (female)	1
*10940	Basal cell naevus syndrome	1
*11030	ABO blood-group incompatibility	13
*11170	Rh incompatibility	53
*11250	Brachydactyly, type A/1	1
11370	Absence of breast and nipples	2
*11420	Camptodactyly	1
11455	Hepatocellular cancer	1
*11570—11680	Cataract	7
*11730	Acute intermittent familial cerebellar ataxia	1
*11960	Cleidocranial dysplasia	2
*12020—12030	Coloboma	1
*12350	Crouzon craniofacial dysostosis	2
*12470—12490	Deafness	2
*12990	EEC syndrome	1
*13000	Ehlers-Danlos syndrome	2
*13370	Multiple exostoses	5
14080	Hereditary haemangioma	3
*14160	Haemachromatosis	2
*14290	Holt-Oram syndrome	7
*14310	Huntington chorea	5
*14350	Hyperbilirubinaemia I (Gilbert disease)	1
*14540	Hypertelorism (Greig syndrome)	2
*14570	Universal hypertrichosis	8
*14670	Ichthyosis vulgaris	3
14830	Keratoconus	1
14880	Kleeblattschädel (cloverleaf skull) syndrome	3
14890	Klipper-Feil syndrome	3
14900	Klippel-Trenaunay-Weber syndrome	1
*15025	Larsen syndrome	2
*15310	Lymphoedema hereditaria I (Nonne-Milroy syndrome)	1
15440	Mandibulofacial dysostosis (Treacher-Collins)	3
*15470	Marfan syndrome	4
15560	Malignant melanoma	2
*15590	Melkersson syndrome	1
*15685	Microphthalmia-cataract syndrome	1
15700	Microphthalmos anterior (microcornea)	1
*15860—15900	Muscular atrophy-dystrophy	7
*15960	Myoclonic epilepsy, Hartung type	1
16190	Familial nephritis	1
*16220	Neurofibromatosis	6
*16300	Naevi flammei, familial, multiple	1
*16310	Nevus flammeus on the nape of the neck	6
*16350	Hemeralopia	1
*16395	Noonan syndrome	1
*16415	Hereditary vertical nystagmus	2
*16540	Congenital optic atrophy	1
*16620	Osteogenesis imperfecta	8
*16660	Osteopetrosis	1
		1

TABLE II (cont.)

No. of entry	Phenotype	No. of cases
16680	Otosclerosis	1
*16830	Paramyotonia congenita of Eulenburg	1
16930	Pectus excavatum	1
*17270	Pick disease of brain	1
*17310	Pituitary dwarfism	1
17380	Poland syndrome	1
*17390	Polycystic kidneys, adult type	5
*17420	Postaxial polydactyly	2
17480	Polyostotic fibrous dysplasia	1
*17510	Intestinal polyposis, type I	2
*17530	Intestinal polyposis, type III	1
*17600	Porphyria, acute, intermittent (Swedish type)	1
17900	Purpura simplex	1
*17980	Renal tubular acidosis I	1
*18002	Retinal cone degeneration	3
*18010	Retinitis pigmentosa	1
*18020	Retinoblastoma	8
18145	Schinzel syndrome	1
*18160	Sclerotylosis	1
*18260	Spastic paraplegia	4
*18360	Split-hand deformity	7
*18390	Spondyloepiphyseal dysplasia, congenital type	1
18420	Spondylolisthesis and spina bifida occulta	1
18430	Spondylosis, cervical	1
18530	Sturge-Weber syndrome	3
18540	Subglottic bar	1
*18550	Supravalvar aortic stenosis	1
*18580	Symphalangism, proximal	1
*18590	Syndactyly, type I (zygodactyly)	2
*18610	Syndactyly, type III	2
*18640	Synostoses	1
*18730	Teleangiectasia, hereditary, haemorrhagic	1
*18800	Thrombocytopaenia	2
*19030	Tremor, hereditary, essential	1
*19110	Tuberous sclerosis	2
*19155	Ureter, bifid or double	3
*19260	Ventricular hypertrophy, hereditary	1
19320	Vitiligo	2
*19340	von Willebrand disease	7
*19350	Waardenburg syndrome	1
Total		280

merly called monogenic. Recessive disorders, however, develop under the effect of two genes and, in addition, gene (allele) series may become attached to the individual loci, therefore the denomination of monolocal abnormality seems more precise and appropriate.) Earlier we grouped the monolocal disorders in categories of congenital abnormalities (CAs) and diseases [2]. This grouping, however, involved difficulties, because in a number of cases it could not be decided where to classify e.g. galactosaemia or Werdnig-Hoffmann disease. Nowadays the mendelian monolocal

TABLE III

Number of probands of autosomal recessive phenotypes in the material of the Genetic Counselling Clinic, 1973—1978

No. of entry	Phenotype	No. of cases
*20060—20061	Achondrogenesis type I and IB	4
*20171—20211	Adrenal hyperplasia	10
*20250	Agammaglobulinaemia (Swiss or alymphocytotic type)	1
*20310—20320	Albinism	2
*20400—20410	Amaurosis congenita of Leber I or II	1
20570	Anaemia, autoimmune, haemolytic	2
20710	Anotia and meatal atresia	1
*20853	Ivemark syndrome	4
*21000	Behr syndrome	1
*21090	Bloom syndrome	2
*21250	Cataract, congenital or juvenile	5
21255	Cataract, microphthalmia, and nystagmus	2
21290	Cerebellar ataxia (Norrie-Marie)	1
21560	Cirrhosis, familial	4
21680	Coloboma of macula and skeletal anomalies	1
21790	Cornelia de Lange syndrome	2
*21870	Athyroitic cretinism	12
*21900	Cryptophthalmos with other malformations	2
*21970	Mucoviscidosis (cystic fibrosis)	28
*22070—22080	Deafness	15
*22260	Diastrophic dwarfism	1
*22490	Ectodermal dysplasia, anhidrotic	1
*22650—22670	Epidermolysis bullosa	5
*22720	Eunochoidism, familial, hypogonadotrophic	1
22820	FFU-femur-fibula-ulna syndrome	1
*22930	Friedreich ataxia	1
*23040	Galactosaemia	10
*23130	Buphthalmos	5
*23200	Glycinaemia	1
*23220	Von Gierke disease (Glycogen storage disease I)	1
23410	Hallermann-Streiff syndrome	1
23500	Haemihypertrophy	2
*24020	Hypoadrenocorticism, familial	1
*24050	Hypogammaglobulinaemia	5
24155	Hypoplastic left heart syndrome	5
*24210	Ichthyosiform erythroderma, Brocq, congenital	1
*24220	Ichthyosiform erythroderma (Sezary)	1
*24230	Ichthyosis congenita	1
*24440	Kartagener sydrome	2
*24520	Krabbe disease	1
*24820	Macular degeneration, juvenile (Stargardt syndrome)	2
*24880	Marinesco-Sjögren syndrome	1
*24900	Meckel-Gruber syndrome	4
*25020	Metachromatic leukodystrophy, juvenile	1
*25120	Microcephaly	9
25150	Microphthalmia and mental deficiency	1
*25160	Microphthalmos	4
*25210	Mohr syndrome (OFD II)	2
*25280—25322	Mucopolysaccharidosis I—VII	2
*25330	Werdnig-Hoffmann disease	26
*25360—25370	Muscular dystrophy I—II	4
25550	Myopia, infantile, severe	3
*25600	Leigh disease	1
*25630	Nephrosis, congenital	3

TABLE III (cont.)

No. of entry	Phenotype	No. of cases
25670	Neuroblastoma	3
*25727	Hemeralopia	1
25770	Goldenhar syndrome (oculo-auriculo-vertebral dysplasia)	1
*25940	Osteogenesis imperfecta (Vrolik type)	1
*25970	Osteopetrosis (Albers-Schönberg disease)	2
*26160	Phenylketonuria	7
*26320	Polycystic kidney	8
26400	Prader-Willi syndrome	1
26410	Progeria	1
*26428	Pseudohermaphroditism, male, internal	3
*26460	Pseudovaginal perineoscrotal hypospadias	1
*26470	Vitamin-D-dependent rickets	1
*26800	Retinitis pigmentosa	1
*26830	Roberts syndrome	5
26860	Rubinstein syndrome	1
26970	Seip syndrome (lipodystrophy)	1
*27040	Smith-Lemli-Opitz syndrome	1
*27060	Spastic diplegia, infantile type	4
*27390	Thrombocytopaenia	1
*27400	TAR-Thrombocytopaenia with absent radius	1
27530	Tracheobronchomegaly	1
*27700	Rokitansky-Küster-Hauser syndrome	1
27780	Wilms tumour	2
*27790	Wilson disease	1
new (?)	Cardiodigital recessive syndrome	1
Total		261

* The clinical diagnosis does not necesserily prove an identical nosological origin.

TABLE IV

Number of probands of X-linked phenotypes in the material of the Genetic Counselling Clinic, 1973—1978

No. of entry	Phenotype	No. of cases
*30100	Aldrich syndrome	1
*30130	Anaemia, hypochromic	1
*30360	Coffin-Lowry syndrome	1
*30510	Ectodermal dysplasia, anhidrotic	3
30570	del Castillo syndrome	4
*30640	Granulomatous disease due to leukocyte malfunction	1
*30670	Haemophilia A	7
*30690	Haemophilia B	1
*30700	X-linked hydrocephalus	3
30890	Leber optic atrophy	1
*30950	Renpenning type mental deficiency	6
*31020	Duchenne type muscular dystrophy	8
*31060	Norrie disease (pseudoglioma)	1
31210	Pseudohermaphroditism, incomplete (male type I)	1
31290	Spastic paraplegia	1
31350	Partial anodontia	1
	Total	41

TABLE V

Number and percentage of probands with chromosomal aberrations in the material of the Genetic Counselling Clinic, 1973—1978. Birth prevalence of the different types of chromosomal aberrations (a) and syndromes (s) and their participation in the chromosomal aberrations

Type of chromosomal aberration	Genetic Counselling Clinic		Birth prevalence		Estimated number per year in Hungary (yearly 180.000 births estimate)
	No.	per cent	per 1000 total births	per cent	
Down s	153	60.2	1.1—1.2	21.3—15.5	200—215
Other autosomal numerical a*	4	1.6	0.2—0.3	3.9—3.8	35—55
Unbalanced autosomal structural a**	20	7.9	0.2—0.3	3.9—3.8	35—55
Balanced autosomal structural a***	34	13.4	1.6—2.1	30.9—26.9	290—370
XO s	24	9.4	0.07—0.1	1.4—1.3	15—20
XXX s	2	0.8	0.4—0.9	7.7—11.5	70—160
XXY s	13	5.1	0.7—1.1	13.5—14.1	125—200
XYY s	1	0.4	0.8—1.6	15.5—20.5	140—290
Other gonosomal a****	3	1.2	0.1—0.2	1.9—2.6	20—35
Total	254	100.0	5.17—7.8	100.0—100.0	930—1400

* 1 Patau s, 1 monosomy 15 mosaicism, 1 trisomy 8 mosaicism, 1 tertiary trisomy

** 6 5p-, 4 marker chromosomes, 2 4p-, 2 10p-, 1 6p+, 1 8q+, 1 12p-, 1 r(14), 1 18p-, 1 18q+

*** 15 inversions, 12 D/D centric fusions, 1 G/G centric fusion, 6 reciprocal translocations.

**** 1 inversion (Y), 1 XXYY, 1 t (X-Y)

TABLE VI

Number and percentage of isolated congenital abnormalities in the material of the Genetic Counselling Clinic, 1973—1978. Aetiology evaluated by the multifactorial threshold model. Birth prevalence of the different types and their participation in the 10 abnormalities

Congenital abnormality	Genetic Counselling Clinic		Birth prevalence for 1000 total births	
	No.	per mil	per mil	per cent
Anencephaly — spina bifida cystica	241	51.0	2.5	3.8
Cleft lip ± palate	90	19.0	1.0	1.5
Congenital infantile hypertrophic pyloric stenosis	1	0.2	1.5	2.3
Congenital cardiovascular malformations (isolated and complex)*	74	15.7	8.0	12.2
Congenital structural talipes equinovarus	12	2.6	1.3	2.0
Congenital dislocation of the hip	11	2.3	28.0	42.6
Congenital inguinal hernia	1	0.2	11.0	16.7
Hypospadias	11	2.3	4.4**	6.7
Undescended testicles	29	6.1	8.0**	12.2
Megacolon cong. Hirschprung	3	0.6	0.02	0.0
Together	473	100.0	65.72	100.0

*— Distribution of congenital cardiovascular malformations: ventricular septal defect, 14; transposition of great vessels, 8; atrial septal defect, 4; coarctation of aorta, 3; Fallot tetrad, 2; pulmonary stenosis, truncus communis, stenosis of aorta, Epstein, Eisenmenger, valvular, 1 each; complex, 19; unknown, 18.

** only in males

TABLE VII

Number and percentage of common diseases in the material of the Genetic Counselling Clinic, 1973—1978. Presumable aetiology evaluated by the multifactorial threshold model. Estimated prevalence and participation in these diseases

Common disease	Estimated prevalence per 1000 persons		Genetic Counselling Clinic	
	per mil	per cent	No.	per cent
Schizophrenia	10.0	6.6	50	34.2
Uni- and bipolar depression	20.0	13.3	9	6.2
Convulsions	10.0	6.6	42	28.8
Diabetes mellitus	20.0	13.3	24	16.4
Early onset acute myocardial infarction	10.0	6.6	0	0.0
Asthma bronchiale	20.0	13.2	8	5.5
Scoliosis, adolescent	5.0	3.3	4	2.7
Rheumatoid arthritis	25.0	16.6	2	1.4
Psoriasis	10.0	6.6	7	4.8
Familial (subcultural) mental subnormality	21.0	13.9	0	0.0
Together	151.0	100.0	146	100.0
Nephrolithiasis	(4.0)		1	
Myopia			3	
Lupus erythematodes			2	
Gout			1	
Bechterew disease	(2.0)		1	
Grand total			154	

TABLE VIII

Number and percentage of persons consulting the Genetic Counselling Clinic in 1973—1978, because of presumable mutagenic noxae

Group	No.	per cent
Radiotherapy (mainly cancer patients)	21	35.6
Radiologists	7	11.9
Severe chemical intoxication including alcohol	8	13.6
Dangerous occupational exposure to chemicals	2	3.3
Maternal age over 38 years	21	35.6
Total	59	100.0

disorders are usually grouped according to the classification of McKusick [7]. We too adhere to this practice. Tables II, III and IV show the classification entries.

Unfortunately, McKusick's classification is not without problems either, when dealing with diseases the heredity of which has not been proven. Some reports treat multiple sclerosis, anencephaly and other diseases, certainly not belonging in this category, as of monolocal heredity. It would be misleading to classify these abnormalities among the monolocal ones and thus defining them as unequivocally genetically determined disorders. Therefore, we listed as monolocal disorders only those accepted as proven (marked with asterisks) when relying on McKusick's entries. Of the doubtful abnormalities only those were included in the category where new literary data supported their correct classification.

(2) The category of *chromosomal aberrations* includes cases verified by karyotyping (Table V). Thus, no diagnostic uncertainties can arise here. Only healthy persons carrying recognized, balanced chromosomal aberrations present some problems. We believe they cannot be regarded as probands, because then also the carriers of recessive and X-linked mutant genes should be evaluated similarly and in this way all persons would become probands. Therefore, only the patient defined so by the counselee should be accepted as proband but when estimating the risk factor chromosomal translocations have also to be taken into consideration.

The disorders of multifactorial origin are divided into two categories because such CAs and diseases can easily be differentiated.

(3) The 9 common isolated CAs and some others of established polygenic liability with environmental triggering

TABLE IX

Number and percentage of consultands for consanguinity in the material of the Genetic Counselling Clinic, 1973—1978

Type	Persons	
	No.	per cent
Half-sib	2	4·5
Cousin	11	25.0
Second-cousin	14	31.8
Between second and third cousin	1	2.3
Third cousin	2	4.6
Total	30	68.2
Consanguinity not between the consultands	14	31.8
Grand total	44	100.0

TABLE X

Number and percentage of congenital abnormalities presumably caused by environmental noxae and diagnosed retrospectively, in the material of the Genetic Counselling Clinic, 1973—1978

Type	Diagnostic criteria	Cases	
		No.	per cent
Microbial			
Congenital rubella syndrome	Anomalies of the eye and heart, deafness; seroconversion of rubella virus, specific IgM	8	
Fetopathy caused by cytomegalovirus	Clinical features (mainly microcephaly) and characteristic retrospective serological findings	8	
Perinatal damage caused by herpes simplex virus type 2	Genital herpes virus infection of the pregnant and characteristic clinical manifestations in the newborn	1	
Connatal toxoplasmosis	Characteristic clinical manifestations in the newborn and positive retrospective serological findings	14	
Total		31	30.4
Chemical			
Alcohol addiction	Mother alcohol addict and signs of fetal alcohol syndrome	2	
Hydantoin drugs	Mother suffering from convulsions and signs of fetal hydantoin syndrome	2	
Streptomycin	Streptomycin therapy in the 7th—8th months of pregnancy and deafness of the baby	2	
Synthetic oestrogens	Fetal masculinization syndrome in female newborn	1	
Total		7	6.9
Maternal			
Endocrine dysfunction	Pill use immediately before conception or abortion attempt with oestrogens in females who previously had had irregular cycles and/or sterility problems and VACTERL or transverse limb reduction in the newborn	45	
Early amniotic rupture and amnionitis	Ring constriction	11	
Intrauterine mechanical effect	Postural deformities after breech presentation	8	
Total		64	62.7
Grand total		102	100.0

TABLE XI

Number of women seeking genetic counsel for teratogenic or maternal noxae during pregnancy

Type	No.	Diagnosis based on	Termination of pregnancy		Induced abortion
			indicated	not indicated	
Microbial					
Cytomegalovirus	3	3 serological finding (accidental)	1	2	2
Influenza	15	15 histories	0	15	1
Hepatitis	1	1 clinical signs	0	1	0
Herpes simplex virus type 2	4	4 clinical signs	0	4*	1
Herpes simplex virus type 1	10	10 clinical signs	0	10	0
Syphilis	1	0 serological finding	0	1	0
Mumps	7	6 serological finding	0	7	3
Rubella	66	7 serological finding (recent infection)	7	59	9
Toxoplasma infection	9	9 serological finding (accidental)	4	5	4
Chickenpox	2	1 serological finding	1	1	1
Total	118	44.4%	13	105	21
Physical					
Diagnostic radiological examination	44	44 histories	2	42	4
IUD	5	5 clinical signs	0	5	1
Psychic trauma	1	1 history	0	1	0
Radiation therapy (cancer)	4	4 histories	4	0	4
Physical trauma	3	3 histories	0	3	0
Total	57	21.4%	6	51	9
Chemical					
Alcohol addiction	4	4 histories	1***	3	1
Contraceptive pills	27	27 histories	0	27	0
Drugs (116 types)	39	39 histories	2**	37	2
Occupational exposure to chemicals	6	6 histories	0	6	0
Total	76	28.6%	3	73	3
Maternal					
Dermatological diseases	2	2 histories	0	2	0
Diabetes mellitus	5	5 histories	2	3	2
Hypo- or hyperthyroidism	3	3 histories	2	1	2
Cardiac diseases	2	2 histories	0	2	1
Renal diseases	3	3 histories	3	0	3
Total	15	5.6%	7	8	8
Grand total	266	100.0%	29	8	41

* Caesarean section indicated. ** Attempted suicide. *** Mother alcohol addict.

factors fall into the category of *multifactorial CA* (Table VI).

(4) *Multifactorial common diseases* are represented in our material only by a few types (Table VII). Their nosological homogeneity is questionable (e.g. schizophrenia, diabetes mellitus, early onset acute myocardial infarction) but in general they are treated as a uniform group.

(5) Persons who had supposedly or actually suffered *mutations* can be divided into 3 main groups (Table VIII). (i) Persons worried because of the health hazard of X-rays, isotope and ionizing radiation in general; (ii) those who had suffered intoxication by some chemical agent; and (iii) women worried of being too old to become mothers (above 38 years of age).

(6) Several family planners called at the clinic because of prospective or present *consanguinity* (Table IX).

TABLE XII

Number and percentage of consultands with sterility, in the material of the Genetic Counselling Clinic, 1973—1978. (Figures in brackets were already listed in the specific nosological categories mentioned earlier)

Sex	Type	Primary sterility		Secondary sterility		Total	
		No.	per cent	No.	per cent	No.	per cent
Male	Mendelian (e.g. del Castillo syndrome)	(8	—)	(0	—)	(8	—)
	Chromosomal (e.g. Klinefelter syndrome)	(11	—)	(0	—)	(11	—)
	Multifactorial abnormality (e.g. undescended testicles)	(19	—)	(0	—)	(19	—)
	Endocrine dysfunction	4	0.7	2	1.3	6	0.8
	Dysspermatogenesis	182	30.2	21	13.3	203	26.7
	Sexual disturbances	5	0.8	0	0.0	5	0.7
	Total	191	31.7	23	14.6	214	28.2
Female	Mendelian (e.g. Rokitansky-Kuster-Hauser syndrome)	(1	—)	(0	—)	(1	—)
	Chromosomal (e.g. Turner syndrome)	(11	—)	(0	—)	(11	—)
	Genital organs	25	4.1	3	1.9	28	3.7
	Occlusion of uterine tube	52	8.6	31	19.6	83	10.9
	Endocrine dysfunction (e.g. anovulation)	78	13.0	18	11.4	96	12.6
	Total	155	25.7	52	32.9	207	27.2
Both male and female		23	3.8	11	7.0	34	4.5
Unknown cause		149	24.8	39	24.6	188	24.7
Cases awaiting clarification		84	14.0	33	20.9	117	15.4
Grand total		602	100.0	158	100.0	760	100.0

TABLE XIII

Number and percentage of consultands with previous fetal death(s) in the material of the Genetic Counselling Clinic, 1973—1978. (Chromosomal aberrations in the parents were evaluated in the respective category)

Type	Miscarriage		Stillbirth		Habitual fetal death		Total	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Mendelian (e.g. lethal anomalies)	+	—	+	—	+	—	+	—
Chromosomal (e.g. structural aberrations)	+	—	+	—	32	7.2	32	—
Diseases of the mother (e.g. diabetes mellitus)	0	0.0	1	3.0	15	3.6	16	3.2
Anomaly of the womb (e.g. uterus bicornis)	10	19.2	0	0.0	44	10.6	54	10.8
Cervical incompetence	0	0.0	0	0.0	80	19.4	80	16.1
Endocrine dysfunction (e.g. corpus luteum insufficiency)	16	30.8	0	0.0	78	18.9	94	18.8
Toxaemia of pregnancy	0	0.0	6	18.2	4	1.0	10	2.0
Anomaly of placenta or of umbilical cord	0	0.0	4	12.1	0	0.0	4	0.8
Anomaly of the embryo or fetus (e.g. anencephaly)	3	5.8	+	—	1	0.2	4	0.8
Intrauterine infection (e.g. toxoplasmosis)	0	0.0	5	15.2	0	0.0	5	1.0
Immunological (e.g. mother-fetus Rh incompatibility)	0	0.0	2	6.1	4	1.0	6	1.2
Spermatological abnormality	0	0.0	0	0.0	28	6.8	28	5.6
Unknown	10	19.2	5	15.1	87	21.1	102	20.5
Awaiting clarification	13	25.0	10	30.3	72	17.4	95	19.2
Total	52	100.0	33	100.0	413	100.0	498	100.0

+ When diagnosed, it is evaluated in the congenital abnormality group

These are grouped according to the degree of relationship. The concern of most of the consultands was unfounded because consanguinity was not between the couples but among their forefathers.

Two categories are listed in the category of *exogenous noxae*.

(7) The category of *CAs* due to *environmental noxae* includes those family planners, where the CA of the progeny was most probably due to teratogenic or maternal noxae exerting their effect during pregnancy (Table X). In these living or dead children, the aetiological role of the specific exogenous effect was rendered likely retrospectively by the clinical manifestations or the laboratory findings. In such cases counselling is helpful just because assurance can be given that there is no or a low risk of recurrence.

(8) The category of *environmental noxae during pregnancy* includes those who sought advice because of a supposed or actual damage suffered during pregnancy (Table XI). Most of them worried unduly or had erroneous ideas, therefore in these cases no ter-

mination of pregnancy was suggested. In some instances, where the risk was considered more founded, if requested, interruption of pregnancy was indicated.

The *symptomatic diagnoses* form the next categories. The denomination is only partly correct, since a nosological diagnosis could be established in a considerable part of our cases. The probands with abnormalities of partly or entirely genetic origin were transferred into some of the "superior" categories. If the role of genetic factors was improbable, they remained in the symptomatic diagnoses category, because a genetic evaluation was not possible. Of the CAs, only those unknown aetiology really belong to this group, since in these cases the actual aetiological factor could not be revealed.

(9) Primary and secondary *sterility*, further affections of the male or the female genital tracts are differentiated in this category (Table XII).

TABLE XIV

Number and percentage of consultands with early death of previous liveborns in the material of the Genetic Counselling Clinic, 1973—1978. (The mendelian, chromosomal and multifactorial anomalies were evaluated in the respective categories)

Type	Early neonatal death (0—6 days)		Early death (infant death from 7th day of life)		Two or more infant and fetal deaths		Total	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Mendelian (e.g. lethal anomalies)	+		+		+		+	
Chromosomal (e.g. Patau s.)	+		+		+		+	
Multifactorial abnormalities (e.g. anencephaly)	+		+		+		+	
Other congenital abnormalities (e.g. multiple)	+		+		+		+	
Diseases of the mother (e.g. diabetes mellitus)	0	0.0	5	8.3	17	29.3	22	12.4
Uterine anomaly (e.g. myoma)	0	0.0	1	1.7	3	5.2	4	2.3
Cervical incompetence	0	0.0	2	3.3	3	5.2	5	2.8
Toxaemia of pregnancy	4	6.8	0	0.0	0	0.0	4	2.2
Anomaly of placenta or of umbilical cord	0	0.0	1	1.7	0	0.0	1	0.6
Perinatal hypoxia	18	30.5	11	18.3	6	10.3	35	19.8
Hyperbilirubinaemia (e.g. mother-fetus Rh incompatibility)	1	1.7	1	1.7	2	3.4	4	2.3
Infections	6	10.2	3	5.0	3	5.2	12	6.8
Respiratory distress syndrome	3	5.1	0	0.0	2	3.4	5	2.8
Sudden infant death	2	3.3	2	3.3	1	1.8	5	2.8
Newborns with birth-weight under 1500 g and no other obvious cause	8	13.6	3	5.0	0	0.0	11	6.2
Unknown	11	18.6	18	30.0	6	10.3	35	19.8
Awaiting clarification	6	10.2	13	21.7	15	25.9	34	19.2
Total	59	100.0	60	100.0	58	100.0	177	100.0

+ Evaluated in previous tables

TABLE XV

Number and percentage of consultands with handicapped children in the material of the Genetic Counselling Clinic, 1973—1978 (The mendelian, chromosomal and multifactorial anomalies were evaluated in the respective categories)

Type	Mental subnormality		Little disease		Deafness		Blindness		Speech defect		Total	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Mendelian (e.g. Renpenning s.)	+		+		+		+		+		+	
Chromosomal (e.g. Down s.)	+		+		+		+		+		+	
Multifactorial (e.g. spina bifida)	+		+		+		+		+		+	
Other congenital abnormalities	+		+		+		+		+		+	
Prenatal (unidentified)	4	5.3	0	0.0	1	16.7	1	20.0	0	0.0	6	5.8
Perinatal (e.g. hypoxia)	41	54.7	11	73.3	0	0.0	2	40.0	2	66.7	56	53.9
Postnatal	8	10.7	2	13.3	2	33.3	0	0.0	0	0.0	12	11.5
Unknown	12	16.0	1	6.7	1	16.7	2	40.0	1	33.3	17	16 3
Awaiting clarification	10	13.3	1	6.7	2	33.3	0	0.0	0	0.0	13	12.5
Total	75	100.0	15	100.0	6	100.0	5	100.0	3	100.0	104	100.0

+ Evaluated in previous Tables

(10) Within the category of *fetal death*, women reporting because of (i) one miscarriage or (ii) stillbirth and those who (iii) had two or more (habitual) miscarriages and/or stillbirths are distinguished (Table XIII).

(11) *Early death* implies the death of live-borns of family planners (Table XIV). The great majority is infant death, in a few cases death occurred after the first year of life. Three types are differentiated: (i) early neonatal death (within the first 6 days), (ii) early death from the seventh day, (iii) cases where infant and/or fetal death occurred on two or more occasions.

(12) The defect or *handicapped* probands are grouped according to the accepted functional classes (Table XV).

(13) *CAs of unknown aetiology* are listed according to the individual types (Table XVI).

(14) The "unwarranted" cases are grouped into the category of *non-genetic diseases* (Table XVII).

(15) Persons in the category of *general information seekers* (Table XVIII) only wanted to know what to do to produce healthy progenies. Also those families referred to the clinic with some sort of diagnosis but where every abnormality could be excluded and the proband proved healthy, are listed in this category. There were counselees who wanted information about "sex choice" or "twin production". Into this category were referred also those who had doubts about paternity or maternity (suspicion that they were given a foreign baby instead of their own).

TABLE XVI

Number and percentage of consultands in the material of the Genetic Counselling Clinic seeking counsel in 1973—1978 because of children with malformations of unknown aetiology

Type	No.	per cent
Isolated congenital abnormalities		
Anal atresia	5	3.1
Omphalocele	6	3.7
Skeletal anomalies**	4	2.5
Posterior cleft palate*	14	8.6
Hernia, diaphragmatic*	4	2.5
Hydrocephaly*	9	5.5
Hydronephrosis	1	0.6
Conjoined twins	1	0.6
Microcephaly*	2	1.2
Oesophageal atresia	5	3.1
Renal agenesis	8	4.9
Caudal regression	8	4.9
Intestinal atresia	1	0.6
Anomaly of lungs	1	0.6
Strabism**	2	1.2
Robin	2	1.2
Unidentified single anomalies	7	4.3
Total	80	49.1
Multiple anomalies		
Schisis association	2	1.2
Unidentified	81	49.7
Total	83	50.9
Grand total	163	100,0

* known types of mendelian or environmental aetiology could not be identified.
** the type presumably includes some different nosological entities.

TABLE XVII

Number and percentage of consultands with non-genetic disease in the material of the Genetic Counselling Clinic, 1973—1978

Type	No.	per cent
Sexual problems	48	61.6
Deviant behaviour (mainly delinquency)	3	3.8
Neurosis	3	3.8
Multiple sclerosis*	6	7.7
Dermatological diseases (prurigo, mycosis)	3	3.8
Infections (recurring)	2	2.6
Tumours in children (e.g. leukaemia)	11	14.1
Ozena**	2	2.6
Total	78	100.0

* Some authors suggest genetic origin; we deem it improbable.
** Two persons from the same family seeking advice independently.

TABLE XVIII

Number and percentage of consultands in the material of the Genetic Counselling Clinic seeking counsel in 1973—1978 for general information

Type	No.	per cent
Preparation for conception	35	54.7
Sex choice	9	14.0
Twin production	3	4.7
Proof of paternity	16	25.0
Proof of maternity	1	1.6
Total	64	100.0

THEORETICAL EXPECTATIONS AND THE PRACTICAL EXPERIENCE

It is an accepted presumption that people call at genetic counselling clinics according to the frequency of the given genetic abnormalities. Our material seems suited to test this presumption in the monolocal, chromosomal and multifactorial categories, which are of some genetic importance. As concerns the values of population occurrence, when known, the prevalence in Hungary [3], and when unknown, the data of Carter [1], were taken as a basis.

The counselees registered by the clinic did not come from the entire ter-

TABLE XIX

Prevalence and participation of the 10 most frequent autosomal dominant disorders, their number and participation in the material of the Genetic Counselling Clinic, 1973—1978, and the further 5 most frequent anomalies encountered in the clinic

Type	Prevalence per 1000 persons	Participation		Cases of the Genetic Counselling Clinic		
	per mil	per cent	(%)	No.	per cent	(%)
Hypercholesterinaemia	2.0	35.1	34.4	0	0.0	0.0
Otosclerosis (adult age onset)	1.0	17.5	17.2	1	2.2	1.2
Polycystic kidney (adult type)	0.8	14.0	13.8	5	10.9	6.0
Huntington chorea	0.5	8.8	8.6	5	10.9	6.0
Multiple exostosis	0.5	8.8	8.6	5	10.9	6.0
Neurofibromatosis	0.4	7.0	6.9	6	13.0	7.1
Myotonic dystrophy	0.2	3.5	3.4	8*	17.4	9.5
Multiple polyposis of the colon	0.1	1.8	1.7	3	6.5	3.6
Blindness, dominant type	0.1	1.7	1.7	13**	28.2	15.5
Dentinogenesis imperfecta	0.1	1.8	1.7	0	0.0	0.0
Total	5.7	100.0		46	100.0	
Osteogenesis imperfecta	0.04	—	0.7	8	—	9.5
Achondroplasia	0.02	—	0.3	8	—	9.5
Retinoblastoma	0.03	—	0.5	8***	—	9.5
von Willebrand disease	0.01	—	0.2	7	—	8.3
Holt-Oram syndrome	0.01	—	0.3	7	—	8.3
Grand total	5.81		(100.0)	84		(100.0)

* 15860—15900, 16830.
** 11570—11680, 15685, 15700, 18002, 18010.
*** The group may include some cases with non-dominant aetiology.

ritory of the country, neither only from a defined area. Therefore, birth prevalence of the individual abnormalities or age-specific prevalence could not be used as a starting point. Nevertheless, prevalence and its percentual participation might be suitable for the comparison.

Out of the 10 most frequent *autosomal dominant* disorders (Table XIX), the actual participation of Huntington chorea, polycystic kidney and multiple exostosis stand nearest to the expected values. More persons than expected called because of neurofibromatosis, myotonic dystrophy and blindness. In contrast, we had no proband because of the most frequent disorder, hypercholesterinaemia, i.e. early onset myocardial infarction.

TABLE XX

Prevalence and participation of the 10 most frequent autosomal recessive disorders, their number and participation in the material of the Genetic Counselling Clinic, 1973—1978

Type	Prevalence per 1000 persons per mil	Participation per cent	Cases of the Genetic Counselling Clinic	
			No.	per cent
Cystic fibrosis	0.5	32.8	28	21.9
Severe congenital deafness	0.2	13.1	15	11.7
Hypothyroidism*	0.2	13.1	12	9.4
Phenylketonuria	0.1	6.5	7	5.5
Adrenal hyperplasia	0.1	6.5	10	7.8
Spinal muscular atrophy (Werdnig-Hoffmann)	0.1	6.5	26	20.3
Microcephaly	0.1	6.5	9	7.0
Polycystic kidney, infantile type	0.1	6.5	8	6.2
Blindness, recessive type**	0.1	6.5	11	8.6
Mucopolysaccharidosis, type I— II	0.03	2.0	2	1.6
Total	1.53	100.0	128	100.0

* Includes several nosological types.
** 20400—20410, 21250—21270, 21255, 24820, 26800.

Only one proband was registered because of the second most frequent disorder, otosclerosis. The five most frequent homogeneous nosological groups of our material are not represented among the ten most frequent dominant anomalies. This suggests that the number of counselees is not related to the frequency of the abnormality but rather to other factors.

The pattern is more balanced in the autosomal recessive abnormalities (Table XX). In cystic fibrosis, the expected figures exceed the observed ones, while in the other cases the values are nearly identical. Only the preponderance of Werdnig-Hoffmann disease is an exception. It seems worth mentioning that we had 6 cases of galactosaemia which has a 0.02% prevalence at birth.

In the group of *X-linked* anomalies, two of the five most frequent types, ichthyosis and ocular albinism, were not represented in our material (Table XXI). The other three showed a greater participation than expected, whereas the occurrence of Duchenne syndrome, the most frequent anomaly in our material is in good agreement with the expected participation.

In *chromosomal aberrations* the picture is unequivocal (Table V). Down syndrome dominates in our material, it is followed by the balanced aberrations indicating their importance in the aetiology of hereditary anomalies (8). Of the sex chromosome aberra-

tions, only persons with Turner disease and those with Klinefelter disease called at the clinic. Their main concern was infertility.

Evaluation of the *multifactorial CA* category is also of interest. Nine common isolated CAs are known in Hungary (Table VI). In view of eventual diagnostic inaccuracies, instead of ventricular septal defect, all the isolated and complex (e.g. Fallot's tetrad) congenital cardiovascular malformations were taken into consideration. The expected and observed percentual participation shows an interesting picture. Again, it is not the frequency but rather the severity which motivates consultation. In anencephaly-spina bifida and in cleft lip ± palate, the effect of preventive programmes and their role in health education have also to be taken into account.

Among the *multifactorial diseases*, the occurrence of schizophrenia and epilepsy exceed the expectations as related to population occurrence (Table VII). In contrast, depressive conditions lag much behind the expected values, not to speak of the absence of familial (simple, subcultural, physiological) mental subnormality, a fact which is easy to understand. The lack of cases of early onset myocardial infarction is more difficult to explain.

The expected and observed prevalence values and their comparison provide a possibility only for informative estimations. Nevertheless, some tendencies are worth mentioning.

(i) It is by no means the frequency of the disorder which primarily motivates the consultation.

(ii) Severity and mainly lethality are important factors for seeking genetic advice.

(iii) More persons seek genetic counselling because of congenital abnormalities and disorders manifesting early after birth, than because of diseases in adult age caused by partially (early onset myocardial infarction) or entirely (e.g. otosclerosis) genetic origin.

(iv) Recognition of the aetiology

TABLE XXI

Prevalence and participation of the 5 most frequent X-linked disorders, their number and participation in the material of the Genetic Counselling Clinic, 1973—1978

Type	Prevalence per 1000 persons	Participation	Cases of the Genetic Counselling Clinic	
	per mil	per cent	No	per cent
Duchenne syndrome	0.2	37.7	8	38.1
Haemophilia A	0.1	18.9	7	33.3
Ichthyosis	0.1	18.9	0	0.0
X-linked mental subnormality (Renpenning)	0.1	18.9	6	28.6
Ocular albinism	0.03	5.6	0	0.0
Total	0.53	100.0	21	100.0

and within it the role of hereditary factors (or of their absence) is also of importance (we refer here again to early onset myocardial infarction).

(v) The on-going preventive programmes (e.g. amniotic alpha-fetoprotein assay for anencephaly-spina bifida), and health education activities (e.g. limb reduction anomalies) (Table X) also considerably influence the type of counselees seeking the advice of genetic counselling clinics.

References

1. Carter, C. O.: The relative contribution of mutant genes and chromosome abnormalities to genetic ill-health in man. In: Progress in Genetic Toxicology, eds D. Scott, B. A. Bridges, F. H. Sobels, Elsevier/North-Holland, Amsterdam 1977. pp. 1–14.
2. Czeizel, A., Osztovics, M., Kiss, P.: Data of three years of genetic counselling. In: Medical Genetics, eds Szabó, G., Papp, Z., Excerpta Medica, Amsterdam 1977. pp. 741–744.
3. Czeizel, A.: Multifactorial aetiology of common congenital malformations. In: Medical Genetics (eds): Szabó, G., Papp, Z., Excerpta Medica, Amsterdam–Oxford 1977. pp. 411–429.
4. Czeizel, A., Métneki, J., Osztovics, M.: Evaluation of an information-guidance genetic counselling. J. med. Genet. (in press)
5. Czeizel, A.: The current issues in the practice of genetic counselling (in press)
6. Evers-Kiebooms, E., van den Berghe, H.: Impact of genetic counselling: A review of published follow-up studies. Clin. Genet. **15**, (1979) 465
7. McKusick, V. A.: Mendelian Inheritance in Man. Fourth Edition. The Johns Hopkins University Press, Baltimore 1975.

A. Czeizel, M. D.
Gyáli út 2
H-1097, Budapest, Hungary