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Surveillance of congenital anomalies in Hungary

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Surveillance of congenital anomalies has various functions *viz.* monitoring (to detect clusters as soon as possible), registering (to contribute to medical care and to provide material for scientific research) and informative. The Hungarian Congenital Malformation Register records the occurrence of malformed babies diagnosed from birth to 1 year of age. The Register has 3 sources (obstetricians, paediatricians, pathologists) and has registered since 1971 over 4000 malformed infants annually, an occurrence of over 28‰. Validity and completeness of notification depend on the type of malformation. A separate Monitor started on January 1st, 1973, is confined to congenital malformations detectable unequivocally and readily during the first seven days of life. So far four real clusters occurred in Hungary but their causes could not be found. Particular stress has been laid upon multiple malformations (syndromes) since all known teratogens affecting humans produce multiple malformations.

The purpose of surveillance is continuously to collect information on congenital anomalies. It is an essential requirement that the types of congenital anomalies of different aetiology be studied separately since congenital rubella syndrome developing as a consequence of an intrauterine virus infection, monogenic achondroplasia occurring due to a major gene defect, Down syndrome attributable to a special numerical chromosome aberration and cleft lip with or without cleft palate showing multifactorial aetiology obviously represent different entities.

Surveillance has various functions.

1. The *monitor* function is a sensitive warning of a temporal clustering of congenital anomalies in a definite population, caused by newly-arisen teratogenic environmental effects. The earliest possible recognition of such clusters and the restriction of the influences of such noxae may prevent injuries in many a fetus. The monitor does not require a complete recording of all congenital anomalies based on personal data. Its sensitivity depends on the rapid notification and monthly processing of certain types of anomalies. Probably, only the so-called sentinel defects of known aetiology are readily detected by the obstetrician or the pathologist at birth and during the first 7 days of life. The purpose is to detect real changes *i.e.* clusters as soon as possible.

2. The *register* function means

"a file of documents containing uniform medical and/or sociodemographic information about individual persons, collected in a systematic and comprehensive way, in order to serve a pre-determined purpose" [21]. There are three essential points in the register of congenital anomalies, *viz.* (i) the permanent record of the affected children identified on the basis of their personal data (name, address, birth-date, etc.); (ii) a continuous or occasional follow-up of the patients' conditions; and (iii) statistical utilization of the data obtained.

Registration of congenital anomalies is important from several points of view.

a) It may help to plan and organize medical care (surgical intervention, prosthetic devices, etc.) and an eventual institutionalization (*e.g.* mentally retarded children). Thus *e.g.* surgical treatment of congenital heart diseases in Hungary had first been planned on the basis of an occurrence estimated at one tenth the actual frequency. This, of course, led to serious problems in the treatment of the affected. The follow-up of cases makes the evaluation of care also possible (*e.g.* in spina bifida cystica). Furthermore, the register may contribute to the propagation of new methods of therapy, rehabilitation and prevention (*e.g.* calling in the mothers who had had a baby with anencephaly and spina bifida, for amniocentesis to determine the alpha-fetoprotein level of amniotic fluid during their subsequent pregnancies.

b) A register containing a high number of unselected cases may offer valuable material for scientific research, even for anomalies as rare as *e.g.* exstrophy of the bladder.

(i) It may provide suitable data for epidemiologic and genetic family studies.

(ii) The register may give information on the total occurrence of each type of anomaly in a given population *i.e.* on p values which are basic data of genetic studies and genetic counselling.

(iii) Differences found in the frequency of congenital anomalies between different countries, geographical or administrative areas [16], may disclose special endemic environmental effects or genetic factors.

(iv) The register may also call attention upon less obvious temporal trends. Thus in Hungary *e.g.* the frequency of patients with Down syndrome showed a gradual decrease parallel to the decrease of maternal age due to the fall of live-birth rate [3].

(v) The register may help to recognize new syndromes and the patterns of their occurrence.

3. The information supplying exact data on congenital anomalies may be useful in many points.

a) It may form a basis of reference in considering presumed "epidemics" of congenital anomalies and to allay public anxiety.

b) Surveillance makes people aware of the significance of congenital anomalies by notification and the continuous publication of data.

c) These data may be of help in teaching.

The importance of congenital anomalies (in Hungary at present more than three times as many infants die of congenital malformations than of all infectious diseases) and the necessity of avoiding another thalidomide catastrophe has prompted several countries to organize a surveillance of congenital anomalies at the national level (Czechoslovakia, 1961; Hungary, 1962; Finland, 1963; England-Wales, 1964; Norway, 1967; Sweden, 1973) or in more restricted areas (British Columbia, 1952, almost a decade earlier than the other programmes; Israel (West Jerusalem), 1964; Sweden, 1965; Canada: Alberta, Manitoba, Ontario, New Brunswick, 1966; Israel (Rehovot), 1966; USA: Nebraska, parts of Georgia and Florida, 1967; France, 1973; USA (all institutions), 1974. Thus, Canada and the United States, as well as Israel and Sweden have 2 surveillance systems; these, however, have worked under fairly different conditions [6, 10, 11, 18, 22] In some countries (*e.g.* Finland, Hungary) notification is compulsory. In some (*e.g.* England-Wales, Canada, USA, Czechoslovakia, Norway) malformations diagnosed during the first seven days are only considered while in others (*e.g.* Hungary, Israel) the age limit is the first year of life or there is no age limit at all (*e.g.* British Columbia). Some surveillances involve only congenital malformations (this term is confined to structural defects present at birth [20]), whereas others involve congenital anomaly (this term includes all biochemical, structural and functional disorders present at birth [20] in addition). In some countries, the monitor function is expressed while in others the register function operates continuously. Recently, the WHO [19, 20, 22], the National Foundation and other organizations [9] have made serious efforts to ensure international co-operation and standardization. The purpose of the present paper is to summarize the results of the surveillance of congenital anomalies with particular reference to Hungarian data and to discuss some unsolved problems.

Hungarian Congenital Malformation Register (HCMR)

In Hungary a continuous and compulsory notification of congenital *malformations* and a HCMR was established by the Ministry of Health in 1962. Since January 1st, 1970, the HCMR has been run in accordance with international recommendations. The aim of HCMR is to determine the occurrence of malformed babies and congenital malformations diagnosed from birth to the age of 1 year. HCMR uses three sources of information:

1. The obstetricians notify the HCMR on a standard form of every diagnosed malformed newborn. At present in Hungary 98% of all deliveries take place in hospitals.

2. The paediatricians notify the HCMR on another standard form of every diagnosed malformed infant.

Notification is made at every admission to any sanitary institution, i.e. repeatedly. In order to minimalize the load of the physicians in charge of notification, the forms contain only the most necessary personal and birth data (name, address, birthdate, sex, single or multiple birth, live or still-birth, infant death, birthweight). The common congenital malformations, about 80% of the total, are indicated so that the physicians only have to underline them. For less frequent anomalies a special column is reserved.

3. The pathologists notify the result of the necropsy of malformed stillborns and babies to the Central Statistical Office which forwards them to HCMR. At present, the majority of stillbirths and all dead infants are subjected to necropsy.

The multiple sources result in a considerable overlap, but multiple counting is eliminated because the HCMR keeps personal record cards. At the same time the overlap increases the efficiency of HCMR and offers a possibility to control notification. [14,15] The data are classified and coded by four digits according to the 8th revision of the International Classification of Diseases (ICD). The occurrence of congenital malformations is checked quarterly, though the data are processed by a punched card system (SZAM made in USSR) annually after March 31st of the next year. As some notifications from the previous year may arrive later, the final closing date is December 31st of the following year. The annual results of HCMR are published officially in the Medical Weekly and a detailed report is sent to the authorities. The data of HCMR are public property so that anybody can use them for practical or scientific work.

The registered number of malformed infants amounts to more than 4000 and due to the extensive information of the physicians, the systematic control of notifications and the continuous publication of the

TABLE I

Number and occurrence of malformed babies and malformations in Hungary, 1970–1974

Year	Number of total births	Number of babies with congenital malformations	Occurrence of malformed babies per 1000 total births	Number of malformations	Total occurrence of malformations per 1000 total births
1970	153.339	3167	20.65	3516	22.93
1971	152.159	4344	28.55	4806	31.59
1972	154.652	4723	30.54	5272	34.09
1973	157.623	4657	29.55	5288	33.55
1974*	187.957	5749	30.59	6414	34.12

* data incomplete (until March 31st, 1975).

data, their occurrence has been over 28‰ since 1971 (Table I). The occurrence of congenital malformations is higher because in this type of processing babies with two malformations are registered doubly. Babies with three or more malformations are evaluated as separate entities; therefore the individual malformations within multiple ones do not score separately. (The frequency of babies with one, two and multiple malformations was 82.7—83.7, 12.4—13.1 and 3.9—4.2%, respectively.)

The total point-prevalences of congenital malformations at birth are higher in Hungary than in other countries except the 5 provinces of Canada [1]. It is supposed that some 5% of all births exhibited congenital diseases [19]. The Hungarian values do not actually indicate a higher occurrence of congenital malformations in general; this is explained by (i) the one year age limit of the subjects to be notified; (ii) the more complete list of congenital malformations which includes congenital hernias (*e.g.* exomphalos-omphalocele and congenital inguinal hernia) and also teratomas (now not included in Chapter XIV entitled Congenital Anomaly of ICD); (iii) the multiple sources of the notification system; and perhaps (iv) the more reliable notification. Considering the individual types of anomalies, only the point-prevalences at birth of the congenital dislocation of the hip is higher in Hungary than in other countries [5].

Some technical problems must also be considered. (i) Studies must be aimed separately at the individual types of congenital malformation *i.e.* at homogeneous entities. It is obvious that *e.g.* an isolated cleft lip with or without cleft palate is a type of malformation completely different from cleft lip with or without cleft palate associated with other malformations such as polydactyly and ocular anomaly [4]. The total occurrence of babies with a single congenital malformation amounts to 2.8% in HCMR, thus the chance association of three malformations has a probability of 0.00042%. Therefore, in the overwhelming majority of mutliple malformations, a chance association could be excluded and patients with 3 or more malformations were evaluated as a separate entity of special aetiology and classified into subcategory 759. (ii) The Congenital Anomaly Chapter XIV in ICD contains only morphological malformations and, as mentioned above, this list is incomplete. In the future, increased attention should be paid to all congenital anomalies including the inborn errors of metabolism (270—277). Moreover, if only for the significant overlaps observed, their uniform judgement with mental subnormatity (310—315) and congenital defects of sense organs (370—379; 388—389) should also be considered. (iii) Minor anomalies (*e.g.* phimosis, hydrocele) also present a problem since their notification depends on the physician's judgement. (iv) Early successful treatments also produce paradoxical situations. Thus, *e.g.* the

registered occurrence of congenital dislocation of the hip is high in Hungary even though — owing to extensive early orthopaedic screening — patients with actual dislocation of the hip are rarely found. Thus the registered value only indicates the "liability" ratio of this malformation. (v) Prevalence values at birth were always calculated for the total number of births and expressed per thousand. (In addition, the data were evaluated according to the number of livebirths and stillbirths, infant deaths, sex ratio, etc.)

The most important features of surveillance are its validity and completeness [12, 8, 13]. As a result of our epidemiologic studies the approximate real occurrence in Hungary of some types of congenital malformation is known. It seems worthwhile to compare them with the registered values (Table II). The ratio of notification in each type of malformation studied increases from 1.6% in the case of a single umbilical artery to over 100% in the case of congenital clubfoot. The deviations may be attributed to differences (i) in the time and reliability of diagnoses (*e.g.* certain congenital heart defects can reliably be recognized only after birth and in some cases only by special techniques); (ii) in the gravity (less severe malformations may be considered less significant, resulting in a lower notification ratio as for

TABLE II

The completeness of notification of some congenital malformations per 1000 total births in 1972

Code number of ICD	Congenital malformations	Approximative real occurrence	Registered occurrence	Completeness of notification per cent
740.	Anencephalus	1.10	1.13	102.73
741.	Spina bifida	1.63	1.33	81.60
742.	Congenital hydrocephalus	0.76	0.74	97.37
746.3	Ventricular septal defect	1.85	1.22	65.95
746.4	Atrial septal defect	0.91	0.26	28.57
747.0	Patent ductus arteriosus	0.86	0.32	37.21
747.5	Single umbilical artery	1.27	0.01	0.79
749.	Cleft palate and cleft lip	1.55	1.60	103.23
750.1	Congenital pyloric stenosis	1.46	0.39	26.71
752.1	Undescended testicle	13.12	0.67	5.11
752.2	Hypospadias	4.31	1.13	26.22
754.	Congenital clubfoot	1.82	2.15	118.13
755.6	Congenital dislocation of hip	27.53	6.10	22.16
759.3	Down disease	1.25	0.73	58.40
550.	Congenital inguinal hernia	12.11	1.90	15.69

instance in the cases of undescended testicles, and in addition only the most serious defects are examined post mortem) and (iii) interpretation of the malformations (congenital inguinal hernia and a single umbilical artery are not considered congenital malformations by a number of clinicians). (iv) In the cases of congenital clubfoot some secondary clubfoot cases, whereas (v) in those of cleft palate and cleft lip some associated multiple anomalies may increase the registered value. All these, of course, also mean that the validity and completeness of notification of the individual malformation types cannot be assessed uniformly.

The objective differences in the recognition of malformations and the fastest possible detection of the possible clusters have prompted us to develop a separate Monitor in Hungary, from January 1st, 1973.

Congenital Malformation Monitor

This Monitor is confined to congenital malformations detectable unequivocally and readily, in general by inspection, during the first seven days of life [2] (Table III). (In certain countries, all congenital malformations are recorded.) Monitoring imposes no surplus work on the physicians making the notification, but in data processing the "monitor" malformations are evaluated separately according to the month of birth and to territorial units. In Hungary, 98% of the deliveries takes place in hospitals and thus the monitor malformations must be diagnosed and notified by the obstetricians, neonatologist-paediatricians working in a considerable proportion of the obstetric institutions, and occasionally by the pathologists during the first seven days of life. An occasional cluster can thus be detected almost immediately.

To analyse changes, particularly increases in the occurrence of special types of malformation, is not a simple task [7, 17]. Separation of random increases from significant "epidemics" attributable to actual environmental effects has been a real problem. At their evaluation, the data obtained during the preceding years were used for comparison, and figures higher than +2 S. D. were regarded as a warning sign. In Hungary some significant increases *i.e.* clusters occurred in special types of congenital malformations both in the Monitor in 1973 (*e.g.* reduction deformities of upper limb and severe malformations of external genitalia in August) and in the Register in 1970—1973. However, increases restricted to one month have not been taken into consideration. In cases of mathematically significant (proven by X^2 test) clusters during two or more months the distorting effect of technical errors (*e.g.* misreporting; a new physician; introduction of new diagnostic procedures) could be excluded. A significant real increase in the special type of malformations persisting through several months was considered an alarm sign. So far four real clusters occurred: one for hypospadias (752.2)

TABLE III

Defects readily detectable at birth (1973 data)

Code number of ICD	Malformations	Occurrence per 1000 births		Monthly values	
		No	0/00	x	2.SD
740.	Anencephalus	137	0.87	11.4	3.01
741.	Spina bifida	173	1.10	14.4	5.52
745.0	Absence of ear or severe malformation	13	0.08	1.1	2.17
748.1	Absence of nose or severe malformation	4	0.03	0.3	1.56
749.	Cleft palate and cleft lip	252	1.60	21.0	12.24
752.8	Absence or severe malformation of external genitalia	311	1.97	25.9	12.24
755.0	Polydactyly	92	0.58	7.7	4.97
755.2	Reduction deformity of upper limb	19	0.12	1.6	2.00
755.3	Reduction deformity of lower limb	9	0.06	0.8	1.51
759.	Congenital syndromes affecting multiple systems	335	2.12	27.9	9.81
Total		1345	8.53	112.1	16.94

TABLE IV

Distribution of notified and registered multiple malformations in 1973

Code number of ICD	Multiple malformations	Notified number	Registered number	
			(plus)	total
759.0	Situs inversus	3	(—)	3
759.1	Conjoined twins and other forms of twin monster	3	(—)	3
759.2	*Major gene defect*	8	(8)	16
759.3	Down syndrome	103	(2)	105
759.4	Other syndromes due to autosomal abnormality	2	(7)	9
759.5	Syndromes due to sex chromosome abnormality	5	(—)	5
759.6	*Major environmental factor*	—	(7)	7
759.7	*Specific syndromes with unknown aetiology*	3	(16)	19
759.8	*Provisional syndromes or associations*	—	(36)	36
759.9	Unspecified syndromes	208	(—)	111
Total		335	(76)	314*

* 21 non-multiple malformations have been subtracted.

for four months in 1971; one for reduction deformity of the upper limb (755.2) for two months in 1971; one for anencephalus (740) for three months in 1972; and one for congenital clubfoot (754) for three months in 1973), but the underlying causes have remained obscure.

Multiple malformations

During monitoring, particular stress has been laid upon multiple malformations, the syndromes, since all known teratogens affecting humans produce multiple malformations. In addition, multiple defects may indicate chromosome aberrations and monogenic syndromes.

Classification of multiple malformations is an unsolved problem. In our Monitor, multiple malformations were classified partly according to the ICD and partly to our purposes (as shown by the underlined terms in Table IV).

Evaluation of multiple malformations is done as follows:

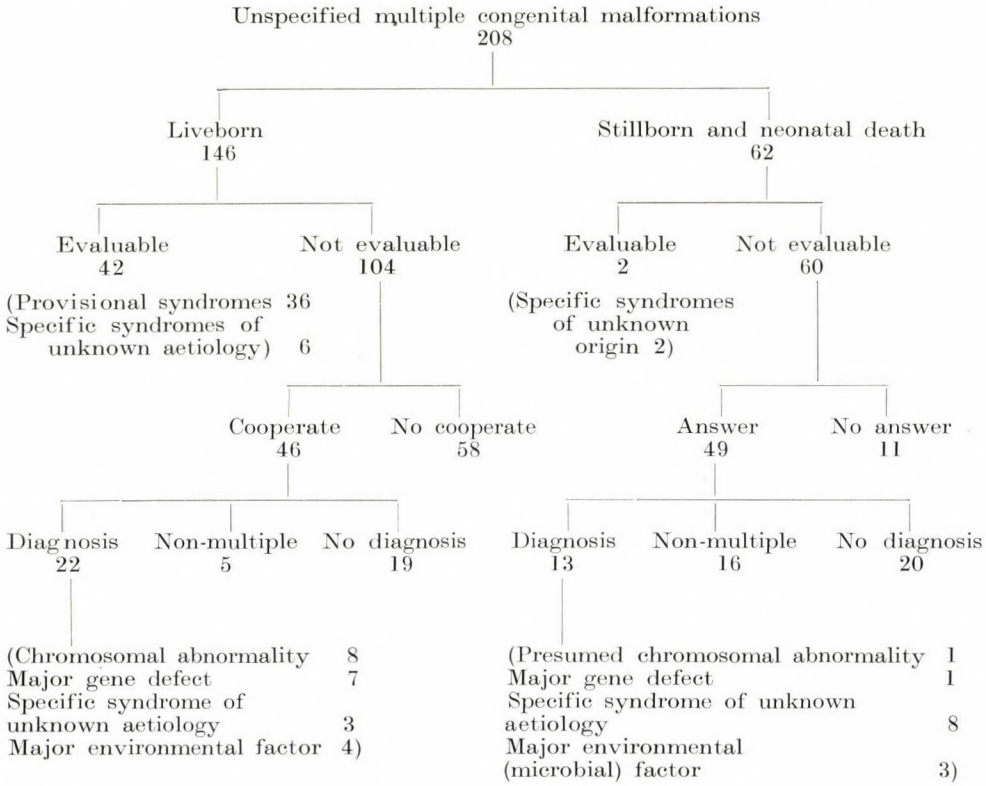
1. Recognition and classification of syndromes is difficult and therefore in the majority of the multiple malformations no exact diagnosis has been supplied; specification was received in 37.9% of the notified multiple malformations belonging to code number 759.

2. In the case of unspecified multiple malformations, during data processing attempts have been made to recognize the syndrome on the basis of the symptoms described (Table V). In this way 42 cases were diagnosed successfully. Three cases notified with a posterior cleft palate, glossoptosis and micrognathia were assessed as probable Robin syndromes. In further 36 patients, "congenital mesenchymosis" was diagnosed as a provisional syndrome. In these cases, 3 or all 4 symptoms, *i.e.* congenital dislocation of the hip, congenital clubfoot, congenital inguinal hernia, and torticollis had combined. (It is, of course, a question, whether all these should be considered a multiple malformation entity.)

3. For the identification of unspecified multiple malformations a special medical system has been established in Hungary. Stillbirths and infant death with unspecified multiple malformations are evaluated through correspondence and the detailed post mortem records are collected from the pathologists. Surviving patients are sent officially to special subcentres where they are examined and diagnosed by specialists. The 5 subcentres are provided by the necessary personal and laboratory facilities (*e.g.* for chromosome analysis) to establish the diagnosis in patients from 3—5 countries. Detailed descriptions of the results of these examinations are sent to the Monitor, supplemented with the presumed diagnosis. From time to time, the leaders of the subcentres meet in order to evaluate the post mortem records. There are three possibilities in these cases. (i) Attempts fail at identifying the multiple malformation in question with any of the known syndromes. (ii) The

TABLE V

The process of evaluation of unspecified multiple congenital malformations in 1973



detailed description reveals that the anomaly under study is not a multiple one. Thus *e.g.* spina bifida with hydrocephalus and congenital clubfoot or anencephaly with cervical vertebrae and facial anomaly are not considered multiple malformations since the latter are secondary consequences. (In this respect, however, we are not strict enough since *e.g.* Robin anomaly, Potter syndrome, Poland syndrome, the defect of prechordal mesoderm, triad syndrome, have been classified as specific syndromes of unknown aetiology even though all these are single syndromic malformations with multiple appearance as a secondary defect.) (iii) The multiple malformation is successfully classified as one of the known syndromes. This at the same time also establishes the aetiology in some syndromes *e.g.* in Marfan and Treacher–Collins syndromes, major gene defects with autosomal dominant inheritance. The result of chromosome studies is often decisive. In 1973, 5 numerical and 3 structural autosomal anomalies were found and the centralized performance of sero-

logical tests promotes the verification of intrauterine infections (*e.g.* rubella or cytomegalovirus). In a number of cases, however, identification of the syndrome fails to reveal the aetiology (Robin syndrome).

Our efforts at recognizing multiple malformations have caused a difference between the notified multiple malformations and the registered ones (Table IV). Yet, the exact diagnosis has remained obscure in 53.4% of the unspecified malformations. This was due partly to the failure of the parents to take affected children to the relevant subcentre (because of the serious condition of the children or simply due to indifference, etc.), and to the fact that identification of syndromes is still a field unsettled in many respects and which needs wide experience.

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