ALFRED CUSCHIERI

A Survey of Congenital Anomalies in Malta

Reprinted from:

Collected Papers

published on the occasion of the
Collegium Melitense
Quatercentenary Celebrations
(1592–1992)

pp. 221–244

University of Malta
1993

A SURVEY OF CONGENITAL ANOMALIES IN MALTA

Alfred Cuschieri

Faculty of Medicine and Surgery

ABSTRACT

This study comprises a register of all cases of congenital anomalies recorded at the time of birth during the nine year period from 1983 to 1991. The occurrence of individual anomalies was analyzed in relation to the maternal age, gestational age, birth weight, twinning, still births, neonatal deaths and geographical distribution. Not only does the study provide accurate prevalence and incidence figures which are of importance to public health and the community as a whole, but it also provides a source of ascertainment of hereditary anomalies with their inherent recurrence risks which are of importance to individuals for genetic counselling. The validity of the register depends on the completeness of ascertainment and the use of a pathological international classification which demands diagnostic precision especially in cases of multiple congenital anomaly syndromes.

The prevalence figures for individual anomalies are compared with those of other countries. The Maltese register forms part of the EUROCAT project (European Register of Congenital Anomalies and Twins), a concerted action project organised by the European Community for the international surveillance of congenital anomalies with the aim of detecting temporal and spacial clustering and the identification of responsible teratogens.

INTRODUCTION

It may be rather disconcerting to realise that no less than two per cent of babies are born with a congenital anomaly ranging from severe multiple malformations, often ending in perinatal death to a barely perceptible extra digit which is usually removed and forgotten. Most cases are a source of grief for the parents who were expecting joy, of lifelong disability for the newborn child, and a challenge to society to improve their well-being and prevent future recurrence.

Surgical correction of congenital malformations and deformities is being increasingly successful while the prevention and treatment of genetic disease are becoming distinctly possible. In many cases, however, the causes of congenital anomalies remain elusive. Why does nature commit so many errors and even propagate some of them as hereditary anomalies? What are the relative contributions of single or multiple genes, of environmental factors, radiation and teratogens to the developmental process leading to congenital malformations?

The starting point in the study of congenital anomalies is the epidemiological approach, starting with an analysis of the frequencies and distributions of congenital anomalies and how they differ among populations. The first surge of interest in the study of birth defects was made in the 1960's when the medical profession became especially concerned with the birth of thalidomide babies with gross limb anomalies. The 'National Foundation – March of Dimes', an organization initially set up to co-ordinate research on the prevention of poliomyelitis, was one of the first to face the challenge of 'Birth Defects'. In 1962 the World Health Organization performed a world-wide survey recording 5500 congenital anomalies in a total of 427 000 consecutive births from 16 different countries over a 4 year period [13]. In 1972 it recommended the establishment of a collaborative reporting system for the monitoring of malformations [16]. Many countries set up National registers and International organizations were established including the 'International Clearing House for Birth Defects Monitoring Systems', founded in 1974 and the 'European Register of Congenital Anomalies and Twins' (EUROCAT), a concerted action project organized by the European Economic Community in 1978. Malta was accepted as a member of EUROCAT in 1986. EUROCAT comprises twenty seven registries from sixteen countries in Europe with its Central Coordinating Registry in Brussels.

Very few early studies on congenital anomalies in Malta have been recorded. A review of 243 postmortem reports on perinatal deaths in Malta over the 10 year period 1957 to 1966 showed that congenital anomalies were present in 15.2% of the cases [14]. A small preliminary survey of congenital anomalies in live-born children was performed in 1972 reporting 20 congenital anomalies in a total of 1016 consecutive births [11]. An initial two-year study of congenital anomalies in Malta was presented at the 1986 EUROCAT meeting [2]. The

present paper is a summary of an extensive study of congenital anomalies recorded in Malta over a nine year period from 1983 to 1991 in a total of 49 415 babies. It is based on an on-going register of congenital anomalies which was initiated in 1984 for continuous monitoring of congenital anomalies detected at birth and which was intended to be as complete and comprehensive as possible.

MATERIALS AND METHODS

Multiple sources of ascertainment of congenital anomalies were used. The main source was direct registration soon after birth before mother and child were discharged from Karen Grech Hospital. Information about affected infants was obtained from the Nursery, the Special Care Baby Unit (SCBU), and the labour ward, postmortem reports and cytogenetic reports. Although information was not obtained regularly from the Hospital in Gozo or from private clinics most affected infants were ascertained from Karen Grech Hospital where they would be referred. Every attempt was made to ensure, as far as possible, completeness and accuracy in ascertainment. In practice this is almost impossible to achieve because of the involvement of many different and sometimes changing staff, limitations in availability of staff for recording the data, and variations in diagnostic criteria and definitions in spite of prescribed criteria for diagnosis and inclusion which might not always be adhered to.

Anomalies were classified and coded according to the 5 digit code of the International Classification of Disease Paediatric Supplement. Recently the seven figure coding classification has been introduced [9]. For each case the birth weight, gestational age, birth outcome and maternal age were recorded and analyzed for the purpose of this study. Other information about maternal illness, twins, gestational exposures to drugs, previous pregnancies, paternal age and illnesses and known history of other affected family members were also recorded but are not included in the present study.

It is very difficult to draw a sharp line of distinction between minor and major anomalies. However, for consistency a standard list of accurately defined exclusions as published by the EUROCAT Central Registry was followed. These included such minor anomalies as positional talipes, clicking hips, glandular and coronal hypospadias, undescended testes, inguinal and umbilical herniae, spina bifida occulta, isolated dysmorphic features, skin tags and birth marks with a surface area of less than 4 cm^2 and other minor conditions which do not require corrective procedures or are not associated with residual disabilities. These would grossly inflate the frequencies of anomalies providing misleading estimates and introducing enormous subjective variations in recording which would reduce the comparative and absolute value of the statistics.

In cases of multiple congenital anomalies each anomaly was recorded and counted separately unless they were parts of the same anomaly or sequence such as spina bifida associated with hydrocephalus, cleft lip and palate, syndactyly and cleft hand and polydactyly affecting more than one limb. However, multiple anomalies constituting a syndrome were recorded and counted separately.

Baseline data were obtained from the labour ward registers of Malta and Gozo. These included the total number of deliveries, stillbirths, live births and neonatal deaths, which were used as denominators for calculating frequencies. Their distributions according to sex, birth weight, gestational age and maternal age were used to estimate population means for the various parameters studied.

RESULTS

This study covers a baseline population of 49 415 babies of which 404 (81.7 per 10 000) were still births. There were 411 (83.8 per 10 000) early neonatal deaths in the first week of life. In all 937 babies with congenital anomalies were registered giving a frequency of 1.9%. Congenital anomalies were present in 1.7% of live births, in 11.2% (45 cases) of stillbirths and in 22.5% (92 cases) of early neonatal deaths. Since a number of affected babies had more than one anomaly the total number of recorded anomalies was 1085.

The distribution of anomalies by system is shown in Fig. 1. in which it is apparent that congenital limb anomalies are the most frequent followed by anomalies of the skin, of the nervous system, chromosome anomalies and cardiovascular anomalies. The frequencies presented in this study include only the congenital anomalies diagnosed at birth. In some categories, where anomalies might not be definitely ascertainable in the early neonatal period, as in some cardiovascular anomalies, metabolic disorders and skeletal disorders the figures underestimate the true frequencies of the condition.

Congenital anomalies include all defects present at the time of birth. Many of them are the result of errors in morphogenesis, operating usually in the embryonic period and particularly, though not exclusively, in the second month of gestation. They include: (a) *malformations*, which are primary defects in the processes of cell proliferation, migration and differentiation, usually causing interrupted development and dysraphic anomalies: (b) *deformations*, which are the result of extraneous influences such as pressure or constriction on a developing primordium; and (c) *disruptions* which result from destruction of previously normally formed body parts, usually by interruption of the blood supply to a region such as occur in most cases of jejunal atresia or porencephaly (absence of a wedge-shaped area of the brain) and amniotic bands which may constrict the blood supply causing limb reduction defects.

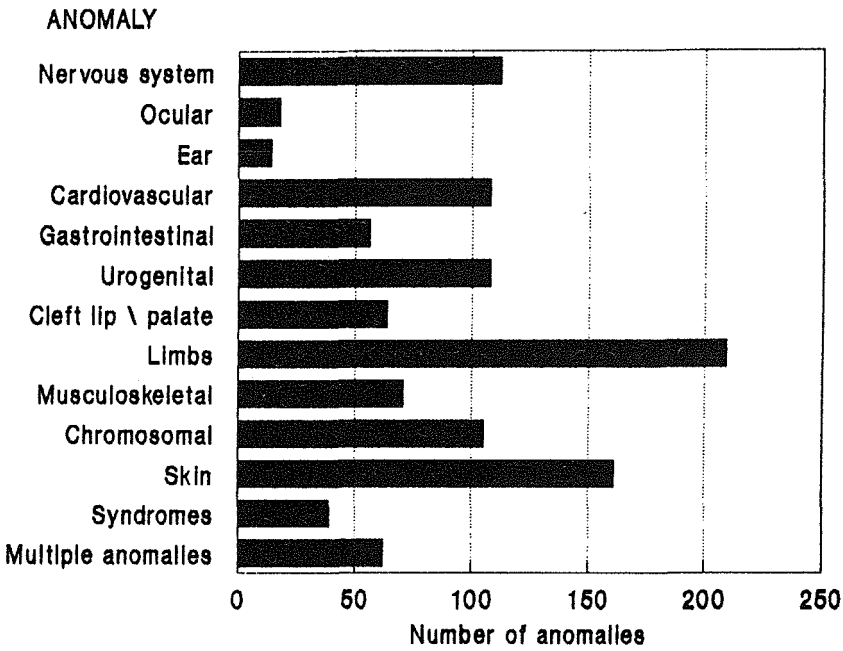

Figure 1. Congenital anomalies in Malta (1983–1991)

Disruptions occurring early in the embryonic period are often termed *atresias* which result in the virtual absence of a part which might be represented only by a fibrous streak. They are morphogenetically different from *agenesis* and *aplasias* which are malformations due to the total initial lack of formation of the embryonic primordium (agenesis) or its subsequent development (aplasia), although the end results are clinically indistinguishable. Thus, although it would be desirable to classify morphogenetic errors on an embryological basis, it may be very difficult, in some cases, to distinguish between malformations, deformations and disruptions or the extent to which they contribute to dysmorphogenesis in a particular anomaly.

It is also very difficult to generalise and classify malformations according to their aetiology. Undoubtedly some malformations and in particular multiple malformation syndromes are inherited as monogenic disorders. Others may be polygenic, chromosomal, the result of a teratogenic insult or sporadic but heterogeneity often precludes a clear-cut classification on a purely clinical basis. The precise aetiology is of utmost importance for genetic counselling but is beyond the scope of this review.

ANOMALIES OF THE NERVOUS SYSTEM

Anomalies of the nervous system arise from developmental defects in the neural tube and surrounding mesoderm which gives rise to the surrounding meninges and vertebral neural arches. They are among the commonest and the most serious of birth defects. In this report they are divided into three categories:

Neural tube defects or dysraphic anomalies of the nervous system are attributable to defects in closure or secondary rupture of the neural tube at the cranial or caudal neuropores during the fourth week of development. They are accompanied by variable defects in the overlying meninges, bones and skin and give rise to meningocoele, meningo-myelocoele, encephalocoele and anencephalus. Spina bifida occulta is excluded. These abnormalities differ from one another in location and extent of neural involvement but are otherwise aetiologically and genetically the same defect following a multifactorial type of inheritance.

Hydrocephalus is characterised by an abnormal increase in the amount of cerebrospinal fluid in the ventricles and subarachnoid space. It is a frequent accompaniment of neural tube defects. However, the prevalence figures for

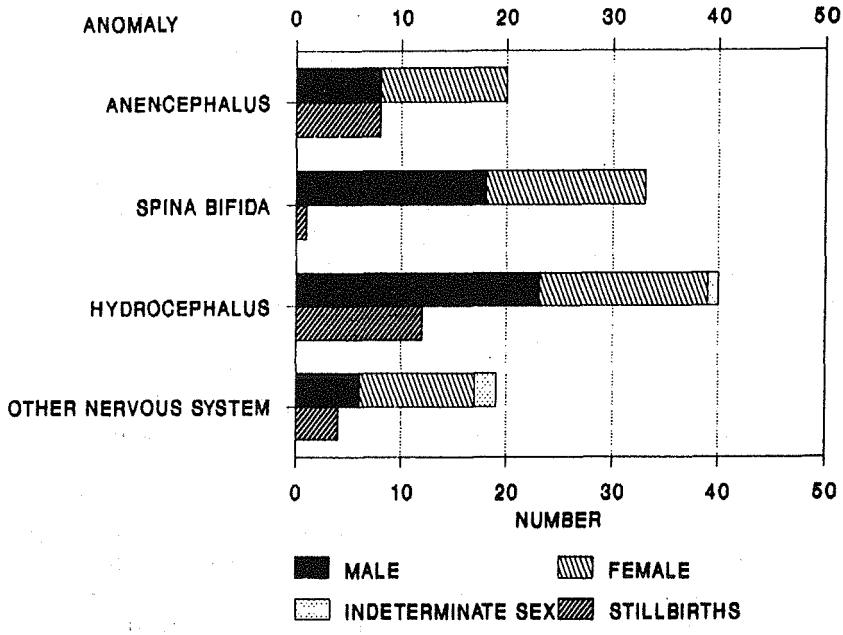

Figure 2. Anomalies of the nervous system

Malta (8.1 per 10 000) refer, in conformity with the system in all other registries, to isolated hydrocephalus. Hydranencephaly is a variety of hydrocephalus in which the cerebral cortex is almost completely atrophied. It should not be included with the neural tube defects

Other anomalies of the nervous system consist of several distinct conditions such as microcephaly, holoprosencephaly, agyria, pachygyria, megalencephaly, amelia, hydromelia and other named anomalies of various parts of the nervous system. Of these microcephaly is the most common and may result from genetic, embryological or acquired causes.

Between 1983 and 1991 there were 114 babies born with an anomaly of the nervous system with a total prevalence of 23 per 10 000 of which 55 (11.1 per 10 000) were neural tube defects (Fig. 2). There is an unequal sex distribution according to the site of the defect, with an excess of females in anencephaly and an excess of males in spina bifida. 40% of anencephalic foetuses were stillbirths and 66% of the live births died in the first week. Hydrocephalus is the most prevalent of the nervous system anomalies. There is an excess of males and 30%

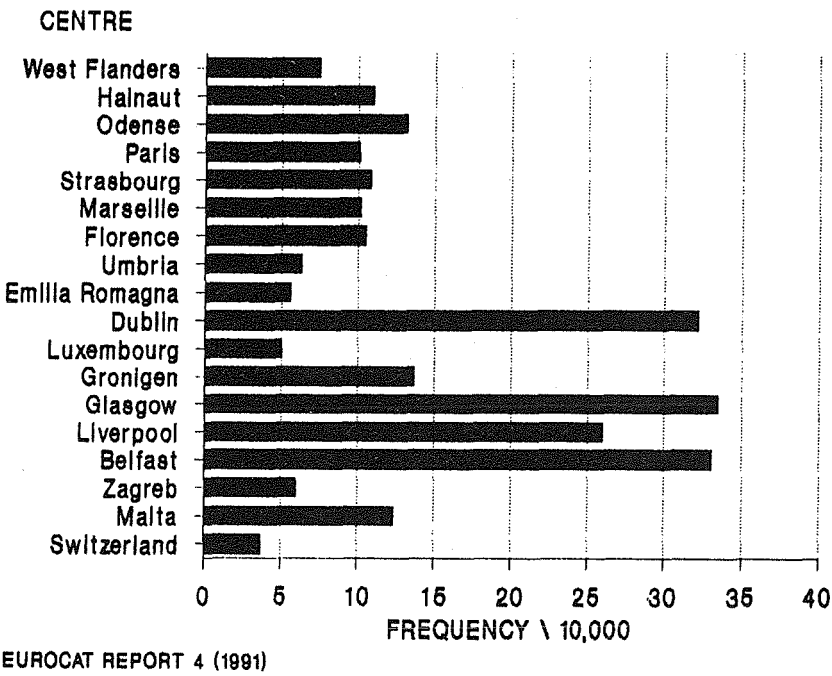

Figure 3. Prevalence rate of neural tube defects in 18 eurocat registries (1980–1988)

of hydrocephalic foetues were stillbirths. Other nervous system anomalies showed an excess of females and 22% were stillbirths.

The prevalence rate of neural tube defects shows marked regional differences in several EUROCAT registries (Fig. 3). In Malta the figures are similar to those in other countries in continental Europe where the rate is fairly homogenous between 10.7 and 14.3 per thousand and is stable over time. In Dublin, Belfast and Glasgow, however, the prevalence is significantly higher at 24.3 to 34.5 per 10 000 and there appears to have been a secular decrease in prevalence over the years [10]. In contrast the prevalence rate of hydrocephalus in Malta (8.1 per 10 000) is the highest among registries in Europe (Fig. 4) with comparable figures recorded in Strasbourg (6.9 per 10 000).

The prevalence chart for microcephaly shows less variations in different countries except for one centre, Glasgow (Fig 5). It has been suggested that there is more complete ascertainment of this anomaly in Glasgow which registers the milder degrees of this condition [7]. There is a lack of uniformity among clinicians regarding the precise definition of microcephaly. It is of particular

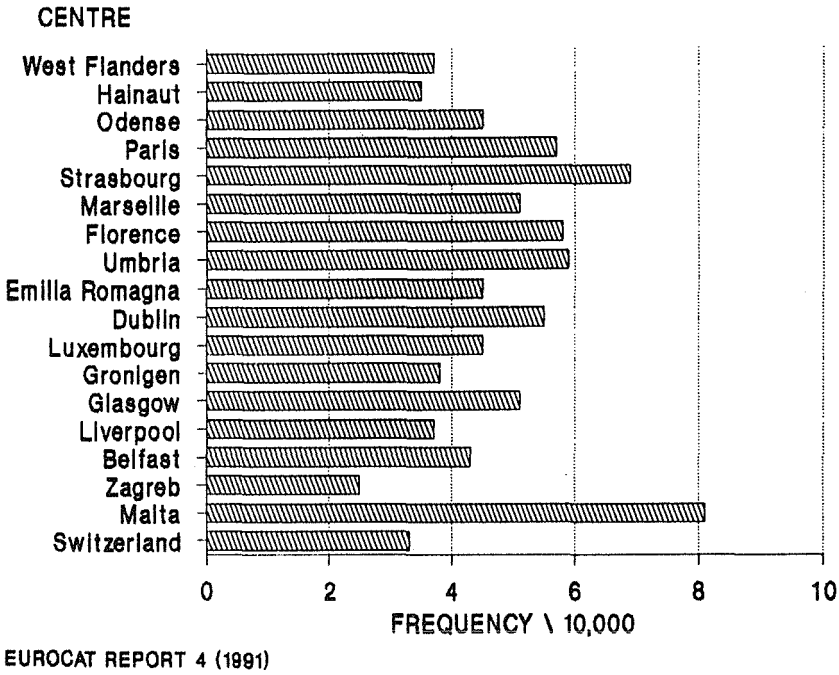

Figure 4. Prevalence rate of hydrocephalus in 18 eurocat registries (1980–1988)

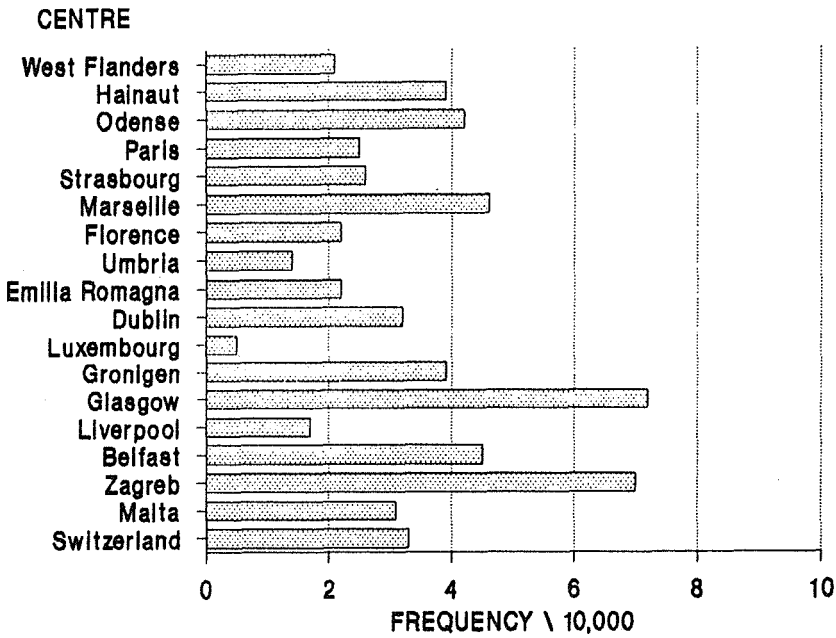

Figure 5. Prevalence rate of microcephalus in 18 eurocat registries (1980–1988)

importance to monitor accurately the frequency of microcephaly in populations since this may be a very sensitive indicator of environmental effects [15], atomic radiation as has been observed in the aftermath of the Hiroshima atomic bomb [17], X-radiation, maternal infections, alcoholism [1] and drugs in pregnancy [12].

The neural tube defects are malformations showing a typical multifactorial inheritance. In contrast hydrocephalus is a heterogenous condition which may be monogenic, sporadic or part of a wider syndrome. A fairly common form of hydrocephalus is the Dandy Walker malformation which is autosomal recessive; X-linked hydrocephalus may also occur. Microcephaly is often a feature of several syndromes which may be monogenic, chromosomal or sporadic in aetiology. Aetiology is very important in genetic counselling as risk estimates should be for the underlying syndrome rather than for the anomaly itself which is not an entity in its own right.

CARDIOVASCULAR ANOMALIES

The prevalence of cardiovascular anomalies and their sex distributions are shown in Fig. 6. The prevalence rate of cardiovascular anomalies (25.7 per 10 000) represents only the cases definitely diagnosed at or soon after birth. Many of the cases of heart murmur are diagnosed on later examination and are not included in the present statistics but will be the subject of a separate study. The prevalence rate is much lower than that recorded in most other EUROCAT Centres where the mean prevalence at birth is 47.2 per 10 000. However, the frequency of transposition of the great vessels and common truncus arteriosus are very close to the mean recorded in other Eurocat registries. 88% of the recorded cardiac anomalies were in live births, in contrast to 95% in other Eurocat registries, probably reflecting a delayed diagnosis of the milder defects in some of the live births.

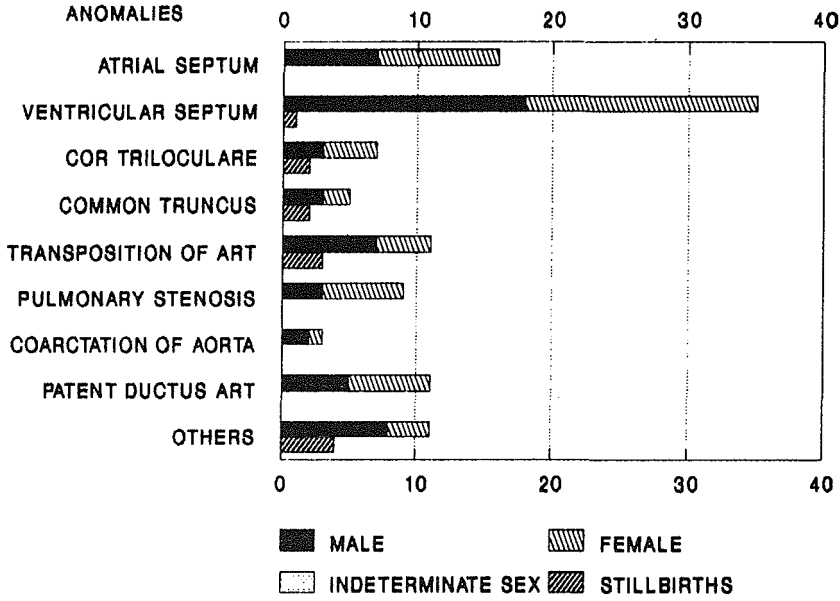

Figure 6. Prevalence of anomalies of the cardiovascular system

GASTROINTESTINAL ANOMALIES

There were 56 cases of anomalies of the gastro-intestinal system giving a total prevalence rate of 11.36 per 10 000 (Fig. 7). Pyloric stenosis was excluded from this study because most cases are diagnosed after discharge from hospital. The

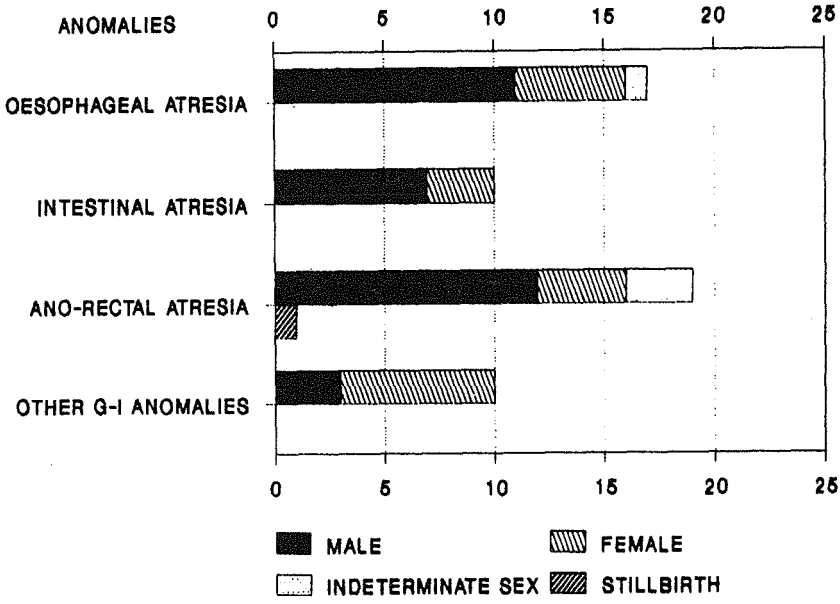

Figure 7. Prevalence of anomalies of the gastrointestinal tract

main anomalies of the alimentary system are atresias classified into three distinct groups, oesophageal, gastro-intestinal and ano-rectal. There is a distinct male predominance (63 to 70%) in gastrointestinal atresias but a female excess for other gastrointestinal anomalies. Stillbirths accounted for about 2% of cases and 20% of the live births with gastrointestinal anomalies died in the first week of life.

Oesophageal and ano-rectal atresias are usually malformations resulting from a defect in the normal developmental programme of proliferation, obliteration and recanalization of the endodermal gut tube. Separation of the laryngo-tracheal tube from the fore-gut occurs concomitantly with this process and failure of recanalization, causing atresia is often accompanied by a tracheo-oesophageal fistula. Similarly ano-rectal atresia is often accompanied by uro-rectal or recto-vaginal fistulae resulting from involvement of the uro-rectal septum which separates the hind gut into rectum and urogenital sinus. In contrast most intestinal atresias are disruptions secondary to obstruction of the superior mesenteric artery or one of its main branches. In addition there were 5 cases of Hirschsprung disease and 7 cases of other anomalies which included duplication of the gut, endomesenteric cyst, two cases of macroglossia (part of the Beckwith-Weidman Syndrome), ranula, anal polyps and ectopic anus.

GENITOURINARY ANOMALIES

Anomalies of the Genito-urinary system (Fig. 8) are divided into three main groups. The first group consists of internal urinary anomalies including renal agenesis, horse-shoe and ectopic kidneys, cystic disease of the kidney, hydronephrosis, and atresia, stenosis or other anomalies of the ureters or urinary bladder. Two or more of these frequently occur together, but according to the general rules are counted only once. There were 39 cases (7.9 per 10 000 births) within this category of anomalies, 4 of which (10%) were stillbirths and 5 (14%) were early neonatal deaths. There was a slight excess of males.

The second group consists of hypospadias which was recorded in 55 cases, a prevalence rate of 11.1 per 10 000 births, obviously occurring entirely in males. There were no stillbirths or early neonatal deaths in this group. Hypospadias, in this study, excludes the glandular and coronal types. However, there appears to have been difficulty in distinguishing between the coronal and penile forms at the time of birth, before the baby was examined by the surgeon with consequent under-reporting of the penile form of this condition.

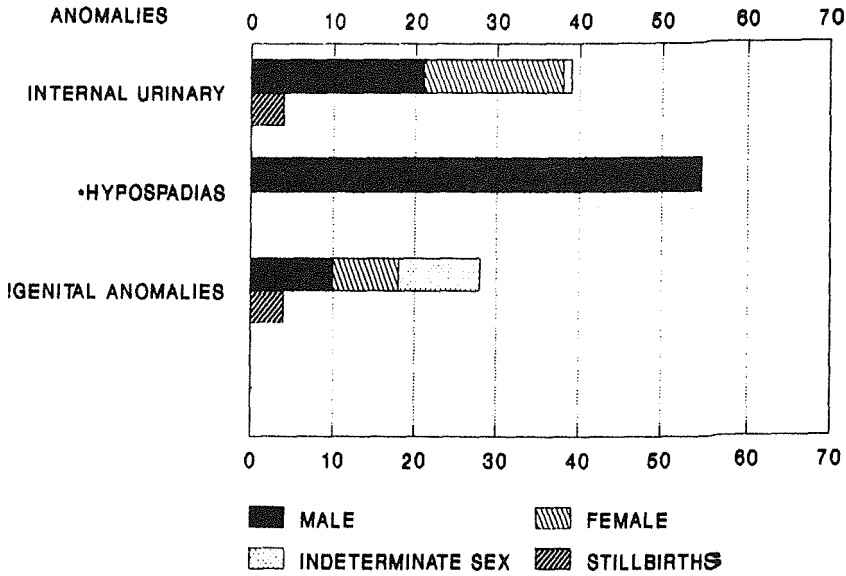

Figure 8. Prevalence of anomalies of the genitourinary system

Other genital anomalies are grouped here under one heading but include a wide variety of conditions including epispadias, bifid scrotum, hypoplastic penis and scrotum, anomalies of the female genital system and pseudohermaphroditism with ambiguity of the external genitalia. There were 28 cases of genital anomalies, excluding hypospadias, a prevalence rate of 5.7 per 10 000; 14% of these cases were stillbirths. 10 cases (36%) were of indeterminate sex. A remarkable feature of genito-urinary anomalies was the high rate with which they were associated with other anomalies – 73% of external genital anomalies, excluding hypospadias, and 48% of internal urinary anomalies were associated with anomalies of other systems.

CLEFT LIP, PALATE AND FACE

The prevalence of facial clefting in Malta was 13.0 per 10 000 (Fig. 9). This includes three entities namely cleft lip (with or without cleft palate), cleft palate alone and cleft face. The three anomalies are genetically distinct although embryologically they appear to differ only in the extent of the malformation.

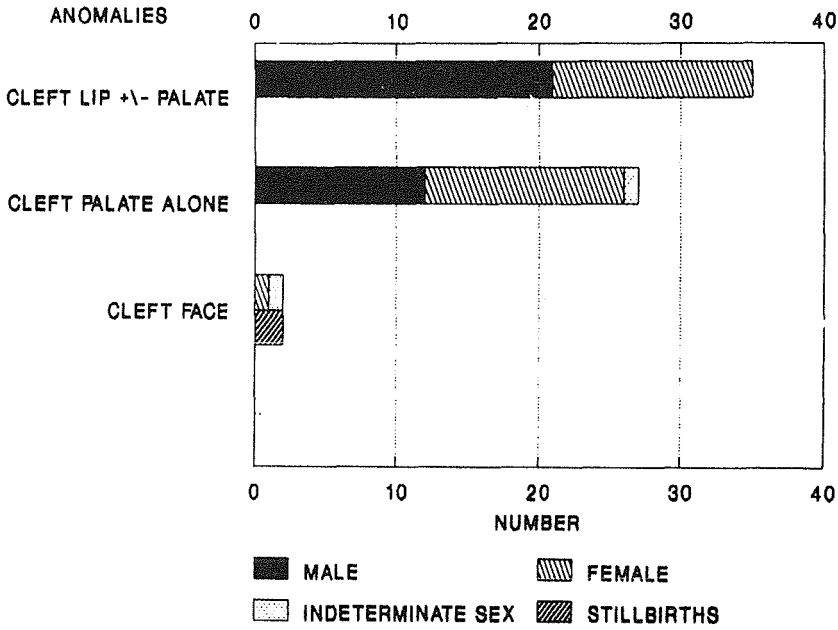

Figure 9. Prevalence of facial clefts

They also differ in sex distribution, cleft lip being commoner in boys whereas cleft palate alone is slightly commoner in girls. There were 35 cases (7.1 per 10 000) of cleft lip with or without cleft palate and 27 cases (5.5 per 10 000) of cleft palate alone. Cleft face is a very rare anomaly resulting from a failure of fusion or secondary rupture of the naso-optic groove. Only two cases 0.4 per 10 000 were encountered, both of which were accompanied by other anomalies. Median cleft lip, which is to be distinguished from bilateral cleft lip is a totally different entity resulting from hypoplasia of the frontonasal process, rather than a fusion defect. It is one manifestation of the holoprosencehaly sequence which is included under anomalies of the nervous system although median cleft lip may be the only anomaly visible externally.

ANOMALIES OF THE LIMBS

These are set apart from the rest of the musculo-skeletal disorders because they are anomalies of the limb buds. They are also numerically one of the commonest groups of abnormalities. Polydactyly and syndactyly are anomalies in the formation of interdigital webs separating the fingers. Reduction defects involve failure of differentiation of the limb mesoderm, leading to absence or severe

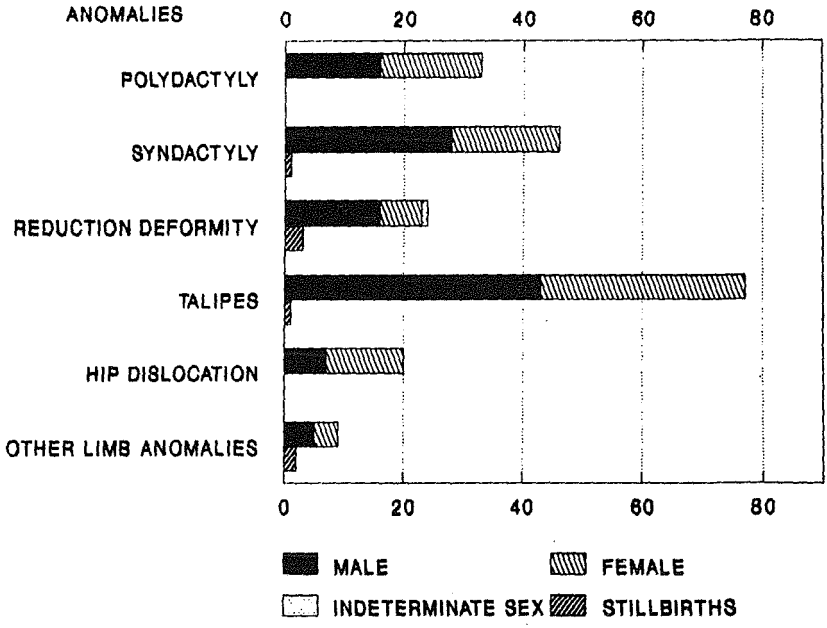

Figure 10. Prevalence of limb anomalies

hypoplasia of skeletal structures in the limbs. Talipes and congenital dislocation of the hip generally result from hypoplasia or incomplete development of the cartilage and ligaments of joints which predispose to subsequent deformity. Other limb defects included conditions such as sirenomelia, campomelia, joint contractures, joint dislocations and amniotic bands.

Congenital limb anomalies occurred in Malta with a prevalence rate of 42.3 per 10 000 births (Fig. 10). Their prevalence by sex and stillbirths are given in Fig. 11. Talipes and syndactyly are the most common of the limb anomalies. Syndactyly and limb reduction anomalies showed a distinct male predominance while congenital dislocation of the hip was commoner (65%) in girls. Over 96% of the limb anomalies occurred in live births while stillbirths occurred in 13% of limb reduction defects and in 22% of babies in the category of 'other' limb anomalies. Partial syndactyly of the 2nd and 3rd toes, which is a very common hereditary variant, is not included. Postural talipes and clicking hips are excluded but variations in interpretation by different observers cause some degree of variability in the reported frequencies. Talipes and syndactyly may each be encountered as isolated anomalies, or in association with other anomalies and frequently as a part of a syndrome.

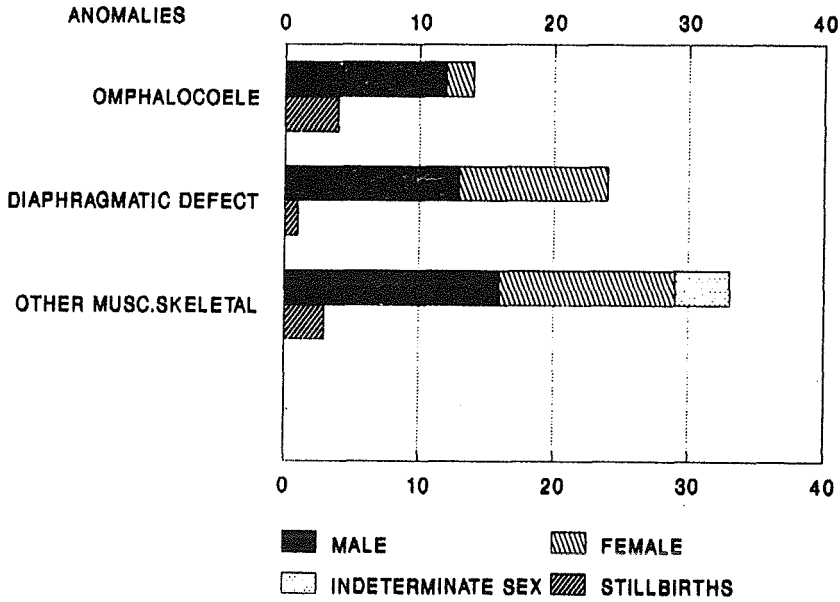

Figure 11. Prevalence of musculoskeletal anomalies other than of the limbs

MUSCULO-SKELETAL ANOMALIES

Musculoskeletal anomalies affect the somatic body wall and include a wide diversity of conditions affecting bone, cartilage, muscle, tendon and connective tissue. Two anomalies are singled out as being the more common ones in this group, apart from limb anomalies which are classified in a separate category. Diaphragmatic defects most commonly results from interrupted development and failure of closure of the foramen of Bochdalek or the foramen of Morgagni. It is usually accompanied by pulmonary hypoplasia. Omphalocoele and gastroschisis are grouped together because they have several common features affecting the development of the anterolateral abdominal wall although they differ morphogenetically. Other musculo-skeletal anomalies may be generalised, such as the various osteo- and chondro-dystrophies and dysplasias, or localised as in anomalies of the vertebrae or facial bones.

Omphalocoele and gastroschisis showed a large male predominance, 86% of these cases occurring in males. There was no marked sex predilection for diaphragmatic defects or other musculo-skeletal disorders. Omphalocoele also showed a high frequency of stillbirths which occurred in 29% of cases. While diaphragmatic defects occurred predominantly in live births, they were associated in 58% of cases with neonatal death in the first week, reflecting a poor prognosis for the surgical outcome.

CHROMOSOME ANOMALIES

Chromosome anomalies were recorded in 105 cases. This figure refers only to babies referred for chromosome analysis in the first week of life. 99% of them were in live births. Trisomy 21 accounted for the vast majority of the cases. Other chromosome anomalies detected at birth were trisomy 18, trisomy 13, 45,X (Turner Syndrome), 45,X\46,XXr mosaic Turner Syndrome, 46,XY 5p- (Cri du Chat syndrome), 46,XY del(1)(q42-qter), 46,XY del(11)(q23-qter) and 46,XX inv dup(4)(q31-q35). Early neonatal deaths accounted for 5% of babies with chromosome anomalies.

MULTIPLE ANOMALIES

Congenital anomalies are often associated with one another. Three classes of 'multiple anomalies' were distinguished:

a) syndromes in which there was a recognisable pattern of malformations such as Apert Syndrome, foetal hydantoin syndrome and congenital rubella syndrome. Chromosome syndromes are excluded from this category.

b) multiple anomalies in which two or more major and unrelated anomalies occurred together and which did not constitute a recognisable syndrome.
c) sequences in which apparently multiple anomalies could be explained as consequences of only one major anomaly as in the holoprosencephaly sequence, sirenomelia and the Pierre Robin sequence.

There were 133 babies (14.4%) where more than one anomaly were recorded in the same baby of which 13.5% were in stillbirths. A diagnosed syndrome was recorded in the early neonatal period in 39 cases, or in 4.2% of babies with anomaly. There were 62 babies (6.6%) with two or more unrelated major anomalies of which 29 had three or more anomalies, and 32 babies (3.4%) with a sequence of anomalies (Fig. 12).

The anomalies found in multiple anomalies are given in Tables 1 and 2. Table 1 lists, in descending order, the anomalies which are most commonly found in babies with multiple anomalies. Table 2 lists in descending order the frequency with which a particular anomaly is found together with another unrelated anomaly. Thus cardiovascular anomalies, talipes, genito-urinary anomalies (excluding hypospadias) are the anomalies most frequently encountered

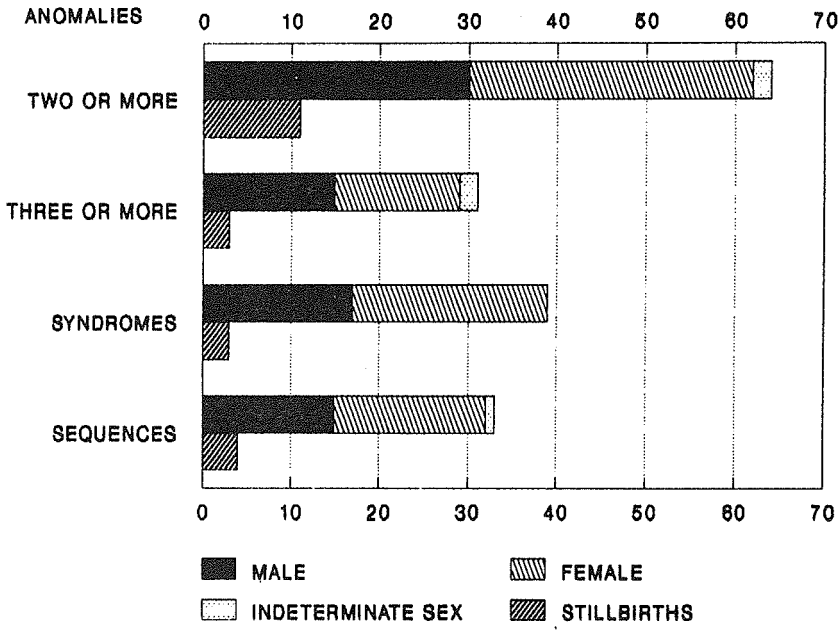

Figure 12. Prevalence of multiple anomalies

TABLE 1
Anomalies most commonly found in multiple anomalies

Cardiovascular anomalies	24%
Talipes	22%
Internal urinary anomalies	20%
Gastrointestinal anomalies	18%
Hypospadias	12%
Diaphragmatic defects	10%
Chromosome anomalies	6%

TABLE 2
Frequency with which anomalies are associated with other anomalies

Urogenital anomalies	53%
Microcephalus	50%
Diaphragmatic defects	45%
Respiratory anomalies	44%
Eye anomalies	44%
Omphalocoele\gastroschisis	33%
Limb reduction defect	33%
Gastrointestinal anomalies	32%
Cleft palate	31%
Anencephalus	21%
Cardiovascular anomalies	20%
Musculoskeletal anomalies	23%
Talipes	15%
Spina bifida	13%
Hypospadias	13%
Hydrocephalus	12%

in multiple anomalies. The converse, however, does not apply because only 20% of cardiovascular anomalies and 15% of talipes were associated with other anomalies. Genitourinary anomalies head the second list as 53% of these were associated with other anomalies and 45 to 50% of cases of microcephalus, diaphragmatic hernia, respiratory anomalies and eye anomalies were associated with one or more other unrelated anomalies.

OUTCOME OF BABIES WITH ANOMALIES

Analysis of anomalies according to foetal outcome showed that 9% of all congenital anomalies occurred in stillbirths and that 11.2% of all stillbirths had a congenital anomaly. The prevalence of anomalies among stillbirths is thus 6.5 times the rate among live-born babies. The anomalies which most frequently resulted in stillbirths (Fig.13) were cleft face (100%), anencephalus (40%), hydrocephalus (30%) and omphalocoele (29%). Among all stillbirths the most prevalent anomalies were those of the nervous system (mainly hydrocephalus and anencephalus) which occurred with a prevalence rate of 6% (600 per 10 000 stillbirths), cardiovascular anomalies with a rate of 2.9% (290 per 10 000 stillbirths), musculoskeletal anomalies with a rate of 1.9% (190 per 10 000), and limb anomalies with a rate of 1.7% (170 per 10 000).

Of live born babies with anomalies the highest frequency of early neonatal deaths (Fig.14) occurred in anencephaly (66%), diaphragmatic hernia (58%), microcephaly and other nervous system anomalies (43%) and cardiovascular

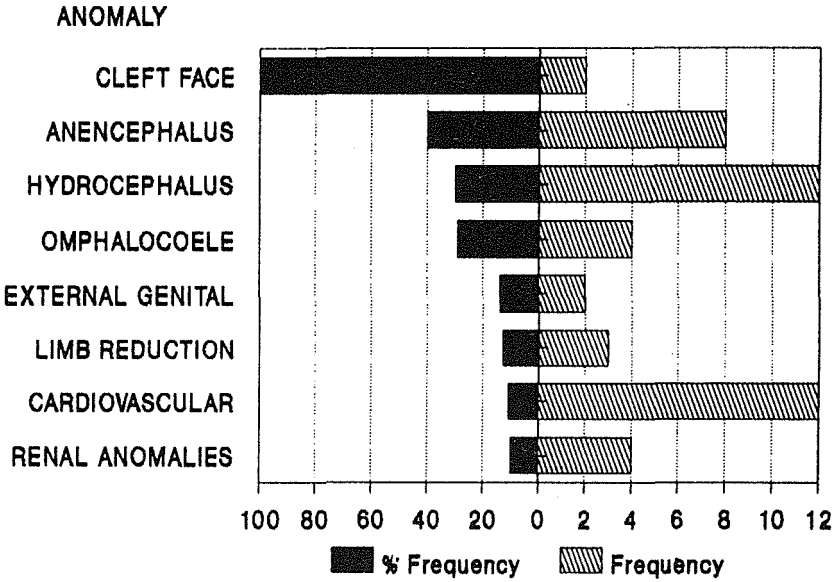

Figure 13. Relative and absolute frequencies of stillbirths in various anomalies

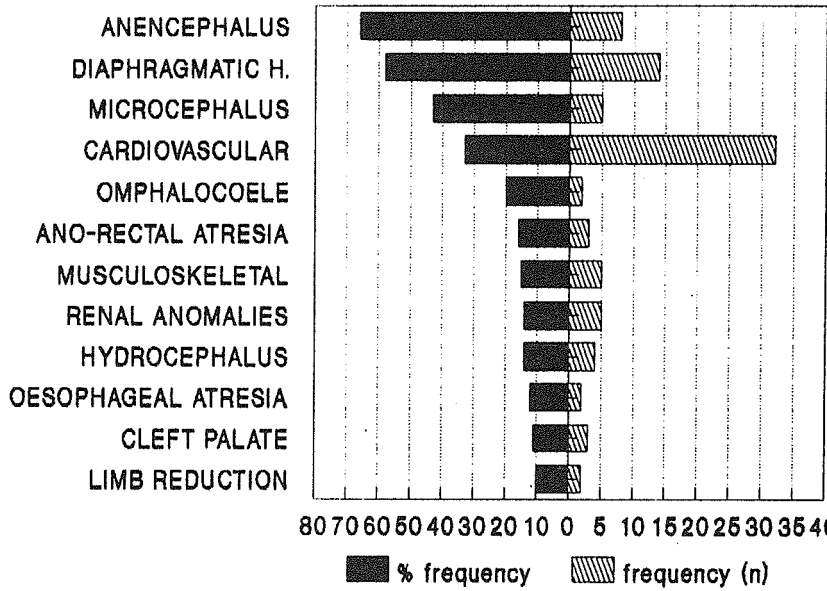

Figure 14. Percentage and absolute frequencies of neonatal deaths in babies with anomalies

anomalies (33%). In all 11.5% of congenital anomalies ended in early neonatal death and 25% of babies who died in the early neonatal period had a congenital anomaly. In this group of babies, the most frequent anomalies were those of the cardiovascular system (7.8 %), musculo skeletal anomalies (5.1%) and anomalies of the nervous system (4.9%). Diaphragmatic hernia and cardiovascular anomalies are amenable to surgical treatment which may reduce these causes of early neonatal.

BIRTH WEIGHT AND PREMATURITY

Mean gestational ages and mean birth weights were estimated for each anomaly and compared with the average values for all babies. The birth weight was markedly reduced in relation to gestational age for anencephalus and microcephalus, the difference being statistically significant at $p < 0.01$ level (Fig.15). It was also significantly reduced for omphalocoele and oesophageal atresia ($p < 0.01$), and for ano-rectal atresia ($0.01 > p < 0.5$) but these were in concordance with the corresponding gestational ages which were also significantly reduced from the expected means. For talipes mean birth weights were not reduced but showed a bimodal distribution with 17% of cases having a birth

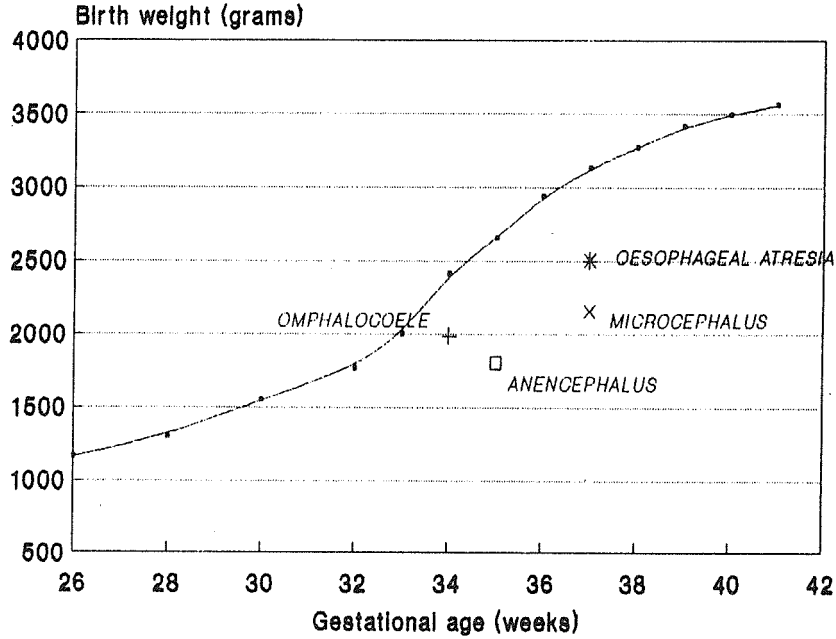

Figure 15. Birth weight and gestational age for selected anomalies

weights of less than 2500 g as compared with the population mean of 5%. These cases are mainly the severe multiple anomaly syndromes in which talipes frequently occurs. The majority of cases of isolated talipes had normal birth weights and gestational ages.

MATERNAL AGE DISTRIBUTION

Mean maternal age for all pregnancies was 28.7 years. Over 40% of all mothers are in the 25–30 year age group. There was an increase in mean maternal age for chromosome anomalies and intestinal atresia, with mean maternal ages of 33.7 and 31.4, years respectively. In both cases approximately 51% of babies with these anomalies were born to mothers above the age of 35 years. For other anomalies there was no significant difference in maternal age distribution.

CONCLUSIONS

The congenital anomalies seen at birth represent only the tip of an iceberg. Most cases of anomalies affecting the embryo, whether from chromosomal, genetic,

developmental or environmental causes end as spontaneous abortions. Other cases of anomalies, although congenital, are detected later in life, and are not reflected in the 19.3\1000 prevalence of birth defects in this report. There are wide variations in reported prevalence rates in different centres. The average prevalence in the 18 EUROCAT registries is 23.2\1000 with variations from 12.3\1000 in West Flanders to 32.2\1000 in Glasgow [8]. In Hungary, where there is a long-standing and comprehensive recording system, the prevalence rate is much higher, at 58.2\1000 [3]. Such a variation among registries, and even within the same registry over time, is partly due to completeness in ascertainment and to the adoption of different criteria for defining congenital anomalies, particularly the minor ones which are liable to be arbitrarily discarded as insignificant by the unwary. However, regional differences may also be due, at least in part, to actual differences such as in Hungary where the incidence of congenital dislocation of the hip is unusually high accounting for no less than half of all the cases of congenital anomaly.

16% of congenital anomalies are lethal in the perinatal period and several more die in infancy or early childhood. About half of congenital anomalies are treatable by surgery. Improvements in surgical techniques can reduce the perinatal mortality and determine the survival and quality of life for affected individuals. About a quarter of babies with congenital anomalies would be expected to survive but would have chronic disability.

In several countries prevalence rates at birth are being affected by prenatal diagnosis with subsequent termination of pregnancy as in the case of Down Syndrome for mothers above the age of 35 years so that prevalence rates range from 5.8 to 20.8 per 10 000 in 19 European populations [5]. Consequently congenital anomalies in terminated pregnancies have to be included in registers in order to be able to detect changing trends in prevalence rates and to be comparable to other countries where pregnancy termination is not performed. A EUROCAT collaborative study (1991) indicates that in some centres pregnancy termination is being performed in up to 80% of cases of anencephaly and 40% of cases of spina bifida thus reducing their prevalence among livebirths. Independently of this there also appears to be a downward secular trend and considerable geographic variation in the prevalence of neural tube defects.

The relatively small sample size obtainable from individual registries indicates the importance of collaborative International studies. The Maltese register has participated in a number of such studies incorporating different regions and countries of Europe, monitoring the impact of prenatal diagnosis, changing trends in prevalence and the influence of environmental factors. In one such study it was shown, for example, that there was no noticeable increase in the frequency of chromosome anomalies [4], and of central nervous system

malformations (EUROCAT working group, 1988) following the Chernobyl radioactive contamination accident.

One of the ultimate aims of the study of congenital anomalies is their prevention. Primary prevention is directed towards the primary causes, the environmental teratogenic agents and the relative genetic factors which first need to be identified. The Maltese register of congenital anomalies is now well established and is addressing some of these problems. However, one large source of congenital anomalies in foetal wastage remains largely untapped and needs to be extensively investigated. It could provide valuable clues for the prevention of congenital anomalies in the community.

REFERENCES

1. J.O.Beattie, R.E.Day, F.Cockburn *et al.*, Alcohol and the foetus in the West of Scotland, *British Medical Journal* 287 (1983) 17–20.
2. A.Cuschieri, Registration of congenital anomalies in Malta, *EUROCAT Report* 2, (1987) 243–249.
3. A.Czeizel K.Sankaranarayanan, The load of genetic and partly genetic disorders in man. 1. Congenital anomalies: estimates of detriment in terms of years of life lost and years of impaired life, *Mutation Research* 128 (1984) 73–103.
4. P. De Wals, F. Bertrand, I. De La Mata, M.F. Le Chat, Evaluation of the genetic impact of the Chernobyl accident. Analysis of the frequency of chromosomal anomalies in 19 EUROCAT Registries Jan. 1906–March 31, 1987, *Acta Paediatrica Latina* 41 supp. 3 (1988) 846–854.
5. H.Dolk, P.De Wals, Y.Gillerot *et al.*, The prevalence at birth of Down Syndrome in 19 regions of Europe 1980–86, in: I.W.Fraser, ed., *Key issues in mental retardation research* (Routledge, 1990) 3–11.
6. H.Dolk, P.De Wals, Y.Gillerot *et al.*, Heterogeneity of neural tube defects in Europe: the significance of site of defect and presence of other major anomalies in relation to geographic differences in prevalence, *Teratology* 44 (1991) 547–59.
7. H.Dolk, P.De Wals, F.Hamilton *et al.*, Investigation of an apparent high rate of microcephaly in Glasgow, and implications for epidemiological surveillance, *EUROCAT Report* 1 (1986) 102–122.
8. Eurocat Report 4. Surveillance of Congenital Anomalies Years 1980–1988. *EUROCAT Central Registry* (Brussels, 1990).
9. EUROCAT Guide 5. Classification and coding of congenital anomalies. *EUROCAT Central Registry* (Brussels, 1990).
10. EUROCAT Working Group. Prevalence of neural tube defects in 20

regions of Europe and the impact of prenatal diagnosis, 1980–1986, *Journal of Epidemiology and Community Health* 45 (1991) 52–58.
11. C.J.Jaccarini, P.Vassallo Agius. Congenital malformations survey. A preliminary report. *St. Luke's Hospital Gazette*, 7 (i) (1972) 25–29.
12. E.J.Lammer, D.T.Chen, R.M.Hoar *et al.*, Retinoic acid embryopathy, *New England Journal of Medicine* 313 (1985) 837–841.
13. A.C.Stevenson, H.A.Johnston, M.I.P.Stewart, D.R.Golding, Congenital malformations, *World Health Organisation* (Geneva, 1966).
14. H.M. Sultana, F. Calleja. Perinatal mortality necropsy findings, 1957–1966, *St. Luke's Hospital Gazette* 2 (i) (1967) 38–41.
15. J.Warkany, *Congenital Malformations*, Year Book Medical Publishers, (Chicago, 1971) 237–244.
16. W.H.O. Report DSI/72.7. Consultation on W.H.O. program of congenital malformations reporting (Geneva, 1972).
17. J.W.Wood, K.G.Johnson, Y.Omori, In Utero exposure to the Hiroshima atomic bomb. An evaluation of head size and mental retardation: Twenty years later, *Paediatrics* 39 (1967) 385–392.