CONGENITAL HEART DISEASE IN MALTA

A thesis submitted in accordance with the requirements of the University of London for the degree of Phil Doct (Ph.D.)

Victor E. Grech
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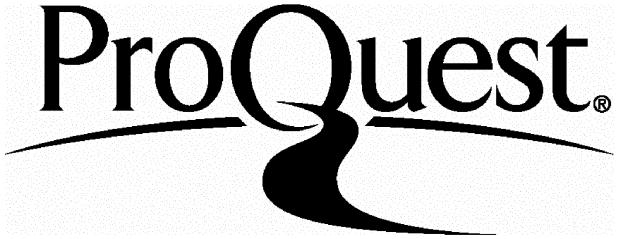

To children and adults with congenital heart disease world-wide

Declaration

This thesis is the result of my own work. The material contained therein has not been presented, nor is currently being presented, wholly or in part, for any other degree or qualification.

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Abbreviations and symbols

θ	theta
χ	chi
AS	aortic stenosis
ASD	atrial septal defect
ASDOS	atrial septal defect occlusion system
AV	aortic valve
AVR	aortic valve replacement
AVSD	atrioventricular septal defect
BAS	balloon atrial septostomy
BAV	bicuspid aortic valve
BHS	Blalock-Hanlon septectomy
Birmingham	Birmingham Children's Hospital, Birmingham
BTS	Blalock-Taussig shunt
CAVSD	complete atrioventricular septal defect
CC	cardiac catheterisation
CGMO	chief government medical officer (health division)
CHD	congenital heart disease
CI	confidence interval/s
Coarctation	coarctation of the aorta
COS	Central Office of Statistics, Malta
DOB	date of birth
DOH	Health Division (formerly Department Of Health), Malta
EC	echocardiography
EUROCAT	European Register of Congenital Anomalies and Twins
GOSHC	Great Ormond Street Hospital for Children NHS Trust
Hammersmith	Hammersmith Hospital, Hammersmith, London
HLHS	Hypoplastic left heart syndrome
IAA	interrupted aortic arch
ICH	Institute of Child Health
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
MAPCAD	Maltese Paediatric Cardiology Database
MBTS	Modified Blalock-Taussig shunt
MI	mitral incompetence
MR	mortality rate
MRI	magnetic resonance imaging
MVP	mitral valve prolapse
NHS	National Health Service (UK NHS unless otherwise specified)
PAB	pulmonary artery band
PAVSD	partial atrioventricular septal defect
PDA	patent ductus arteriosus
PFO	patent foramen ovale
PM	perioperative mortality
PS	pulmonary stenosis
PV	pulmonary valve

RVOT	right ventricular outflow tract
RVOTO	right ventricular outflow tract obstruction
SAS	subaortic stenosis
SLH	St. Luke's Hospital, Malta
SPSS	Statistical Package for Social Sciences
St. Mary	St. Mary's Hospital, Paddington, London
SVD	sinus venosus defect
TGA	transposition of the great arteries
TOE	transoesophageal echocardiography
TOF	tetralogy of Fallot
Truncus	truncus arteriosus
UK	United Kingdom
VACTER	Vertebral, Anal, Cardiac, Tracheal, Esophageal, Radial and Renal anomalies
VCC	visiting consultant clinic
VSD	ventricular septal defect
WHO	World Health Organisation

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Abstract

Introduction

Congenital malformations are important causes of morbidity and mortality. Congenital heart disease (CHD) is a label for a heterogeneous group of lesions which comprise the commonest group of malformations. Treatment of CHD has only been available for the past half-century, making paediatric cardiology and cardiac surgery relatively new subspecialities.

Malta provides an ideal location for historical and epidemiological studies dealing with congenital malformations due to its relatively closed population and lack of antenatal screening programs due to unavailability of termination of pregnancy.

Epidemiology

Analysis of the epidemiology of CHD in Malta over 1990-94 showed a significant excess of minor ventricular septal defects, which is attributed to high-quality clinical services which diagnose these defects prior to spontaneous closure. A significant excess of lesions causing right ventricular outflow tract obstruction, particularly Fallot's tetralogy, and a relative scarcity of lesions causing left ventricular outflow tract obstruction were also found. A genetic predisposition to right ventricular outflow tract obstruction may be inherent in the Maltese population.

A significant seasonal variation in lesions requiring intervention was found with a peak in the third quarter of the year. These deliveries are conceived in the last half of the year with the first trimester occurring in the peak of the coldest weather. Environmental factors may be influencing predisposed fetuses, precipitating CHD.

A significant North-South variation in the overall birth prevalence of CHD was also found, with a higher prevalence in the Southern part of the Island. The demographic trends suggest that environmental factors, rather than genetic factors, may be causing a higher rate of CHD in the South.

Historical trends

This study has also shown that diagnosis and intervention in all types of CHD has occurred progressively earlier in childhood, with an ever decreasing delay in the application of new techniques to Maltese patients with CHD. These trends were significant and were associated with a significant declining mortality from CHD, both perioperatively and as a crude specific population mortality rate.

Conclusion

Treatment of CHD has been very successful with a substantial decrease in mortality, increasing the pool of survivors and hence the need for health services.

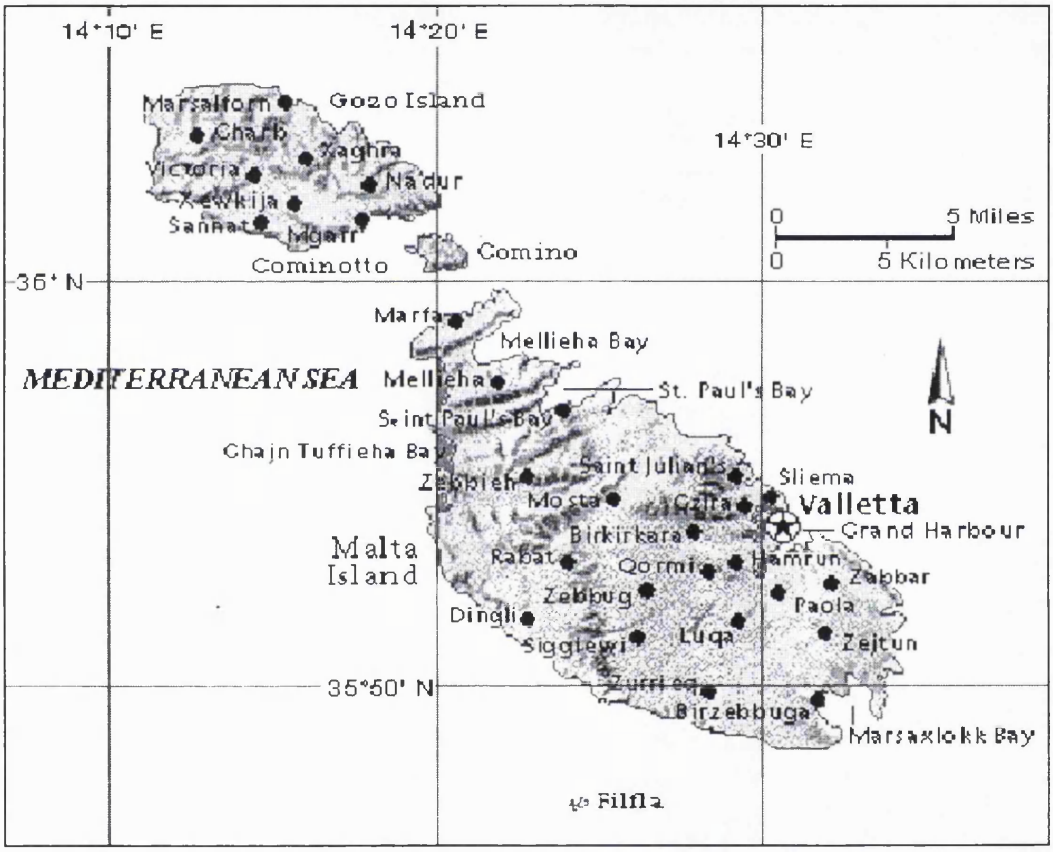
Further work regarding possible environmental conditions which may precipitate CHD could isolate avoidable predisposing factors, allowing a reduction in live births with CHD.

1. Introduction

1.1 The geography of the Maltese Islands

The Maltese Archipelago comprises the islands of Malta, Gozo and Comino (figure 1.1) which are inhabited, together with a few other islets. The largest island is Malta with a maximum length and breadth of 27.36 km by 14.48 km respectively, and an area of 246 km^2. The second largest island is Gozo with an area of only 67 km^2.

Figure 1.1: The Maltese Archipelago



The archipelago is situated in the centre of the Mediterranean Sea, 93 km south of Sicily and 288 km north of North Africa. Alexandria lies 1519 km to the east whilst Gibraltar lies 1826 km to the west. At their extreme points the Maltese Islands fall within the following co-ordinates: Northern latitude 36°35'00", Southern latitude 35°48'00"; Eastern longitude 14°35'00", Western longitude 14°10'30" (Schembri 1994).

1.2 Historical and cultural background

The exact origins of the Maltese people remain uncertain. Archaeological remains indicate that the first settlers came from Sicily towards the end of the fifth millennium BC. Dolicocephalic skulls dating from the Neolithic age have been excavated from various tombs in Malta. These skulls demonstrate a long-headed race with Armenoid features typical of other Mediterranean races. The Neolithic skulls differ from modern Maltese skulls only by being consistently longer and narrower (Dudley Buxton 1922).

Throughout history, there have been major influences on Malta by neighbouring circum-Mediterranean races. The genetic make-up of the Maltese race is the result of these influences and the legacy of numerous successful invasions of the Islands. This has led to the present genetic mix which is primarily Levantine with strong Greco-Roman and Arabic influences. European blood, particularly Italian, Spanish, French and Anglo-Saxon, was assimilated later (Gerada-Azzopardi and Zuber 1981).

Foreign influences have also affected various aspects of Maltese life and this is especially noticeable in the language, although this is a language in its own right. While basically Semitic, Maltese is an off-shoot of Phoenician with a heavy infiltration of Arabic and the romance languages, and is written with a Latin alphabet (Aquilina 1981).

1.3 Demography and health statistics

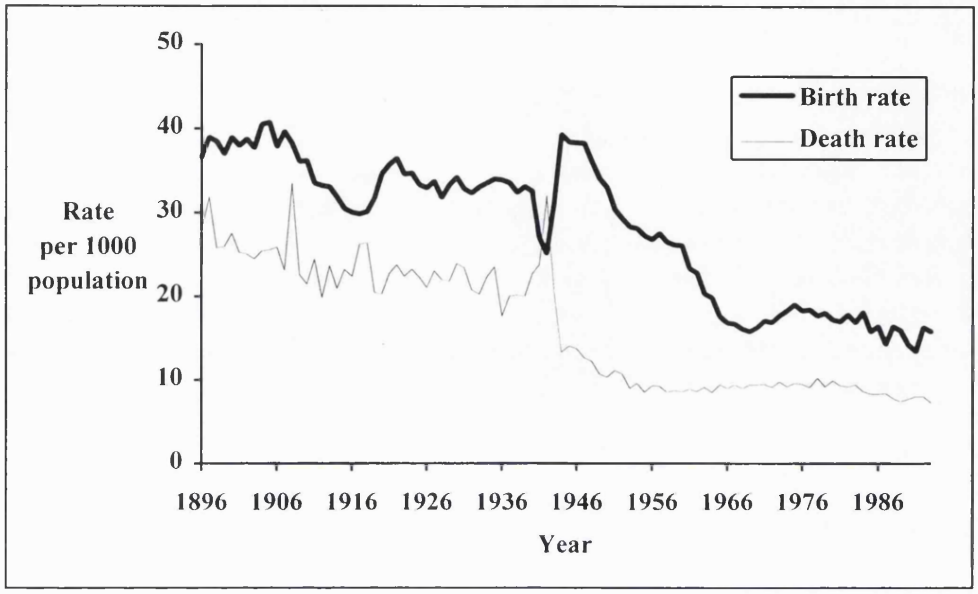
The health status of any community is based on a complex interplay of disease, environment, education and socio-economic status. The first census in a series of regular population censuses was carried out in 1842. There has been a steady population growth during each intercensal period except in 1911-1921 and 1957-1967, when the population decreased because of emigration. The Maltese population stood at 376,335 in the 1995 census (COS 1996).

Birth rate

The crude birth rate is defined as the number of births in one year per 1000 population. The Maltese birth rate prior to the Second World War (1939-1945) varied little (figure 1.2) but fell during the war years. The aftermath of the war brought a 'baby-boom' which persisted until 1950, before diminishing to 15.4 live births per 1000 population in the last decade.

The birth rate is expected to decline further, and by the year 2000 will be at 13.7 per 1000 population (Savona-Ventura and Grech 1986, Savona-Ventura 1990, Savona-Ventura 1995a, DOH 1896-1961, COS 1961-1994).

Figure 1.2: Trends in birth and death rates (1896-1993)



Mortality statistics

Routine mortality statistics have a limited but useful role in evaluating the health status of a community. Mortality statistics do not take into account other problems which may significantly disable the individual but not cause death. They also fail to discriminate between potentially preventable and unpreventable diseases and deaths. Cause-specific mortality is often questioned since it is dependent on a doctor correctly identifying cause of death, as well as the method used for such identification. More sensitive mortality statistics are the maternal, perinatal and infant MR. However, these must be viewed cautiously as the annual number of births in the Maltese Islands is small which may cause marked annual fluctuations in rates.

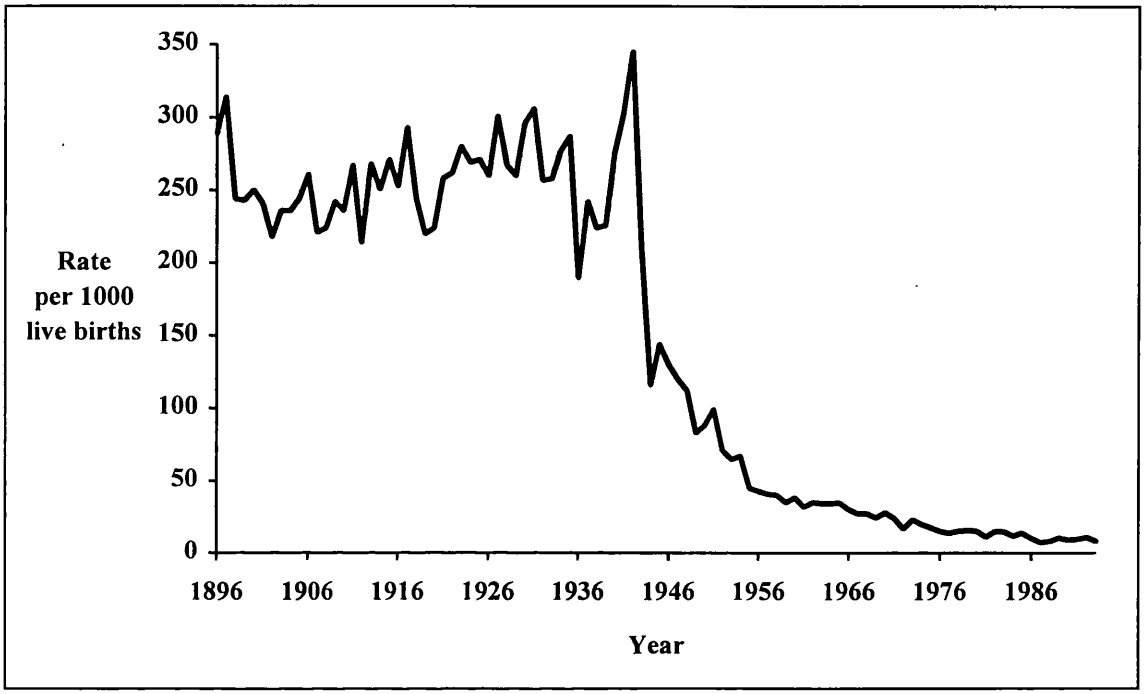
The crude MR is defined as the number of deaths in one year per 1000 population. In the 1930s, this averaged 21.2 per 1000 population (Figure 1.2), mainly due to a high infant MR. It decreased slowly and trends in death rates from all causes over the last 15 years show a marked decline (DOH 1896-1961, COS 1961-1994).

Perinatal, neonatal and infant mortality

The infant MR is defined as the number of deaths under one year of age in one year per 1000 livebirths, and is one of the main indicators of quality of health care in the community. Prior to the 1940s, the main cause of death in the infant group was infectious diseases, especially diarrhoeal diseases, all of which are related to poor social conditions. At this time the infant MR was approximately 250 per 1000 live births (figure 1.3). The mid-1940s brought a sharp decline due to a lower incidence of infectious disease. This was due to the increased prosperity of many strata of the population, better nutrition, the availability of immunisation and antibiotics, the intensive work of health visitors and the greater attention bestowed in general to health requirements.

In addition, the post-war marriage boom resulted in a greater proportion of births being first-born infants allowing better infant care from their mothers. The infant MR continued to fall progressively to reach an average figure of 10 per 1000 live births, the majority of which are early (first week) neonatal deaths (Savona-Ventura 1990, Savona-Ventura 1995b, COS 1961-1994).

Figure 1.3: Infant mortality rate (1896-1993)

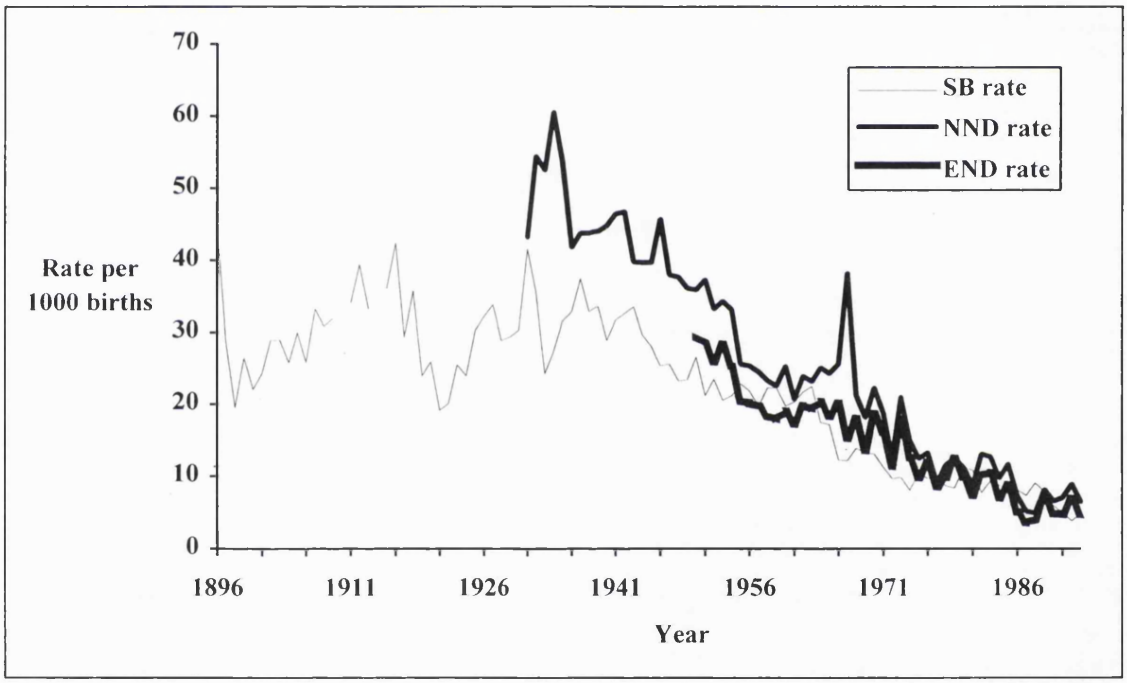


The neonatal death rate is defined as the number of deaths under 28 days of age in one year per 1000 live births. Information about neonatal deaths has been officially published since 1935, while early neonatal deaths were considered separately only after 1951 (figure 1.4). This data shows a gradual decline in neonatal mortality which started in the mid-1940s coinciding with the fall in infant death rate. However, it was more gradual since diarrhoeal disease accounted for a smaller proportion of neonatal deaths. The neonatal MR in the last decade averaged 7.5 per 1000 live births.

The early neonatal death rate is defined as the number of deaths under 7 days of age in one year per 1000 livebirths. It has declined progressively (figure 1.4) and the two major contributions are deaths associated with low birth weight infants, and conditions associated with pregnancy or delivery giving rise to fetal hypoxia. The last decade had an average rate of 5.6 per 1000 live births. Other causes of early neonatal deaths include congenital abnormalities and a variety of less important causes, including infections and isoimmunization. These have maintained an approximately steady trend contributing only minimally to neonatal deaths (Savona-Ventura 1990, Savona-Ventura and Grech 1986, COS 1961-1994).

The stillbirth rate is defined as the number of fetal deaths over 28 elapsed weeks of gestation in one year per 1000 livebirths and stillbirths. These Maltese rates are available for the entire twentieth century (Figure 1.4). The first part of the century showed a rise in stillbirth rates which may be partly attributed to improved registration practices. The first marked drop in stillbirth rates occurred in the mid-1940s and is attributed to better antenatal supervision that had been initiated by war conditions, and the increase in the proportion of supervised hospital confinements. Another sharp fall in stillbirth rate occurred after 1963. This drop has been ascribed to the decrease in birth rate which occurred during this period and reduced the work load on antenatal services. The stillbirth rate in the last decade averaged 6.8 per 1000 total births (Savona-Ventura 1990, Savona-Ventura 1995b, Grech and Savona-Ventura 1986, COS 1961-1994).

Figure 1.4: Stillbirth and neonatal mortality rate trends (1896-1993)



SB rate: Stillbirth rate
NND rate: Neonatal death rate
END rate: Early neonatal death rate
Stillbirth rates per 1000 total births; Neonatal death rates per 1000 live births

1.4 Organisation of health services

The health of the Maltese population falls under the responsibility of the Health Ministry. The Department of Health has a civil service structure and is headed by the CGMO who also functions as Superintendent of Public Health. A change is being implemented towards a more compartmentalised structure with various Directorates falling under a Director General who will replace the CGMO. Access to state health care is free of charge at all levels to all Maltese citizens, irrespective of income or financial status.

There are seven state hospitals which provide a total of 3200 beds, 1200 of which are designated for acute care (i.e. 3.4 acute beds per 1000 population). Primary health care services are based around six health centres. These provide a variety of services including domiciliary visits by general medical practitioners, community nursing, midwifery care, physiotherapy, speech therapy, psychiatric social work, chiropody, child psychology, dentistry, diabetes clinics, psychiatric clinics, child health services and immunisation facilities. The Department of Health is also responsible for industrial health and hygiene and the School Medical Services.

A Health Education Unit was set up in 1982 in order to promote healthy lifestyles and to advise on the prevention and control of health hazards. Recent programs were directed against tobacco smoking, inappropriate nutrition and Human Immunodeficiency virus (DOH 1986).

In addition, a widespread network of private medical services, including two hospitals, is available and includes virtually all subspecialities.

Over 99% of all deliveries in Malta take place in the two main State hospitals (St. Luke's Hospital and Gozo General Hospital). Hence, it is unlikely that any significant cardiac malformations would be missed in the few deliveries occurring in private clinics or as home deliveries.

1.5 Malformations

1.5.1 Introduction

Since the mid-twentieth century many important discoveries have been made particularly in the areas of hereditary mechanisms, environmental teratogenesis, prenatal diagnosis and medical/surgical management of affected individuals.

The history of malformations in the Maltese Islands reflects the cultural links with the mainland Mediterranean. The attitude towards congenital malformations can be divided into two periods.

1.5.2 The period of superstitious beliefs: prehistory to the seventeenth century

Congenital malformations causing deformities have been described since early times. Primitive man's interest in these phenomena has found expression in drawings, carvings and sculptures throughout the world including Australia, the South Pacific Islands, and the Americas.

Written records of congenital malformations have come down from Babylon in the form of clay tablets from the Royal Library of Nineveh which was assembled by the Assyrian King Asshurbanipal (c.700 BC). These tablets include a list of sixty-two human malformations with their associated prophetic implications (Brodsky 1943). It is believed that these records date back to 4000 BC.

Direct evidence of congenital malformations in primitive cultures were found in skeletal remains of affected individuals, such as a specimen of an open sacrum and a femur described from Neolithic France with changes suggestive of congenital dislocation of the hip (Sigerist 1967).

The first treatise on monsters appeared in the sixth century AD by Isidore of Seville who described numerous abnormalities and tried to give natural reasons for their occurrence, although supernatural causes were not discounted. From the mid-16th to the mid-17th centuries, several books on monstrous births were published and a number of authors published a variety of collections of such births and discussions on their cause (Barrow 1971).

The earliest recorded congenital malformations in Malta date from the Neolithic era and include cases of abnormalities of the hand: one with three digits and one with six digits. These representations were discovered in an incised decoration from Gzibbu Tombs at Zebbug and a statuette from Hagar Qim (Zammit and Singer 1972).

The theory of supernatural causes for the development of congenital malformations held sway from prehistoric time well into the seventeenth century. Another aetiological theory was that of maternal impressions i.e. states of mind, affecting fetal development. However, John Hunter presented scientific evidence against maternal impressions in the late 18th century (Barrow 1971). In Malta maternal impressions were also considered important aetiological factors. In 1749, the Maltese physician Dr. Salvatore Bernard adhered to the theory that the 'fantasy organ' of the pregnant woman communicated by means of animal spirits with the equivalent organ of the fetus producing an impression on the fetal mind which moulded the form of its body (Cassar 1949).

1.5.3 The modern period: eighteenth century to date

The eighteenth century saw the beginnings of modern attitudes towards the aetiology of malformations. The developmental arrest theory of teratogenesis was first developed by William Harvey (1651) who reasoned that cleft lip in human infants was very similar to the normal situation found in early embryos. This concept was extended to explain ectopia cordis and gastroschisis. Although not totally understood, inherited anomalies had been recognised by Ambroise Pare (1649) and John Hunter (1775). However the genetic theory as a cause of malformations gained momentum when the inheritance laws described by Gregor Johann Mendel (1865) were rediscovered in 1900 by Carl Correns, Hugo de Vries, and Erich von Tschermak (Sturtevant 1965).

Medical publications in Malta during the nineteenth century do not shed light on the beliefs prevalent among Maltese practitioners regarding the aetiology of congenital malformations. However, the description of a Maltese family in 1891 with a genetic predisposition to having twenty-four digits suggests that the hereditary theory was being entertained for at least some anomalies (Gulia 1891).

There are no sources which give indications of the incidence of congenital malformations in the Maltese population prior to the mid-twentieth century. Apart from a number of studies aimed at identifying the prevalence patterns of some specific anomalies in the 1960-70s, no large-scale population-based epidemiological studies were undertaken in Malta until the 1980s (Vella 1962, Cachia and Fenech 1966, Cauchi 1968). This lack of data is not surprising in view of the fact that before the First International Conference on Congenital Malformations in 1960, there were very few studies in the world literature on incidence of congenital malformations.

A small preliminary survey of congenital anomalies in live-born Maltese children was performed in 1972 reporting 20 anomalies in a total of 1016 consecutive births (Jaccarini and Vassallo-Agius 1972). In 1983, a computer-based database was initiated in the Department of Obstetrics and Gynaecology for the registration of all the births and malformations which occurred in SLH. Another database was initiated in 1986 by the Departments of Genetics and Obstetrics-Gynaecology in conjunction with the EUROCAT Project (Eurocat, 1987).

1.5.4 Historical background to cardiac malformations

The importance of the heart in sustaining life was recognised by Aurignacian man at least 20,000 years ago. This hunter drew an outline of a mammoth with the heart marked in red ochre in the cave of Pindal in Northern Spain.

Aristotle is credited with the earliest observations of normal cardiovascular function by describing the fetal pulsations in a chick embryo. However, it was Galen who first attempted to explain the anatomical and physiological function of the arterial duct and the foramen ovale with blood being generated by the liver.

Descriptions of cardiac malformations date back even earlier to 4000 BC. The earliest cardiac malformation comes from a clay tablet from the Royal Library of Nineveh (Brodsky 1943). This details ectopia cordis and was associated with calamities for the entire country.

Modern Science was born in the 15th and 16th centuries during the Italian Renaissance. Indeed, the next description of a cardiac malformation came from Leonardo da Vinci (1452-1519) who drew and described an ASD in 1513. Leonardo subscribed to the Galenic theory of flux and reflux through the veins (Thiene 1996). Andreas Vesalius (1514-1564) proposed that the heart was the centre of the network of blood vessels and believed that the pulmonary veins carried air from the lungs to the left atrium (Vesalius 1540). Realdus Colombus (1516-1559) discovered that the pulmonary veins carry blood, not air (Thiene 1996). Hieronymus Fabricius ab Acquapendente (1533-1619) described valves in veins (Acquapendente 1603) and William Harvey (1578-1657) realised their function in maintaining centripetal flow in veins, thus establishing the true concept of circulation (Harvey 1579).

Several more descriptions of CHD lesions followed in the 17th century including Fallot's tetralogy which was described by Steno well before the condition's clinical aspects were emphasised (Fallot 1888, Warburg 1942). A long debate arose for almost a century as to whether cyanosis was primarily caused by mixing of blood in the heart or by obstruction. From the 19th century, various detailed descriptions of CHD began to be published leading to today's understanding of the pathophysiology of the numerous lesions which comprise CHD (Rashkind 1979).

1.5.5 Mortality trends from malformations

Congenital malformations are important contributors towards perinatal deaths. Mortality statistics can be used to identify trends of certain severe lethal abnormalities. However, it must be remembered that the actual reporting of birth defects may vary considerably due to differences in definition and terminology over the years.

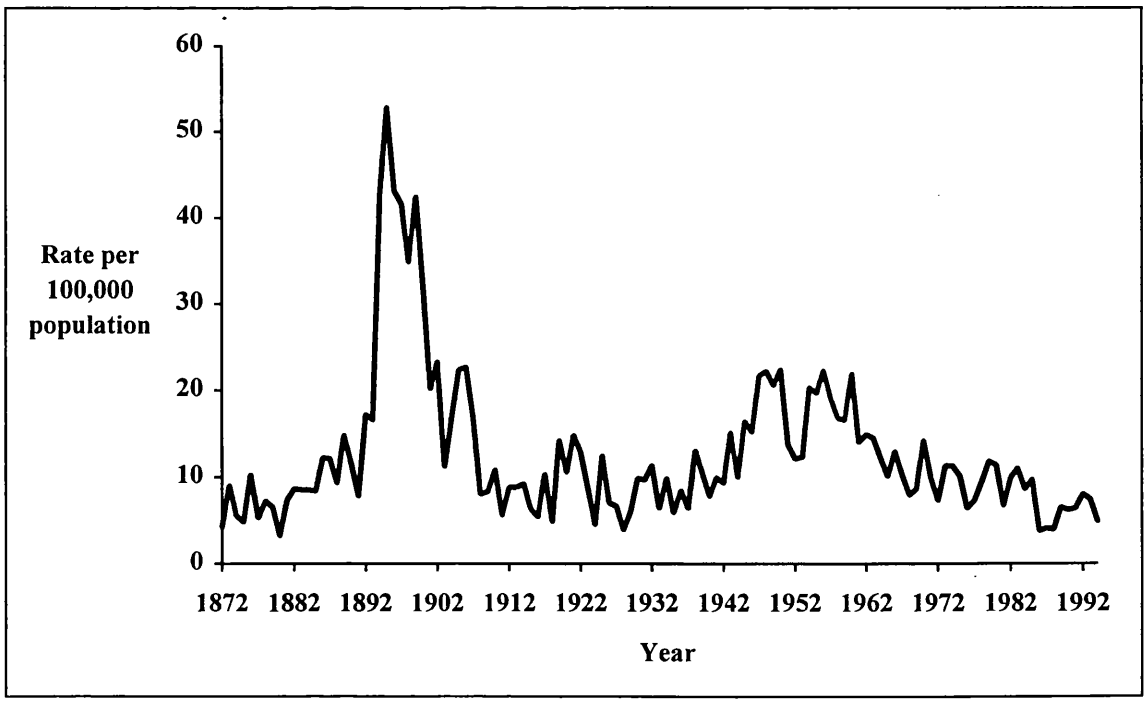
Published mortality data by cause of death is available in Malta since May 1872 in the form of fortnightly reports published by the Chief Police Physician (the forerunner of the CGMO). Annual reports have been published by the CGMO since 1896. Cause-specific MRs for the Maltese Islands are available, but breakdown by specific causes was not published for certain years (DOH 1872-1971).

Interpretation of mortality trends is difficult as cause-specific mortality is dependent on a correct diagnosis of the cause of death. In addition, the small numbers involved in Malta result in wide annual fluctuations.

The mean overall specific MR from malformations for the decade 1873-1882 was 6.8 per 100,000 population (Figure 1.5). This figure is a likely to be an underestimation as a result of misdiagnosis and misregistration as to cause of death. This rate was maintained until the mid-1890s when a rise in anomalies-specific MR was reported. In 1899 the specific MR was 42.4 per 100,000 population. The number of deaths from malformations decreased and this rate was maintained during the First World War of 1914-18 which did not adversely affect the Maltese population (Savona-Ventura 1995b). The rate rose after this war, an era associated with a marked deterioration in the social circumstances of the population. A similar rise can be noted for the overall mortality from congenital anomalies after the Second World War of 1939-1945 (Savona-Ventura 1990a).

The low socio-economic status of the population which has been associated with adverse environmental factors including nutritional deficiencies, may be partly contributory towards an increased incidence of unviable congenital malformations. Another likely contribution to this increased rate is an increase in the identification and registration of congenital disorders as causes of death. Haemophilia, thalassaemia major, coeliac disease and gangliosidosis were identified by Maltese clinicians during the 1950-70s. After the 1950s, the specific MR declined to a mean of 7 per 100,000 population in the 1980s.

Figure 1.5: Specific mortality from congenital malformations (1872-1993)



A gradual decrease in MR caused by congenital malformations has also been reported from other European countries in the last decades of the twentieth century. The anomalies-specific MR in the European region decreased from a mean of 9.2 per 100,000 population in the late 1960s to 4.3 in the early 1990s (table 1.1-WHO 1967-1995).

Table 1.1: Infant mortality rate from congenital anomalies per 100,000 population, and percentage dying in infancy

Country	1967		1978		1993	
	Rate	% < 1 yr.	Rate	% < 1 yr.	Rate	% <1 yr.
Austria	9.5	85.5%	5.3	76.6%	3.2	70.4%
Denmark	8.0	70.5%	5.8	56.4%	5.1	56.4%
France	7.6	79.8%	4.6	66.1%	3.0	72.7%
Germany	8.2	80.2%	4.7	67.1%	3.1	59.8%
Greece	8.8	85.0%	8.6	81.4%	4.5	76.0%
Hungary	10.4	87.4%	10.5	77.6%	5.8	58.3%
Ireland	17.1	80.6%	10.3	77.1%	6.4	61.2%
Italy	8.3	78.9%	6.7	74.8%	3.3	63.1%
Luxembourg	8.4	89.3%	4.2	46.7%	2.1	75.0%
Netherlands	10.1	64.6%	6.1	60.2%	4.8	65.2%
Norway	7.1	64.0%	5.8	55.7%	4.8	53.1%
Poland	9.2	87.2%	11.5	82.9%	6.6	78.1%
Portugal	7.2	78.9%	7.3	79.7%	4.4	67.0%
Spain	4.9	83.3%	8.4	83.5%	3.6	62.7%
Sweden	6.5	62.8%	5.3	59.6%	4.3	57.9%
Switzerland	9.8	71.6%	5.4	62.7%	3.5	65.4%
UK: Engl. & Wales	9.4	70.5%	5.9	57.7%	4.4	46.3%
UK: N. Ireland	14.5	82.5%	10.1	63.9%	4.8	66.2%
UK: Scotland	10.3	73.4%	5.1	62.3%	4.1	65.6%
Maltese Islands	10.0	80.5%	9.0	76.8%	6.6	68.9%

Maltese Islands: Means of 1965-69, 1975-79, 1900-94

The majority of deaths from congenital anomalies in the Malta in the twentieth century occurred during childhood, mainly during the first year of life.

In a study of 243 perinatal deaths occurring in Malta who underwent post-mortem examination during the period 1957-66, congenital malformations were identified as being the second commonest cause of perinatal loss accounting for 15.2% of deaths, 73.3% being early neonatal deaths (Grech and Savona-Ventura 1986). Congenital anomalies accounted for 16.8% of all perinatal deaths during the period 1979-82 and 23.5% during 1983-86 (Sultana and Calleja 1967).

The overall incidence of severe congenital anomalies in Malta during 1983-91 has been estimated at 19 per 1000 total births. The stillbirth rate from congenital anomalies amounted to 0.91 per 1000 total births, while the early neonatal death rate from malformations amounted to 1.86 per 1000 total births. During the same period, a total of 163 post-perinatal deaths were registered as being caused by congenital anomalies, a specific MR of 3.3 per 1000 total births. These figures suggest that approximately a third of infants with congenital anomalies died from their disorder/s during the perinatal period. The commonest cause of death was CHD and the second commonest were central nervous system malformations, especially spina bifida and hydrocephalus (Cuschieri 1993).

1.5.6 Differences in malformation rates

The rates of malformations can be shown to vary significantly between different countries, and indeed, between different centres in the same countries (table 1.2-Eurocat 1987). Variations in rates of malformations may be due not only to inherent differences in the populations but also to different definitions and methodologies. This will be discussed in further detail in relation to CHD chapter 5.

Table 1.2: Rates of common anomalies in Malta and in other Eurocat registries per 1000 births for live births+fetal deaths from 20 weeks of gestation+termination of pregnancy

Defect	Malta	Rest of Eurocat Registries
Neural tube defects	1.11	1.07-1.43
Internal genitourinary anomalies	0.74	0.99-4.79
Hypospadias	1.21	0.25-2.41
Cleft lip±cleft palate	0.45	0.57-1.59

(No terminations of pregnancy recorded in Malta)

Aetiology of congenital heart disease

CHD is believed to be caused by genetic-environmental interactions in the vast proportion of cases (Nora 1994). However, some causes of CHD are well known.

Chromosomal/genetic predisposition

The commonest known genomic predisposition to the development of CHD is Down's syndrome, which causes 5% of all CHD (Kenna et al 1975). Other trisomies such as Edward's and Patau's syndromes (trisomy 18 and 13 respectively) are also associated with CHD, but these are much rarer. Another chromosomal abnormality associated with CHD is Turner's syndrome. Microdeletions are increasingly implicated as predisposing to CHD, particularly 22q11 in relation with conotruncal anomalies (Wilson et al 1992).

Teratogens

Teratogens have also been linked with cardiac malformations, but are believed to be far rarer causes of CHD. Teratogens include maternal medication such as lithium, heavy maternal alcohol abuse, metabolic disorders such as poorly controlled diabetes and phenylketonuria during pregnancy, and infections in the first trimester of pregnancy such as rubella (Nora and Nora 1978). It is important to note that there is a high uptake of rubella vaccination in Malta, with very rare cases of congenital rubella.

2. The importance of a study on CHD in Malta

Epidemiological studies that deal with malformations are important for several reasons.

1. Clusters in time and/or space may provide clues as to the aetiology.
2. Quantification of incidence, prevalence and spectrum of malformations, along with analysis of past trends in management allow for planning of future provision of health services.
3. Outcome, including survival rates and long-term complications of disease and treatment can be assessed.
4. Recurrence risks for siblings and offspring can be calculated.

Certain conditions are essential for an epidemiological study on congenital malformations to be valid and useful.

1. The catchment area must be clearly defined.
2. There must be clearly identified referral routes for patients with suspected CHD.
3. Methods used for reaching a diagnosis must be objective and reliable.
4. Accurate and retrievable records must be available.
5. There must be precise registration of births and deaths with post-mortems carried out on all deaths without a known diagnosis.

All of these conditions were satisfied for CHD in Malta since approximately 1990.

The primary aim of this study was to establish the epidemiological characteristics of CHD in Malta including birth prevalence and spectrum. All Maltese patients who have had a definitive diagnosis of CHD have been recruited into this study. This study will show that ascertainment of CHD in Malta is extremely high for the years 1990-1994. Data from this 5-year period is compared with results from previous studies performed in other countries. This was used to test the null hypothesis that a small Island population with a relatively restricted gene pool will show no differences in birth prevalence or spectrum of CHD.

The secondary aims were to evaluate trends in diagnosis, treatment and short-term outcome of CHD overall, and by individual lesions.

It is important to stress the uniqueness of this study due to the properties of the Maltese population, which is relatively small, captive and possesses accurate record keeping, allowing the true birth prevalence of CHD to be calculated. This is in contrast to a tertiary referral centre which is likely to have referrals from other geographical regions, including other countries. Referrals will tend to be cases of severe CHD, and therefore require intervention. This will skew patient composition giving a falsely severe impression of the spectrum of CHD.

Furthermore, the total number of Maltese patients who have ever been diagnosed as having CHD is small enough to allow one researcher to enter and analyse all of the trends in the diagnosis and treatment of CHD since the birth of paediatric cardiology and cardiac surgery which occurred in the middle of the 20th century (table 4.1).

The Maltese Medical School one of the oldest in the world but there are insufficient doctors in training to allow the establishment of local postgraduate examination boards. Malta has strong medical links with the UK which date back to the First World War. It has been the custom for the majority of postgraduate trainees to undergo further training and examination in the UK, which has further strengthened the medical links between the two countries.

This has led to visiting cardiologists over the past 30 years all being based in England. Hence, the developments in local paediatric cardiology services have run in parallel with services in the UK. The small size of the country enabled all patients diagnosed as having CHD to be identified and entered onto a database by a single person, ensuring complete ascertainment and accuracy of all diagnosed cases.

Since diagnostic and interventional decisions were undertaken by the above-mentioned consultants, it is reasonable to assume that the trends found locally can be extrapolated to larger countries.

3. Materials and methods

3.1 Literature search, ethical approval and tuition

A literature search regarding the epidemiology of CHD was carried out in 1994. A detailed proposal was completed and accepted by the ICH. Ethical approval was sought and obtained from the Ethics Committee of GOSHC (appendix 1) and by the Ethics Committee, University of Malta, Medical School (appendix 2). The proposal was then presented to the Health Authorities in Malta who agreed to finance tuition fees and provide paid study leave.

3.2 Definitions and exclusions

For the purposes of this study, CHD was defined as a structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance (Mitchell et al 1971). This definition encompasses a wide variety of defects hence the term CHD is a label for a very heterogeneous group of lesions. The following conditions were excluded:

1. Arrhythmias unless accompanying structural abnormalities.
2. PDA occurring in association with prematurity and which resolved spontaneously or required treatment before 3 months of age.
3. BAV in the absence of AS.
4. Isolated MVP with or without MI.
5. Isolated dextrocardia in the absence of accompanying structural abnormalities.
6. ASDs which closed spontaneously on follow up or were shown at EC to be haemodynamically insignificant and therefore did not require intervention.
7. Dilated and hypertrophic cardiomyopathies.

In this study, PS was defined on EC as a velocity >2m/s across the pulmonary valve (Wilson et al 1985) associated with clinical signs of pulmonary stenosis.

AS was defined on EC as a velocity >2m/s across the aortic valve (Wilson et al 1985) associated with clinical signs of aortic stenosis.

DORV was defined as an outlet VSD with ≥ 90% override of both great arteries on parasternal long axis view at EC.

Partial AVSD was defined as AVSD (formerly atrioventricular canal/endocardial cushion defect) with only interatrial communication. Complete AVSD was defined as AVSD with both interatrial and interventricular defects.

3.3 Confirmation of CHD

Diagnosis of CHD was only accepted if confirmed by EC, CC, surgery or post-mortem. Recent studies dealing with the epidemiology of CHD have only included live-born patients diagnosed in infancy i.e. by one year of age. Due to the historical and epidemiological nature of the study, this condition was not applied except for epidemiological calculations in the 5 year period 1990-94. Mention will be made in the text when this condition was applied.

3.4 Classification

Cases with multiple CHD diagnoses had their lesions classified hierarchically. The primary lesion was considered that lesion which first required intervention. In cases where no intervention was necessary, the primary lesion was considered that which produced the most haemodynamic disturbance.

3.5 Subdivision

Lesions which may or may not require intervention, depending on the severity of the condition, were subdivided into mild and severe groups. Mild conditions (e.g. small ASD) were those which had not required intervention, or were not believed to require intervention in future. Severe conditions (e.g. large ASD) were those which required or are anticipated to require some form of intervention. Severe conditions were subdivided further for analysis of surgical trends in chapter 9.

3.6 Patients and population

The catchment area for this study were the Maltese Islands. SLH is the only regional hospital in Malta and caters for the investigation of all patients suspected of having CHD, and their follow up. Official Maltese publications provided total livebirths from 1990 to 1994 for epidemiological calculations (COS 1990-1994). The population of Malta is around 360,000 and there were 26,117 livebirths in 1990-1994 with an annual mean of 5223 livebirths.

The official religion is Roman Catholic, **termination of pregnancy is illegal** and there is no organised antenatal screening program for CHD.

3.7 Data sources

Data acquisition was prospective for patients born between October 1994 to December 1994 and continued to the end of 1995. Retrospective sources included:

1. Children being followed up at COP for CHD with or without other problems.
2. Copies of all the paediatric EC reports are kept in the EC department and date back to 1987. All the reports were scrutinised to identify cases of CHD diagnosed or followed up by EC.
3. Patients with CHD may require urgent investigations not available in Malta - mainly CC - or intervention, again by CC or surgery. Such patients are recorded in registers dating back to 1956 when the policy of sending patients for treatment abroad was first implemented. All of the registers were inspected to compile a list of patients with CHD. These registers point to a central file maintained by the Health Division which is separate from the clinical case notes and contains all of the paperwork involved in such transfers. It also includes the original summary compiled by the referring consultant from Malta and the discharge summary sent back with the patient from the tertiary referral centre. The individual files of patients sent abroad prior to 1988 were obtained from Mount Carmel Hospital, where they are stored. The more recent files were obtained from the Health Division in Valletta.
4. Up to the time of writing, all elective CC performed locally on children with CHD are done by visiting consultant paediatric cardiologists in batches. A Health

Division file was available for all of these sessions along with reports on all catheterised patients.

5. The same applied to cardiac surgery on children with CHD - all but one were operated by a visiting consultant paediatric cardiothoracic surgeon.
6. All of the severe cases and most of the minor cases of CHD are followed up locally at a visiting consultant paediatric cardiologist clinic which is held 3-4 times a year. Again, a Health Division file was available for all sessions. This included a list of all patients seen at the clinic.
7. Post-mortem reports from 1977 were scrutinised for individuals dying of unsuspected CHD. All deaths in Malta of uncertain cause must legally undergo post-mortem examination.

3.8 Data collected

Interviews were carried out on parents of surviving patients with CHD and the patients themselves were examined. The data collected related to this study fell into these categories:

1. Demographic details
2. Diagnoses
3. Age and mode of presentation and method of diagnosis
4. Investigations particularly CC and EC
5. Interventions, both surgical and by CC, and complications thereof
6. Family history of CHD.

(see appendix 3)

3.9 Maltese government statistics

Official Maltese Government publications were used for the calculation of rates (DOH 1896-1995, COS 1961-1994, COS 1996).

The demographic data, particularly the age-specific population, was based on the official censuses conducted every decade with interruption during the period 1941-1951 (due to the Second World War) and during the period 1971-1981. For the latter period, the mean of the 1967 and the 1985 census data was used instead.

3.10 Hardware and software

A notebook 486 computer was purchased (later upgraded to a Pentium) and a dedicated database was constructed using dBASE for data entry. Data entry was performed directly to notebook during patient interviews, which commenced in September 1994. The database incorporates coloured schematic images of CHD lesions and operations which were found useful for re-explaining past problems which had been incompletely understood, and any likely future requirements to parents and patients alike.

Diagnoses, procedures and complications were coded manually using a Read Codes Version 2 browser which provided a 5 alphanumeric character code.

An interlocking series of programs were written in dBASE which automatically extract required data from the database file and write it to separate text files on the computer hard disk (appendix 4 and 5 for examples of program and text file). A number of Excel spreadsheets were constructed along with a series of macros which automatically paste these updated text files into Excel spreadsheets, instantly amending tables and graphs. These formatted tables and graphs can be viewed from the spreadsheet itself or via a PowerPoint presentation which was also constructed with the ability to refresh its tables and graphs from the spreadsheet. The ability to completely preview the data at any time during the collection process as formatted tables and graphs was extremely useful. Trends were identified early on in the study and attention was focused on particular aspects of data collection.

3.11 Statistics

Excel 5.0 was the spreadsheet used throughout. Exact confidence intervals for single proportions using the binomial distribution (not the normal approximation) were used to calculate confidence intervals for birth prevalence of CHD lesions (Fleiss 1981- appendix 6) by setting up the calculations in an Excel spreadsheet.

All graphs were generated with Excel except for step plots and confidence intervals plots (range graphs) which were generated with Statistica 5.0.

SPSS 6.0 was used for Pearson correlation to analyse trends over time including specific mortality from CHD, age at diagnosis, age at CC and at first surgery overall, and for specific lesions.

Seasonality of CHD births was evaluated by Edwards' method (Edwards 1961a, Edwards 1961b). Correction was made for the monthly variation in the total number of live births (Rothman and Fyler 1975). The method was also set up in an Excel spreadsheet.

Excel and Statcalc (EpiInfo) were used for χ^2 analysis of contingency tables and Statcalc was also used for χ^2 analysis of trend and for Fisher's Exact test.

A p value ≤ 0.05 was taken to indicate statistical significance.

4. Mortality from CHD and introduction of new interventions

4.1 Introduction

Without treatment, 85-95% of live births with severe CHD die before adolescence (MacMahon et al 1953, Ferencz et al 1985) which makes this group of congenital malformations an important public health issue. In the last 5 decades, tremendous progress has been achieved in the diagnosis and treatment of CHD world-wide.

4.1.1 Local services

Deficiencies in local medical services in general were highlighted in the late 1930s when radiotherapy for the treatment of malignancies began to show promising results in other countries (Galea-Curmi 1982). Efforts were made in this particular speciality to obtain equipment and personnel in order to be able to treat malignancies locally. In the meantime, selected patients were sent abroad for the treatment of malignancies. This evolved into a scheme whereby patients with other diseases were also sent for treatment abroad. The first "blue baby" was sent to the U.K. for operation in 1950 (Vassallo-Agius 1991).

It was eventually realised that bringing visiting consultants from tertiary referral centres over to Malta would be more cost-effective than sending individual patients. These consultants could not only see and advise on patient management but also perform investigations or interventions during their stay, including surgery.

4.1.2 Milestones in paediatric cardiology services in Malta

Milestones in the provision of paediatric cardiology services in Malta include the setting up of an specific clinic for patients with CHD in the 1950s and early 1960s. This clinic was performed by Dr. V. Captur, a local adult cardiologist with an interest in CHD (Captur and Rizzo-Naudi 1973).

Patients with CHD first began to be seen by visiting consultants from tertiary referral centres in 1966 when the first VCC was performed by Dr. E.M.M. Besterman, an adult cardiologist from St. Mary's Hospital, Paddington (Galea-Curmi 1982). Patients were selected by hospital consultants to be examined at SLH by visiting consultants. These included children, with rheumatic heart disease and CHD. In the following year, the clinics were also attended by Mr. M.L. Bromley - Consultant Cardiac Surgeon - also from St. Mary's Hospital. Over the years, the cardiac problems seen in childhood evolved from mostly rheumatic fever sequelae to predominantly CHD (Besterman 1982). The number of visiting consultants increased steadily over the next years, as did the types of subspecialities catered for.

Children with cardiac problems began to be seen by the late Dr. K. A. Hallidie-Smith in 1985. This was an important milestone as Dr. Hallidie-Smith was a Paediatric Cardiologist who visited the Island twice a year. Children who required investigation and/or treatment of CHD were transferred to the Hammersmith Hospital, London, where she was based. She has been succeeded by Dr. P.G. Rees, Consultant Paediatric Cardiologist, GOSHC.

In 1985, Dr. Hallidie-Smith organised training in paediatric EC at the Hammersmith Hospital for two Maltese doctors. Although the only available EC machine in Malta was quite primitive by current standards, diagnosis and follow-up of CHD became possible in Malta prior to patient transfer. This allows a more informed decision to be made regarding suitability, timing and method of transfer in conjunction with the overseas cardiologist.

Due to problems with running paediatric open heart surgery at Hammersmith, more and more children were investigated at Hammersmith and then referred to GOSHC for surgery. The majority of cases have been operated by Mr. M. Elliott - Consultant Paediatric Cardiothoracic Surgeon.

Paediatric Cardiology VCC have also held by Dr. J. DeGiovanni, Consultant Paediatric Cardiologist at Birmingham Children's Hospital, from 1988. Diagnostic facilities were enhanced by the purchase of a colour-Doppler EC machine for combined paediatric and adult use in the same year.

The link with Hammersmith was severed when Dr. Hallidie-Smith retired in 1989 and moved to GOSHC as an Honorary Consultant Paediatric Cardiologist. Patients began to be transferred directly to GOSHC under the combined care of Dr. Hallidie-Smith, Dr. Rees, and Mr. Elliott. In the same year, the first of several one week sessions of diagnostic and interventional CC on Maltese patients with CHD were carried out by Dr. Hallidie-Smith and a visiting team of technicians and nurses. Diagnostic and interventional CC (including radiofrequency ablations for arrhythmias) also began to be performed locally by Dr. DeGiovanni. This was also the year when Mr. Elliott and complete surgical team visited the Island for the first of a series of regular, biennial visits to perform a whole week of surgery for relatively simple cases of CHD.

4.1.3 Specific mortality from CHD

The improvement in paediatric cardiology services in Malta should be reflected by a declining specific MR from CHD. Cause-specific MR for the Maltese Islands have been available since the turn of the twentieth century. MR from CHD were analysed for the years 1912-1993 and compared with the availability of innovative interventions and techniques related to CHD in Malta.

4.2 Methods

4.2.1 Innovations

Important milestones in the management of CHD reported in the literature were compiled (Rashkind 1979, Tynan 1991, Kachaner 1994). The first Maltese patients to benefit from these advances were extracted from MAPCAD and the delays in years to application of techniques were calculated (table 4.1).

4.2.2 Mortality data

Demographic data, particularly the age-specific population figures, was based on the official censuses conducted every decade for the period 1912-1993 with interruption during the period 1941-1951 (due to the Second World War) and during the period 1971-1981. For the latter period, the mean population of the two censuses conducted in 1967 and 1985 was taken as representative of the population during this period (DOH 1896-1971, DOH 1973-1993, COS 1961-1994, COS 1959, COS 1986). The ten-year mean age-specific MR from CHD was calculated.

Mortality data was subdivided according to patient age. The publications for the periods 1897-1911 and 1940-1950 did not list CHD as a specific disorder, but included CHD under the general heading of 'deaths from congenital disorders'. Mortality data from CHD for these years was therefore not available. Separate neonatal mortality data was only available after 1951. Data regarding cause-specific stillbirth mortality is not documented in official national statistics and was therefore not available.

The ten-year mean early childhood (<5 years) MR was based on the total live births reported during the year of the censuses. The specific annual MR from CHD was calculated using the estimated end of year population.

The published statistics do not break down mortality from CHD by different lesions, therefore the specific MR rates for individual lesions could not be calculated.

MR were calculated per 100,000 population. These were further analysed according to the age at death and these results were calculated per 1000 live births.

4.4 Results

4.4.1 Innovations

The last column in table 4.1 shows a progressive decline in the delay in applying new techniques of diagnosis or intervention to Maltese patients. The year of first report of a new milestone and delay to application to Maltese patient were analysed for correlation. A significant negative correlation was found ($r = -0.4$, $p = 0.04$ - figure 4.1).

Table 4.1: First applications of diagnostic and interventional techniques to Maltese patients, locally and abroad

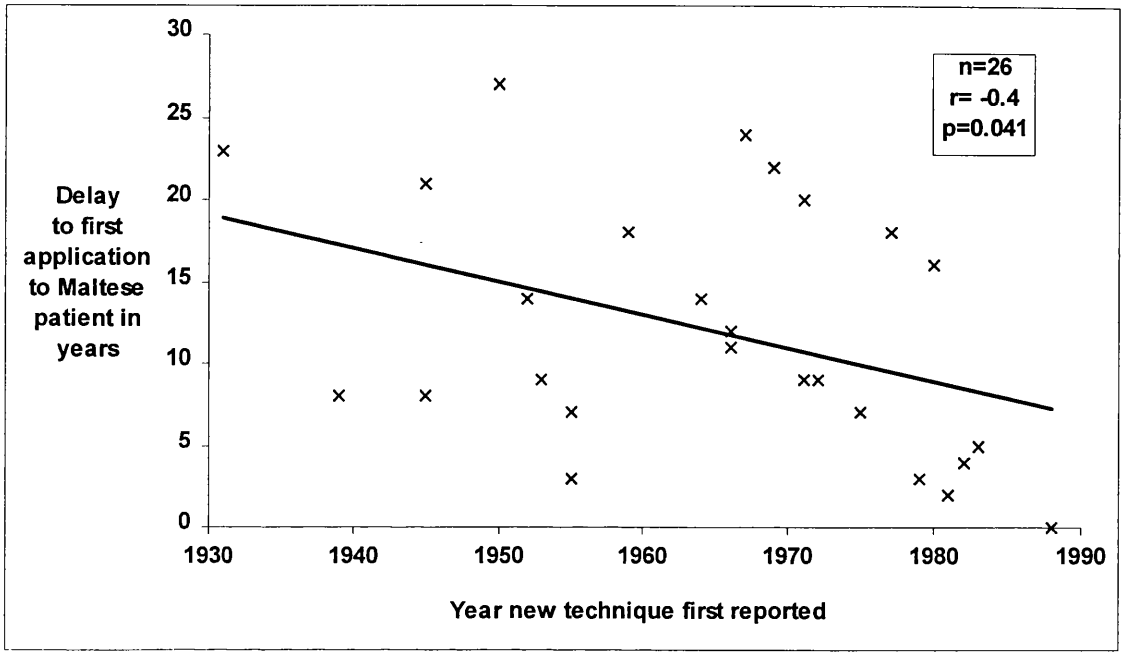
New Milestone	First Report	Maltese First	Delay (Years)
Possibly 1st human cardiac catheterisation (Dieffenbach 1832)	1832	-	-
Failed PS relief in a patient with Fallot's tetralogy (Doyen 1913)	1913	-	-
1st definite human cardiac catheterisation (Forsmann 1929)	1929	-	-
Contrast injected into heart (Forsmann 1931)	1931	1954	23
Ligation of patent ductus arteriosus (Gross and Hubbard 1939)	1939	1947	8
Shunt increasing pulmonary flow (Blalock and Taussig 1945)	1945	1953	8
Resection of coarctation of the aorta (Crafoord and Nylin 1945)	1945	1966	21
Surgical atrial septectomy to increase mixing in TGA (Blalock and Hanlon 1950)	1950	1977	27
Pulmonary artery banding (Muller and Dammann 1952)	1952	1966	14
Closure of secundum ASD - total cardiopulmonary bypass (Gibbon 1953)	1953	1962	9
Closure of VSD (Kirklin et al 1955)	1955	1958	3
Correction of Fallot's tetralogy (Lilehei 1955)	1955	1962	7
Physiological correction of transposition of great arteries at atrial level (Senning 1959)	1959	1977	18
Physiological correction of transposition at atrial level (Mustard 1964)	1964	1978	14
RV to PA homograft for pulmonary atresia (Ross and Somerville 1966)	1966	1978	12

Table 4.1 (cont.): First applications of diagnostic and interventional techniques to Maltese patients, locally and abroad

New Milestone	First Report	Maltese First	Delay (Years)
Balloon atrial septostomy for TGA (Rashkind and Miller 1966)	1966	1977	11
Aortic homograft from RV to PA for truncus arteriosus (Rastelli 1967)	1967	1991	24
RV to PA conduit in TGA with LV outflow obstruction (Rastelli 1969)	1969	1991	22
Transcatheter device occlusion of PDA (Porstmann et al 1971)	1971	1991	20
Univentricular repair of tricuspid atresia (Fontan and Baudet 1971)	1971	1980	9
Arterial switch - anatomic repair of transposition of great arteries (Jatene et al 1972)	1972	1981	9
M mode EC	Mid 70s	1982	7
Conventional 2 dimensional EC (Shinebourne et al 1976)	Late 70s	1982	3
Extracorporeal membrane oxygenation (Bartlett 1977)	1977	1995	18
Doppler - measurement of velocities → gradients (Leung et al 1986)	Early 80s	1988	5
Prostaglandin infusion for duct dependent CHD (Freed et al 1981)	1981	Early 1980s	2
Staged univentricular palliation* (Norwood 1980)	1980	1996	16
Balloon pulmonary valvuloplasty (Kan et al 1982)	1982	1986	4
Colour doppler	Late 80s	1988	0

* Norwood staged series undertaken for one patient with DILV, discordant ventriculo-arterial connections and hypoplastic aortic arch i.e. not HLHS

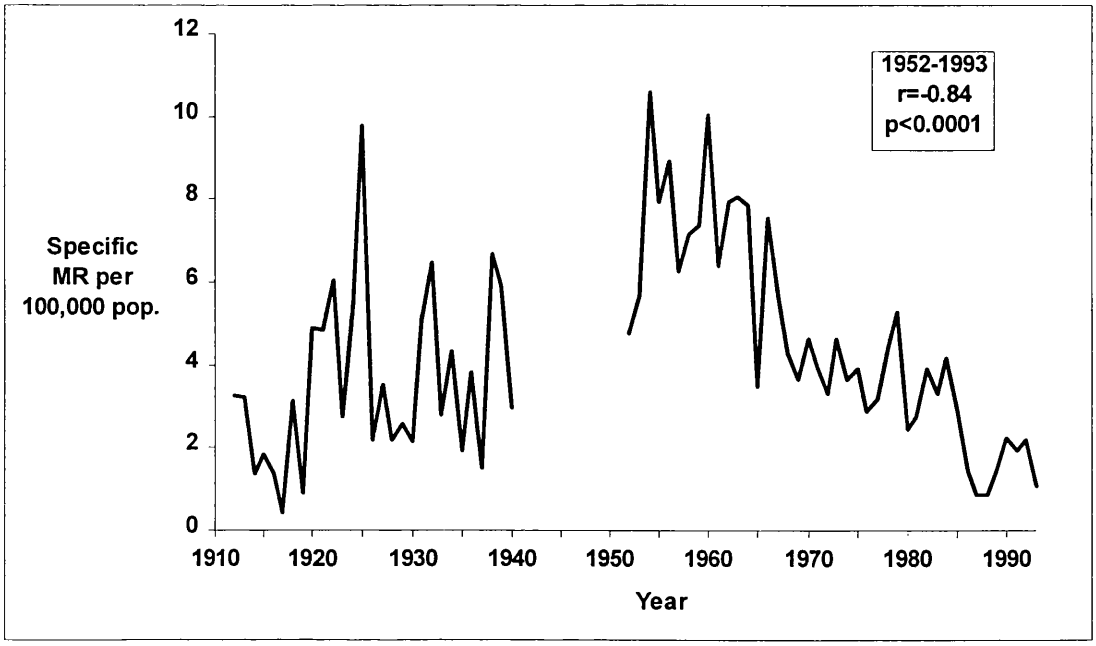
Figure 4.1: Trend towards earlier application of new techniques in CHD to Maltese patients



4.4.2 Annual trends in specific mortality rates

The annual specific MR for CHD shows an overall decline in mortality from CHD (figure 4.2).

Figure 4.2: Specific mortality rate from CHD in Malta (1912-1993)



However, during the 81 year study period, there were marked fluctuations in rates:

1912-1952

The specific MR from CHD rose from 2.34 per 100,000 population in 1912-20 to 4.43 in 1931-40. Rates could not be calculated for the period 1941-1951 due to the absence of a population census during World War II.

1952-1993

The rate rose to 7.65 per 100,000 population in the period 1951-60, and thereafter gradually fell to 2.38 per 100,000 population in 1989-90 (table 4.2). The trend in decreasing specific MR from CHD for the period 1952-1993 was significant ($r=-0.84$, $p<0.0001$).

Table 4.2: Age-specific MR for CHD
Decennial average per 100,000 age-specific population (census year)

Year	<5 yrs	5-14 yrs	15-24 yrs	25-44 yrs	>45 yrs	Total
1911-20	17.85	0.49	0.27	0.21	0	2.34
1921-30	39.18	0.68	0	0	0	4.36
1931-40	37.28	1.01	0	0	0	4.43
1941-50	-	-	-	-	-	-
1951-60	56.23	1.10	1.63	1.20	0.14	7.65
1961-70	58.92	1.93	1.88	0.54	0.36	5.95
1971-80	36.20	1.63	2.43	0.44	0.11	3.57
1981-90	31.62	0.18	0.20	0.74	0.10	2.38

Data for 1911 and 1941-51 unavailable
Means for 1911-20 and 1951-60 based on nine year averages

4.3.3 Annual specific mortality rates by age

The specific MR were further analysed by age at death (table 4.3). There was a declining trend in mortality from 1950-1991 in all ages except in the early neonatal period (<1 week of age). The majority of deaths from CHD occurred in the first year of life. The specific MR from CHD in the first year averaged 1.18 per 1000 livebirths in 1981-90, while the mortality in children age 1-5 years averaged 1.30 per 1000 livebirths for the same decade. This higher mortality after the first year of life can be noted throughout all the decades studied, both pre- and post-1940s (table 4.3).

Table 4.3: Childhood specific MR for CHD
Decennial average per 1000 livebirths (Census Year)

Year	<1 wk	1-4 wks	4 wks-1 yr	Total <1 yr
1911-20	-	-	-	0.55
1921-30	-	-	-	0.95
1931-40	-	-	-	1.05
1941-50	-	-	-	-
1951-60	0.42	0.35	1.23	2.00
1961-70	0.85	0.58	1.17	2.59
1971-80	0.49	0.21	0.66	1.36
1981-90	0.72	0.20	0.26	1.18

Year	1-2 yrs	2-3 yrs	3-4 yrs	4-5 yrs	Total <5 yrs
1911-20	0.05	0.03	0	0	0.63
1921-30	0.10	0.04	0.03	0.05	1.17
1931-40	0.17	0.04	0.01	0.04	1.31
1941-50	-	-	-	-	-
1951-60	0.24	0.09	0.09	0.06	2.48
1961-70	0.25	0.10	0.04	0.02	3.00
1971-80	0.11	0.04	0	0.04	1.55
1981-90	0.02	0.06	0.02	0.02	1.30

Data for 1911 and 1941-51 unavailable
Means for 1911-20 and 1951-60 based on nine year averages

4.4 Discussion

Routine mortality statistics have a useful, albeit limited role in evaluating the health status of the community. These statistics are dependent on the correct diagnosis being recorded by the doctor certifying the cause of death. Within these limitations, trends in cause-specific MR can be used to evaluate the impact of innovative medical interventions, and can provide a means of audit of health services.

4.4.1 Mortality from CHD pre-1941

The ten-year average MR indicates an overall increase in deaths from CHD from 1912 to 1941. The MR are less than those recorded after 1951. Indeed, the specific mortality in 1912 was 2.34 per 100,000 population as compared with 2.38 per 100,000 population in 1993. This almost certainly reflects diagnostic inaccuracies, with less cases being identified as dying from CHD before 1941. These problems preclude accurate interpretation and comparison of the figures obtained between the pre-1941 and post-1951 periods.

4.4.2 Mortality from CHD post-1951

No calculations were possible between 1941-1951 due to the lack of a census during this decade. After 1951, the specific MR for CHD in Malta declined significantly from 7.65 per 100,000 population in 1951 to 2.38 in 1993. This declining trend does not yet show any signs of reaching a plateau.

Analysis of these trends by age at death shows that the early neonatal mortality appears to have been little affected (table 4.3). However, the death rate from CHD in the first 2 years of life has decreased considerably.

Changes in trends in specific mortality rate in late childhood (5-14 years) are difficult to assess due to the small numbers involved which cause wide fluctuations. However, there does appear to have been a fall in the specific mortality rates in the 5-24 years age groups in the last decade (table 4.2), although this change is not yet significant.

4.5 Conclusion

There have been tremendous advances in the relatively young subspecialities of paediatric cardiology and cardiac surgery in the past 50 years.

In this study, a significant decline in MR from CHD was found over the period 1952-1994. This was paralleled by the introduction of new diagnostic and interventional techniques to Maltese patients with CHD. CHD is one of the few areas where improvements in Health Services, with the inevitable associated financial costs, have had a significant impact on outcome in terms of mortality.

The exact impact of the introduction of prostaglandin E1 to maintain ductal patency in infants with ductus arteriosus-dependent congenital heart disease cannot be assessed in this study as it was not possible to ascertain when this was first locally introduced (Freed et al 1981). However, once introduced, prostaglandin must have played a significant role in reducing mortality and morbidity by allowing transfer of critically sick infants, such as neonates with TGA, to tertiary referral centres in the UK for treatment.

Although new techniques have become progressively more complex, the delay in their introduction to Maltese patients with CHD has diminished over the years and there is no reason why this should not continue to be the case.

Additional improvements in the care of children with CHD should further diminish the mortality of this common group of congenital disorders.

5. Birth prevalence of CHD

5.1 Introduction

Numerous epidemiological studies dealing with CHD have been carried out since the middle of this century (Carlgren 1959) but there is no agreed, standardised methodology for data collection or analysis. Hence, differences in birth prevalences of CHD in different geographical areas overall, or for specific lesions may only reflect differences in methodology. For example, a previous study of CHD in Malta reported birth prevalence of CHD of only 2.57/1000 live births, but this was limited to patients diagnosed in early infancy (Cuschieri 1993).

Older studies were hampered by lack of a non-invasive diagnostic technique. Mild lesions were often diagnosed clinically only as the alternative was CC. Some mild lesions may not have been included if spontaneous resolution occurred on follow up (e.g. VSD) with disappearance of clinical signs (Evans et al 1960). This may have led to erroneous diagnoses or non-inclusion of mild lesions in epidemiological series, as the alternative was to subject the patient to CC, a technique not without risks (Fyler et al 1980). The availability of high quality EC and colour Doppler since the late 1980s has allowed the confident diagnosis of mild lesions and increased diagnosis of mild aortic and pulmonary stenosis (Fixler et al 1990).

These confounding factors would change all of the proportions of a reported spectrum of CHD. On the other hand, comparison of rates of specific lesions (instead of percentages) is more accurate as the rate of each specific lesion is independent of the rest.

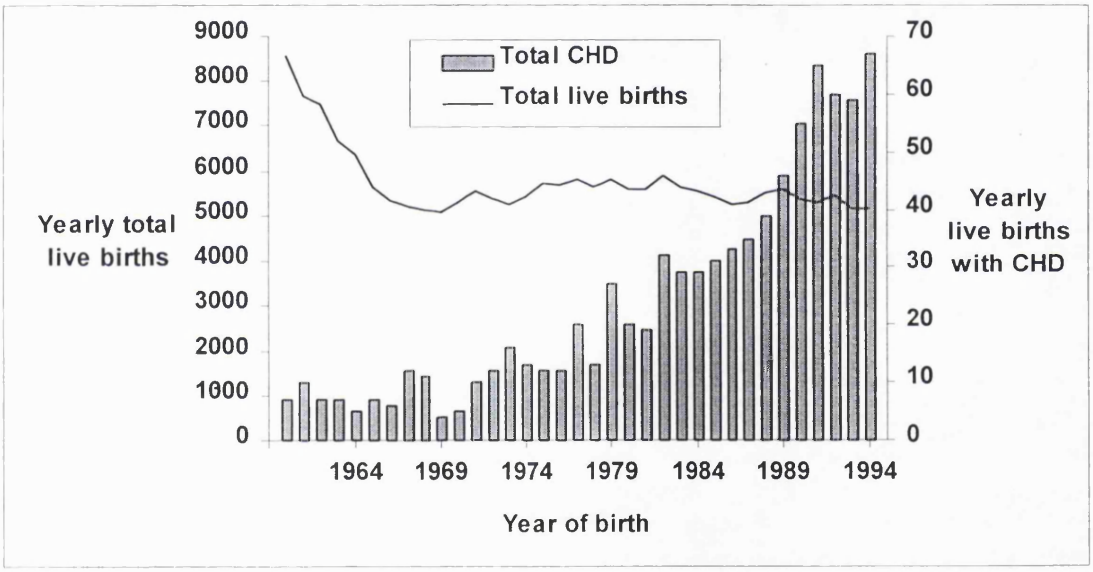
Malta is a small country with one hospital providing centralised antenatal, natal and postnatal services. With the local availability of high quality echocardiography, the Island potentially provides an ideal location for epidemiological studies dealing with CHD.

5.1.1 Methods

The literature was reviewed to obtain studies which reported spectrum of CHD and quoted actual number of patients or percentage of patients for each lesion and total number of live births for the period under study. This allowed rates per 1000 live births to be calculated for each lesion in each study, and calculation of CI where relevant.

A review of MAPCAD showed a decline in identified cases of CHD born prior to 1990 (figure 5.1), which was attributed to incomplete ascertainment of cases. When the review was limited to patients diagnosed by 1 year of age, the resultant decline prior to 1990 was even steeper. For this reason, only live births with CHD born in the 5-year period 1990-1994 were analysed and compared with the above-mentioned studies.

Figure 5.1: Annual total live births and live births with CHD (1960-1994)



5.2 Results

5.2.1 Incidence and spectrum of CHD

There were 230 cases of live born CHD in the 5 year period 1990-1994 inclusive with a birth prevalence of 8.8/1000 livebirths. The female:male ratio was 0.8 (p=NS). The spectrum and percentage of CHD are shown in table 5.1. The commonest lesions were VSD, PS and TOF.

Table 5.1: Spectrum of CHD in Malta (1990-1994)

Lesion	n	%
VSD	103	45%
PS	42	18%
TOF	21	9%
ASD*	11	5%
AVSD**	10	4%
DORV	7	3%
Coarctation	6	3%
TGA	6	3%
PDA	5	2%
Truncus	4	2%
TAPVD	3	1%
AS	2	1%
TA	2	1%
PA	2	1%
HLHS	0	0%
Miscellaneous***	6	3%
Total CHD	230	

* ASD not included if haemodynamically insignificant and no intervention had been undertaken/was planned to be undertaken.

** AVSD includes 3 partial and 7 complete defects

*** Miscellaneous includes 3 cases of congenitally corrected transposition, 2 cases of congenital MI (not associated with mitral valve prolapse) and 1 case of SAS.

Rates per 1000 livebirths in Malta are compared with older studies in table 5.2.

Table 5.2: Spectrum of CHD in present and previous studies

Reference	Carlgren 1959	Gardiner 1951	Mustacci 1963	Feldt 1971	Bound 1971	Mitchell 1971	Hoffman 1978	Dickinson 1981
Locality	Gothenburg	Toronto	San Francisco	Minnesota	Blackpool	USA multicentre	California	Liverpool
Years studied	1941-50	1948-49	1949-51	1950-69	1957-71	1958-65	1959-1966	1960-69
Livebirths	58105	134367	47137	32393	56982	54765	19044	160480
CHD livebirths	369	292	277	179	338	420	163	884
Per 1000 livebirths	6.4	2.2	5.9	5.1	5.9	7.7	8.8	5
VSD	1.72	0.78	2.6	1.92	1.67	2.46	2.68	1.8
PDA	0.6	0.26	0.58	0.22	0.39	0.64	0.47	0.65
ASD	0.27	0.12	0.72	0.4	0.49	0.57	0.52	0.32
AVSD	0.19	0	0	0.25	0.44	0.28	0.32	0.13
PVS	0.24	0.11	0.82	0.28	0.16	0.86	1.16	0.42
AVS	0.34	0.13	0.38	0.34	0.24	0.29	0.32	0.28
CoAo	0.62	0.07	0.48	0.31	0.33	0.51	0.47	0.35
TGA	0.38	0.07	-	0.43	0.33	0.2	0.32	0.27
TOF	0.26	0.16	-	0.28	0.51	0.29	0.23	0.32
Truncus	0.09	0.02	-	0	0.07	0.13	0.15	0.06
HLHS	0.05	-	-	0.25	0.19	0.24	0.05	0.16
HRH	0.15	-	-	0	0.09	-	0.05	-
DIV/UVH	0	0.01	-	0	0.09	0.05	0.05	0.09
DORV	0	-	-	0	0	0.07	0.05	0.05
TAPVD	0.05	-	-	0.16	0.12	-	0.05	0.07
TA	0	-	-	0.18	see HRH	0.09	0.05	0.09
PA	0	-	-	-	see HRH	0.09	-	0.04
Misc.	1.38	-	-	0.15	0.81	0.69	1.52	0.26

(Rates of total CHD and for individual lesions are per 1000 live births)
Some studies quoted rates for DIV under UVH.
Some studies quoted rates for tricuspid and/or pulmonary atresia under HRH.
All except Samanek, Ferencz, Jackson and present study included clinical diagnoses.
PDA was not included if associated with prematurity in Feldt and Mayberry.
Pulmonary atresia included with pulmonary stenosis in Mayberry and Mitchell.
Bound, Mitchell and Hoffman included congenital heart block, endocardial fibroelastosis, dilated cardiomyopathy and isolated dextrocardia under misc.

Table 5.2 (continued): Spectrum of CHD in present and previous studies

Reference	Laursen 1980	Mayberry 1990	Fixler 1990	Manetti 1993	Samanek 1989	Ferencz 1987	Jackson 1996	Present study
Locality	Denmark	Arizona	Dallas	Florence	Bohemia	BWIS	Merseyside	Malta
Years studied	1963-73	1970-88	1971-84	1975-84	1980	1981-82	1979-88	1990-94
Livebirths	854886	11429	379561	46895	91823	368889	203880	26117
CHD livebirths	5249	120	2,509	579	589	1494	1543	230
Per 1000 livebirths	6.1	6.7	6.6	12.3	6.4	4	7.6	8.8
VSD	1.47	2.9	2.83	6.65	2.01	1.07	2.74	3.9
PDA	0.77	0.35	0.35	2.11	0.3	0.11	0.68	0.2
ASD	0.58	0.43	0.46	0.45	0.72	0.3	0.37	0.4
AVSD	0.16	0.08	0.34	0.79	0.26	0.35	0.31	0.4
PVS	0.36	0.96	0.59	0.38	0.45	0.28	0.7	1.6
AVS	0.29	0.26	0.29	0.04	0.49	0.13	0.38	0.1
CoAo	0.43	0	0.25	0.26	0.37	0.28	0.35	0.2
TGA	0.29	0.35	0.23	0.45	0.34	0.2	0.3	0.2
TOF	0.36	0.35	0.22	0.22	0.23	0.37	0.32	0.8
Truncus	0.09	-	0.04	0.14	0.08	0.06	0.06	0.2
HLHS	0.18	-	0.22	0.3	0.26	0.23	0.19	0.0
HRH	0.11	-	0.17	0	-	0	-	-
DIV/UVH	0.09	-	0.06	0.13	0.01	0	-	-
DORV	0	0.26	0.08	0	0.08	0	-	0.3
TAPVD	0.09	0	0.09	0.04	0.04	0.07	0.16	0.1
TA	0	0.26	see HRH	0.02	0.05	0	-	0.1
PA	0	0	see HRH	0.13	0.15	0.13	0.17	0.1
Misc.	0.96	0.17	0	0	-	0	0.84	0.2

(Rates of total CHD and for individual lesions are per 1000 live births)
Some studies quoted rates for DIV under UVH.
Some studies quoted rates for tricuspid and/or pulmonary atresia under HRH.
CHD associated with congenital rubella syndrome or with recognised chromosomal abnormalities was not included in Mayberry.
In Hoffman, the population studied came from a health plan surveillance scheme. This would tend to produce a selection bias excluding the very affluent and the very poor.
Partial AVSDs included with ASD in Laursen.

The birth prevalences of individual lesions appear to vary enormously between studies. Maximum and minimum prevalences of lesions of all of the studies in table 5.2 and for the last 4 studies in table 5.2 are shown in table 5.3. The high ratios of maximum to minimum prevalences for all lesions highlight the variation in rates over 1941-1996. The ratios decrease when the same ratios are compared for more recent studies with similar methodologies.

Table 5.3: Maximum and minimum rates of CHD lesions per 1000 live births and maximum:minimum ratios for studies in table 5.2, sorted by ratio

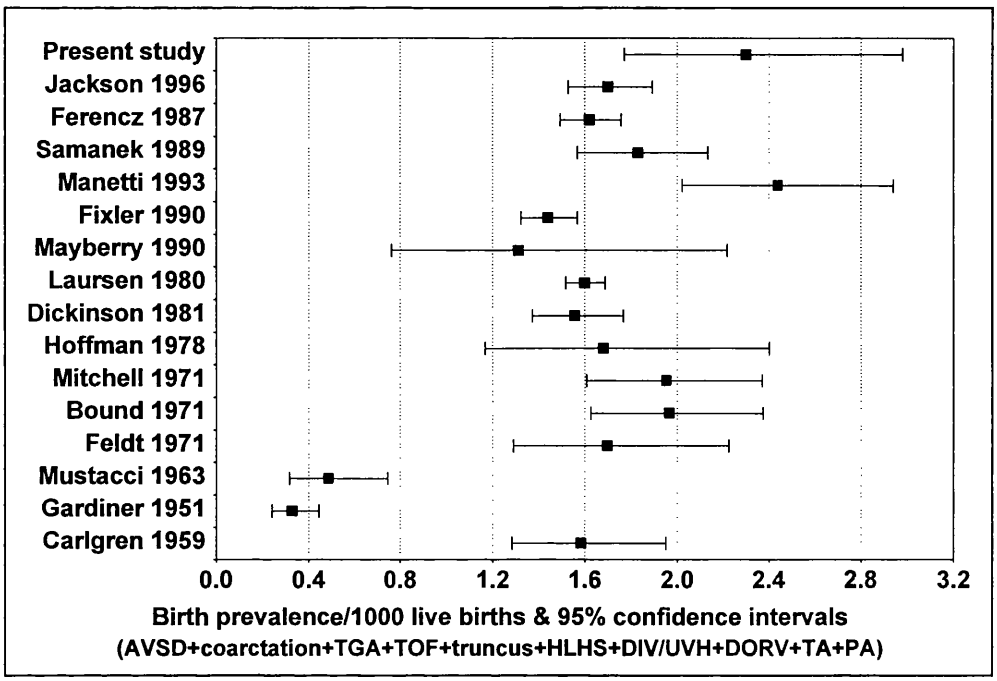
All studies in table 5.2				Last 4 studies in table 5.2			
	Max.	Min.	Max./Min.		Max.	Min.	Max./Min.
PDA	2.11	0.11	19.2	**PDA**	0.68	0.11	6.2
PVS	1.55	0.11	14.1	**AVS**	0.49	0.08	6.1
DIV/UVH	0.13	0.01	13.0	**PVS**	1.65	0.28	5.9
TA	0.26	0.02	13.0	**TAPVD**	0.16	0.04	4.0
AVS	0.49	0.04	12.3	**VSD**	3.94	1.07	3.7
AVSD	0.79	0.08	9.9	**TOF**	0.80	0.23	3.5
Coarctation	0.62	0.07	8.9	**Truncus**	0.15	0.06	2.5
VSD	6.65	0.78	8.5	**ASD**	0.72	0.30	2.4
Truncus	0.15	0.02	7.5	**PA**	0.17	0.08	2.1
TGA	0.45	0.07	6.4	**TGA**	0.34	0.20	1.7
ASD	0.72	0.12	6.0	**Coarctation**	0.37	0.23	1.6
HLHS	0.3	0.05	6.0	**AVSD**	0.38	0.26	1.5
DORV	0.26	0.05	5.2				
TOF	0.79	0.16	4.9				
TAPVD	0.16	0.04	4.0				
PA	0.15	0.04	3.8				
HRH	0.17	0.05	3.4				

AVSD, coarctation, TGA, TOF, truncus, HLHS, DIV/UVH, DORV, TA and PA are lesions which present early in life due to severity of associated clinical signs and symptoms.

The rates of these lesions in the above studies were summated in an attempt to reduce the errors brought on by methodological differences. The ensuing rates and 95% CI are shown in figure 5.2 (data shown in appendix 7). The relatively small numbers produce wide CI. If the studies by Mustacci and Gardiner are not considered, a relatively narrow range for very severe lesions is observed ranging between 1.3-2.4/1000 live births (widest CI 0.76-2.98/1000 live births).

Clearly, methodological differences can greatly influence results, producing wide disparities in rates of individual lesions and overall rate of CHD.

Figure 5.2: Birth prevalence and 95% confidence intervals of lesions which would tend to present in infancy



The rates of VSD, PS, TOF and DORV in Malta are consistently higher than rates in previous studies (table 5.2). Furthermore, the rates of AS, coarctation and HLHS are lower. A series of 2 by 2 contingency tables were used to compare the Maltese data with the data from 2 studies with similar methodologies and overall CHD rates (Samanek et al 1989, Jackson et al 1996). Birth prevalences and 95% CI for all lesions are shown in figure 5.3. The table of data from which this figure is drawn is shown in appendix 8. An abridged version of the entire table showing only those lesions which displayed significant differences is shown in table 5.4.

In Malta, there were significantly higher rates of VSD and lesions causing RVOTO including PS, TOF and DORV. In contrast, there were lower rates of lesions causing LVOTO but these only reached statistical significance in AS.

VSD in Malta was comprised of 81 mild defects and 22 severe defects which required surgery, giving rates of 3.10 and 0.84/1000 live births respectively. PS was comprised of 28 mild cases and 14 cases which required intervention, which gave rates of 1.11 and 0.53/1000 live births respectively.

Figure 5.3: Comparison of CHD lesions in 2 recent studies with present study

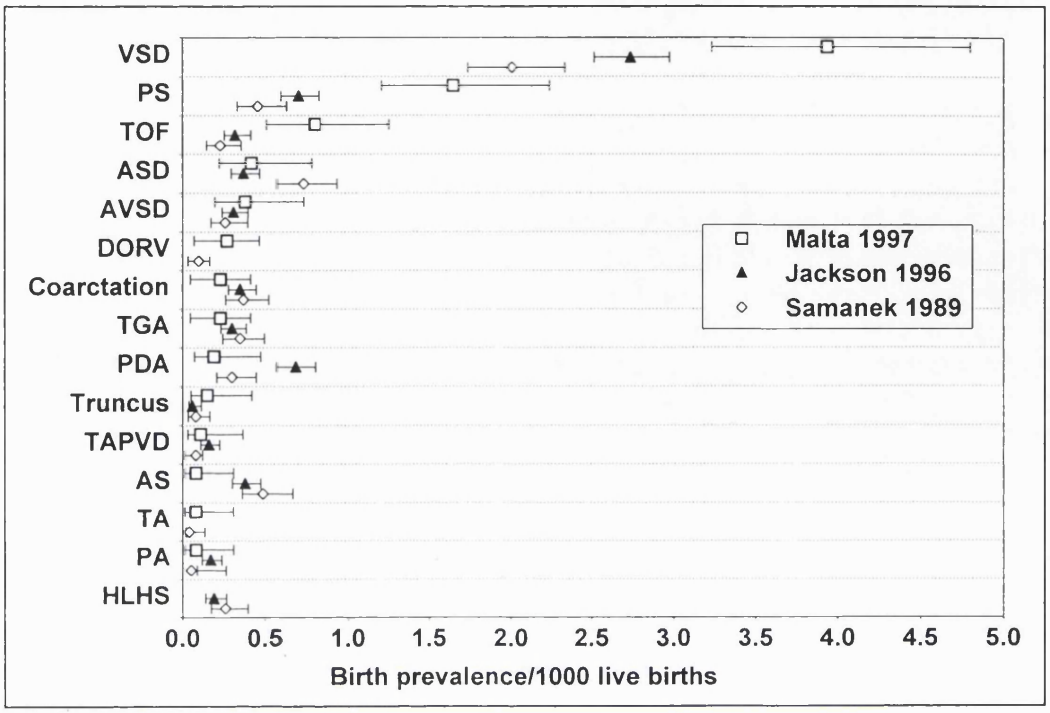


Table 5.4: Comparison of rates of CHD lesions in 2 recent studies with present study

	Present Study	95% CI		Samanek 1989	95% CI			Jackson 1996	95% CI		
Years studied	1990-94			1980				1979-88			
Livebirths	26117			91823				203880			
CHD livebirths	230			589				1543			
Per 1000 live births	8.84	7.67	9.94	6.41	5.90	6.93		7.57	7.19	7.94	
VSD	3.94	3.18	4.70	2.01	1.72	2.30	*	2.74	2.51	2.96	*
PS	1.65	1.15	2.14	0.46	0.32	0.60	*	0.7	0.58	0.81	*
TOF	0.80	0.46	1.15	0.23	0.13	0.33	*	0.32	0.25	0.40	+
DORV	0.27	0.07	0.47	0.1	0.02	0.13	#	-	-	-	
PDA	0.19	0.02	0.36	0.3	0.19	0.42		0.68	0.56	0.79	*
AS	0.08	0.00	0.18	0.49	0.35	0.63	~	0.38	0.29	0.46	#

* p<0.0001 + p=0.0003 ~ p= 0.005 # p=0.02

Consanguinity

There were no consanguineous marriages up to second degree relatives for the 230 patients diagnosed as having CHD born in the period 1990-1994.

5.3 Discussion

Certain conditions such as ASD (Oakley 1996) and coarctation (Campbell 1970) exhibit relatively soft clinical signs which may delay diagnosis until beyond the arbitrary 1 year of age cut-off which has been adopted by researchers studying the epidemiology of CHD. This may lead to incomplete ascertainment of cases in epidemiological studies. However, comparisons can only be made between studies with similar methodologies, therefore this condition was applied to the current study.

5.3.1 Left to right shunts

VSD

There appears to be a significantly higher birth prevalence of VSD in Malta. This is almost certainly due to the easy availability of EC. St. Lukes Hospital caters for >95% of all deliveries in Malta and EC is carried out prior to discharge or within a fortnight in all neonates suspected of having CHD. EC studies which screened neonates for VSD gave birth prevalences of 20-53.1/1000 live births (Hiraishi et al 1992, Roguin et al 1996), 75% of which closed spontaneously. The high rate of this defect in Malta may therefore reflect a higher than average pick-up rate prior to spontaneous closure.

PDA

The Maltese prevalence for PDA was lower than reported in previous studies, but this almost certainly reflects different definitions for inclusion of this lesion in epidemiological studies such as association with prematurity.

5.3.2 Right ventricular outflow tract obstruction

PS

The birth prevalence of PS was also significantly higher than previous studies. Again, this may be due to methodological divergences due to different definitions of what constitutes mild PS. The Maltese rate of severe stenosis (0.53/1000 livebirths requiring intervention) is more in keeping with previously reported rates (table 5.2). In addition, the easy availability of EC may also result in a higher pick-up of milder forms of this condition (chapter 12).

TOF and DORV

The Maltese rate of TOF and DORV is more than double that of previous studies. This is highly unlikely to be due to diagnostic or methodological inaccuracies as the birth prevalence rates of other severe lesions in this study such as TGA, TA, PA, TAPVD and AVSD are similar to previous studies.

DORV also suffers from definition inaccuracies, with some extreme variants of TOF or TGA with malaligned VSD being classified under this heading. However, if this were the case with the Maltese rates, it would only serve to further inflate the rate of TOF.

5.3.3 Left ventricular outflow tract obstruction

In contrast to RVOTO, there were lower rates for all lesions causing LVOTO, although this only reached statistical significance in AS due to the wider CI produced by the low rates. For example, there were no cases of classical HLHS.

In conclusion, the overall birth prevalence of CHD in Malta is similar to that reported in earlier studies. However, the spectrum appears to be different with higher rates of lesions causing RVOTO and lower rates of lesions causing LVOTO.

These differences may be due to genetic or environmental factors. Although environmental factor/s could conceivably predispose to the development of RVOTO, this is unlikely to concurrently produce a low rate of LVOTO.

Microdeletions of chromosome 22 have been found to be associated with conotruncal heart defects including TOF, up to 50% of which may be caused by this genetic anomaly (Wilson et al 1992).

The Maltese predisposition to RVOTO may be due to an unusually high prevalence of 22q11 microdeletion in the population and a longer study, preferably with genetic input, may help to confirm this susceptibility.

Although there were no cases of HLHS in Malta over 1990-94, the upper 95% CI for this sample size is 0.18/1000 live births, which is significantly less than the rate for Liverpool (0.26/1000 live births - 95% CI 0.17-0.40 - p=0.02 - Jackson et al 1996) and for Bohemia (0.19/1000 live births - 95% CI 0.13-0.25 - p=0.02 - Samanek et al 1989).

6. Seasonality of CHD

6.1 Introduction

Seasonal variations in live births with malformations have been reported in the past. This chapter briefly reviews the techniques in statistical analysis of seasonal variation and applies these techniques to live births with CHD in Malta.

6.2 Methods

MAPCAD was queried to obtain month of birth and severity of all patients diagnosed as having CHD by one year of age, born in the 5 year period 1990-1994 inclusive. Analysis was carried out by Edward's method (Edwards 1961a) as modified by Rothman (Rothman and Fyler 1975) to correct for variation in total monthly deliveries. Seasonal analysis was also carried out with conventional χ^2.

This technique was effectively used to map cases of CHD (corrected for the monthly variation in live births) on the circumference of in imaginary circle by month. Each month is allocated a sector on the circle, separated from other months by an angle of 15°. The weighting applied by said numbers shifts the centre of the circle towards the edge of the circle with the greatest weighting. Edward's method can be applied using any annual subdivision, and quarterly analysis was also used, with quarters being separated by an angle of 45°. This method does not work effectively if the trends being analysed exhibit more than 1 peak in the year/s being studied.

Unoperated cases of ASD and PDA were only included if intervention was planned in future. For this reason, such cases were counted with the severe group although no intervention had been yet been carried out.

6.3 Results

There were 230 cases of CHD which were subdivided into 113 cases of mild CHD and 117 cases of severe CHD.

6.3.1 Seasonality of CHD in Malta by Edwards' method

Total monthly deliveries for 1990-1994 (COS 1994) are shown in appendix 9. Total CHD livebirths for this period did not demonstrate any seasonal variation. However, when analysed separately, the severe CHD group (table 6.1) showed a significant peak in June-July ($p=0.03$, $\theta=184°$). Analysis by season strengthened the seasonal peak ($p=0.003$, $\theta=192°$-appendix 10). The mild CHD group failed to show any seasonal trend.

Table 6.1: Analysis of monthly distribution of Maltese livebirths with severe CHD for 1990-1994

Month	θ	Severe CHD	All live births	Corrected CHD	√n	sin(θ)	√n sin(θ)	cos(θ)	√n cos(θ)
Jan	15°	5	2239	4.9	2.20	0.26	0.57	0.97	2.13
Feb	45°	4	2002	4.3	2.09	0.71	1.47	0.71	1.47
Mar	75°	7	2124	7.2	2.68	0.97	2.59	0.26	0.69
Apr	105°	13	2079	13.6	3.69	0.97	3.56	-0.26	-0.95
May	135°	6	2152	6.1	2.46	0.71	1.74	-0.71	-1.74
Jun	165°	5	2093	5.2	2.28	0.26	0.59	-0.97	-2.20
Jul	195°	14	2338	11.2	3.61	-0.26	-0.93	-0.97	-3.49
Aug	225°	14	2252	11.6	3.68	-0.71	-2.60	-0.71	-2.60
Sep	255°	10	2274	8.6	3.09	-0.97	-2.99	-0.26	-0.80
Oct	285°	13	2182	11.0	3.60	-0.97	-3.48	0.26	0.93
Nov	315°	15	2142	15.2	3.90	-0.71	-2.76	0.71	2.76
Dec	345°	11	2240	9.7	3.27	-0.26	-0.85	0.97	3.16
Totals		n=117	n=26117		W=36.6		S=-3.1		C=-0.64

Mean Monthly deliveries=2176.4

x=-0.26	$d=V(S^2+C^2)/W=0.086$	**p=0.03**
y=-0.05	a=4d=0.34	**θ=192°**
d=0.26	2/n=0.017	

χ^2 (2 degrees of freedom)= 6.7

6.3.2 Seasonality of CHD in Malta by χ^2

Monthly analysis of severe CHD by a conventional 2 by 12 table using χ^2 showed no significant deviations from the χ distribution but χ^2 for trend from January to December showed a significant trend towards a higher proportion of live births with severe CHD at the end of the year (χ^2=8.02, p=0.0046). Analysis by quarter confirmed the trend (table 6.2). A conventional 2 by 4 contingency table was constructed to analyse quarterly variations in CHD live births using χ^2 . This also showed a significant deviation from the χ distribution (p=0.015). The same data was analysed using χ^2 for trend from first to last quarter i.e. in order as in table 6.2. A significant trend was also found (p=0.003).

Table 6.2: Analysis of quarterly distribution of Maltese livebirths with severe CHD for 1990-1994 with χ^2-conventional and trend

Quarter	With CHD	Without CHD
1	16	6349
2	24	6300
3	38	6826
4	39	6525

Conventional χ^2	11.0	p=0.011
χ^2 for trend	10.5	p=0.0012

6.4 Discussion

6.4.1 Analysis of seasonality

Seasonal variations in live births with malformations have often been reported (Edwards 1961b). Previous studies have shown seasonal trends for some but not all lesions (Feldt et al 1971, Bound and Logan 1977), or different seasonal trends for different lesions (Samanek 1989). Many such studies have used conventional χ^2 for analysis. This is not an ideal way to analyse cyclical trends as a 2 by 12 table for analysis by month or a 2 by 4 table for analysis by season will obscure relatively small deviations from the norm due to the small numbers involved which reduce the power of the test. In addition, although a significant deviation may be found, the timing of the deviation cannot be accurately demonstrated in a table larger than 2 by 2. Furthermore, a series of 2 by 2 tables to compare individual months or seasons runs the risk of a type 1 error.

Edwards' method (Edwards 1961a) analyses the entire collection of data by month and is more sensitive than χ^2. Correction for background monthly variation in total live births is essential as this itself may cause seasonal variation in the data being analysed (Rothman and Fyler 1975). A significant peak in CHD births in the second half of the year was only evident for the severe group.

χ^2 for trend is another useful technique to analyse a changing proportion of CHD live births by month or by season.

6.4.2 Seasonality of CHD in Malta

Although some definite genetic causes of CHD are recognised, the overall aetiology of CHD is unknown and it is believed that CHD arises from a multilevel genetic-environmental interaction (Nora 1994). There is a seasonal variation in Malta for severe CHD in pregnancies conceived around October. The first trimester of such pregnancies coincides with the peak of the coldest weather in Malta. Environmental factors may unfavourably affect predisposed fetuses conceived around October, precipitating severe CHD in the first trimester of pregnancy (October-January). The cause of this seasonality may be multifactorial but viral respiratory tract infections in Malta peak in this period and may be implicated. Another possible explanation related to viral infections is medication used for treatment of said infections, which may potentially be teratogenic. Other possible explanations include seasonal variations in diet, with possible deficiencies or excesses such as a possible excessive intake of alcohol in the December-January, in the first trimester of affected pregnancies.

The mild CHD group is dominated by small VSDs and mild PS which have been found in excess in this study (chapters 5 and 12). It may be argued that these may not be true CHD but variations of the norm which occur at a constant rate throughout the year, unlike the more severe forms of CHD.

7. North-South regional differences in birth prevalence of CHD

7.1 Introduction

This study was carried out to test the null hypothesis that there is no regional variation in live births with CHD in Malta.

7.2 Methods

7.2.1 Patients

Statistics on all the live births for 1990-1994 were collected from official Maltese Government publications (COS 1994) which also subdivided individuals according to parents' address at time of delivery. Patients diagnosed as having CHD over the same period were extracted from MAPCAD, along with their mothers' addresses during the first trimester of pregnancy. Patients with recognised syndromes were also extracted.

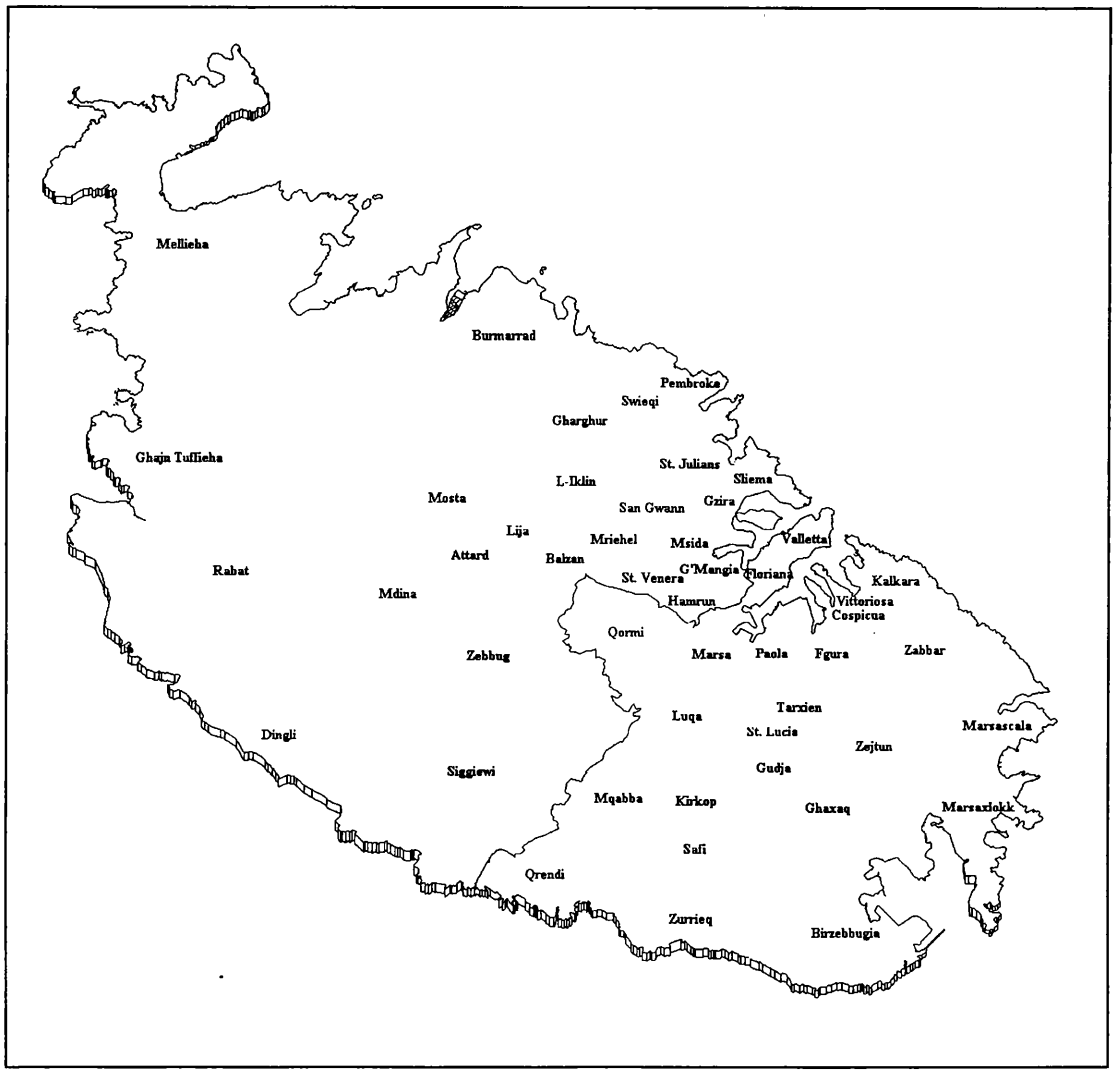
7.2.2 Geographical Regions

The data on live births that involved CHD and total live births were subdivided into ten regions in a geographic distribution devised by the Department of Health Information (table 7.1). The regions were also amalgamated into two groups of five which represented North-West and South-East Malta (figure 7.1). Gozo was considered separately.

Table 7.1: Localities represented by regions

North-West group of regions				
West	North	Central	Central North	Central West
Zebbug	Mellieha	Hamrun	Sliema	Attard
Siggiewi	Mgarr	Sta Venera	St. Julian's	Balzan
Mdina	St Paul	Msida/G'Mangia/Pieta	San Gwann	Birkirkara
Dingli	Gharghur	Gzira/Ta' Xbiex		Lija/Iklin
Rabat	Mosta			
	Naxxar			
South-East group of regions				
Central East	Harbour	Central South	South	East
Fgura	Valletta	Qormi	Gudja	Zejtun
Paola	Floriana	Marsa	Kirkop	Birzebbugia
Sta Lucia	Vittoriosa		Luqa	Ghaxaq
Tarxien	Senglea		Mqabba	Marsaxlokk
	Cospicua		Qrendi	Zabbar/Xghajra
	Kalkara		Safi	Marsascala
			Zurrieq	

Figure 7.1: Division of Malta into North-West and South-East regions



7.2.3 Birth prevalences

Birth prevalences of CHD per 1000 live births were calculated for all 10 regions, as well as for North-West Malta, South-East Malta and Gozo.

7.2.4 Populations

The locality population figures reported in the censuses conducted in 1985 (COS 1985) and 1995 (COS 1995) were used to establish population totals in the regions mentioned above along with population growth rates over this decade. Population totals were used in conjunction with the total live births over the same period to calculate live births and deaths per 1000 total population.

7.2.5 Statistics

A series of 2 by 2 contingency tables using χ^2 (with Yates continuity correction) were constructed to compare live births, with and without CHD, in North-West and South-East Malta, in Malta and Gozo, and in the 10 regions mentioned above with the totals for the country.

A further series of 2 by 2 contingency tables were constructed by subdividing CHD into mild and severe groups. Population growth rates were also compared using χ^2. The Mann-Whitney U test was used to compare the distribution of ranked birth prevalences in the above geographical regions.

7.3 Results

7.3.1 Birth prevalence of CHD

The birth prevalence of CHD in the South-East region was significantly higher than in the North-West (10.1 and 7.4 per 1000 live births respectively, p=0.03). Comparison of individual regions with the whole for the country showed no significant differences except for the Central-East region (birth prevalence 13.9/1000 live births, p=0.03 - table 7.2).

No significant difference was noted when the same analysis was carried out on mild and severe CHD. The Mann-Whitney U test showed a significant difference in the distribution of birth prevalence of CHD in the 10 regions (2 tailed p=0.016-- data used from 4th column in table 7.2). There was no significant difference in birth prevalences of CHD between Malta and Gozo due to the relatively small number of births in Gozo.

Table 7.2: Live births and CHD, total number and rates for 1990-1994

	Total LB	CHD	CHD/1000 LB	Total population*	LB/1000 population**
West	2349	21	8.9	32833	14.3
North	3843	32	8.3	35096	21.9
Central	1891	15	7.9	43115	8.8
Central North	2436	16	6.6	33011	14.8
Central West	2774	15	5.4	36110	15.4
Central East	1874	26	13.9	31832	11.8
Harbour	1487	15	10.1	30312	9.8
Central South	1764	18	9.6	27770	12.7
South	1906	18	9.4	24620	15.5
East	3812	33	8.7	41408	18.4
North-West	13293	99	7.4	180165	14.8
South-East	10843	110	10.1	155942	13.9
Malta	24136	209	8.6	336107	14.4
Gozo	1981	21	11.6	26870	14.7
Total	26117	230	8.8	362977	14.4

LB	Live births	*	Population totals for 1992	**	Mean for 1990-1994

7.3.2 CHD associated with syndromes

25 of 230 patients had a recognised syndrome (chapter 19). 19 had Down's syndrome. The overall birth prevalence of syndromic CHD was 1.0/1000 live births. The prevalence of Down's syndrome with CHD was 0.77/1000 live births. There were no regional differences in syndromic births overall, or in the Down's syndrome group.

7.3.3 Population growth

The total population of Malta increased from 345,418 to 376,335 (table 7.3) between 1985 and 1995, a growth of 9%. The population of North-West Malta increased significantly more than in the South-East ($p=0.0001$). There was no significant difference between North-West and South-East death rates.

Table 7.3: Population growth in Malta - 1985 to 1995

	1985	1995	Increase	% Increase
North-West	172162	196569	24407	14%
South-East	147574	150693	3119	2%
Gozo	25682	29073	3391	13%
Total	345418	376335	30917	9%

7.3.4 Births per 1000 population

The live birth rate per 1000 population in the North-West was significantly higher than in the South-East (14.8 and 13.9/10,000 live births respectively, $p<0.0001$).

7.4 Discussion

Epidemiological studies dealing with malformations have always sought disparities in birth prevalences in time and/or geographical areas as these differences may yield clues as to the aetiology of specific lesions. Discordant birth prevalences for CHD have frequently been quoted between different countries for various lesions (Leung et al 1996, Manetti et al 1996). However, these studies may have reported variations in study methodologies rather than true discrepancies in birth prevalences. These differences may not only be due to the inherent nature of the study designs, but also because of different availabilities of diagnostic techniques. Recently however, differing rates of CHD have also been reported in regions with comparable catchment areas (Jackson et al, 1996).

A conventional North-West, South-East division of Malta with similar numbers of live births allows comparison to be made between different geographical areas.

A significantly higher rate of CHD was found in the South-East of Malta (p=0.03) when compared to the North-West. Subdivision into mild and severe CHD lesions reduced the numbers and hence the power of the tests, resulting in no significant differences being found. Analysis using the 10 localities in table 1 showed a significantly higher rate of CHD in the Central-East region (Paola, Fgura, Sta Lucia, Tarxien - 13.9/1000 live births, p=0.03). These higher rates may be due to genetic and/or environmental factors.

It is believed that the aetiology of CHD is multifactorial, i.e. a genetic-environmental interaction (Nora 1994). The North-West and South-East parts of Malta are traditionally and geographically considered to be separate areas of the Island with little population flux from one part to the other, despite intraregional population migration. Population growth over 1985-1995 was used to indirectly examine the possibility that the two areas are genetically dissimilar. The censuses show an efflux of population from the South-East regions, with a population growth much lower than would be accounted for by the lower birth rate when compared to the North-West regions (table 7.2).

The probability of this migration having occurred is reinforced by the higher birth rate in the North-West regions. Younger couples would tend to migrate out of their area of origin more than older couples with established homes and families. Younger couples would tend to do so on marrying, prior to having children. Therefore, these couples increased the live-birth rate in the North-West regions, consequently decreasing the birth rate of the South-East regions, and the total population in this part of the Island.

A genetic predisposition to CHD would have migrated to the North-West region in the same fashion, and no significant differences would have been found between the two groups of regions.

There may be an environmental factor in the South-East group of regions which increases the rate of CHD in this area. This factor is decreased in individuals who, although originally from the South-East, move to the North-West part of Malta. The Southern part of the Island is more industrialised than the North, and air- or water-borne pollution may play a role in inducing CHD in predisposed fetuses.

Environmental factors may also play a significant role if the lifestyles in the two parts of the Island are significantly different, particularly if the social class distribution is dissimilar. However, social class itself has not been found to play a significant role in birth prevalence of CHD (Fixler 1993).

Yet another factor may be a higher mean parental age in the South-East region due to outward movement of younger couples from this area. This is not supported by the Down's syndrome data, but the numbers are too small to allow proper analysis.

Further work on population movement dynamics and known risk factors for CHD in this cohort of patients may provide additional clues regarding the aetiology of CHD.

Particular attention should be given to the heavy industries in the Southern part of the Island, which is far more industrialised than the North. The industries in the South include a ship repair yard and a shipbuilding yard, the power stations along with open-air coal storage facilities, zinc galvanising plants, a semiconductor factory, soft drinks and alcoholic beverages plants and bottling factories, an incinerator and other small manufacturing plants. Teratogens are known predisposing factors to CHD(Nora and Nora 1978). Some or all of the works listed above may be producing substantial environmental pollution, possibly including a teratogen which may predispose to CHD.

Furthermore, the water supply in the South has a higher proportion of water pumped up from the overworked water table than the North, which has a higher proportion of water produced from reverse osmosis plants. This leads to a higher mineral and sea water content in the drinking water in the South, which may also conceivably play a role in teratogenesis.

8. Diagnostic trends

8.1 Introduction

This chapter analyses historical trends in diagnosis of CHD in Malta, with special reference to the impact of EC.

8.2 Methods

MAPCAD was interrogated to extract age at diagnosis, cumulative percentage diagnosis by age and mode of diagnosis for patients diagnosed as having CHD born in 1947-1994. Due to the historical nature of this study, all cases of CHD, irrespective of age at diagnosis, were included in this study.

8.3 Results

A total of 966 patients were diagnosed as having CHD born between January 1945 and September 1996. In 13 of these, the date and/or mode of initial definitive diagnosis were unknown and they were excluded. The remaining 953 were comprised of 344 mild CHD, and 609 severe CHD.

8.3.1 Cumulative percentage diagnosis

Cumulative percentage diagnosis by age was calculated in 10 year intervals from 1945-1954 to 1985-1994 (table 8.1). A progressively earlier cumulative percentage age at diagnosis was observed for both mild and severe groups.

As would be expected, for the last 2 decades, cumulative percentage diagnosis was higher for severe than for mild CHD at the same age.

The number of diagnosed cases of CHD has increased in both groups over the decades. This is particularly evident in the mild CHD group where the number of lesions diagnosed tripled from 1975-1984 (n=70) to 1985-1994 (n=218). This rapid increase coincided with introduction of EC in Malta in the late 1980s. Minimum, maximum and mean ages at diagnosis of CHD in months are shown in appendix 11.

Table 8.1: Cumulative percentage diagnosis of CHD by age

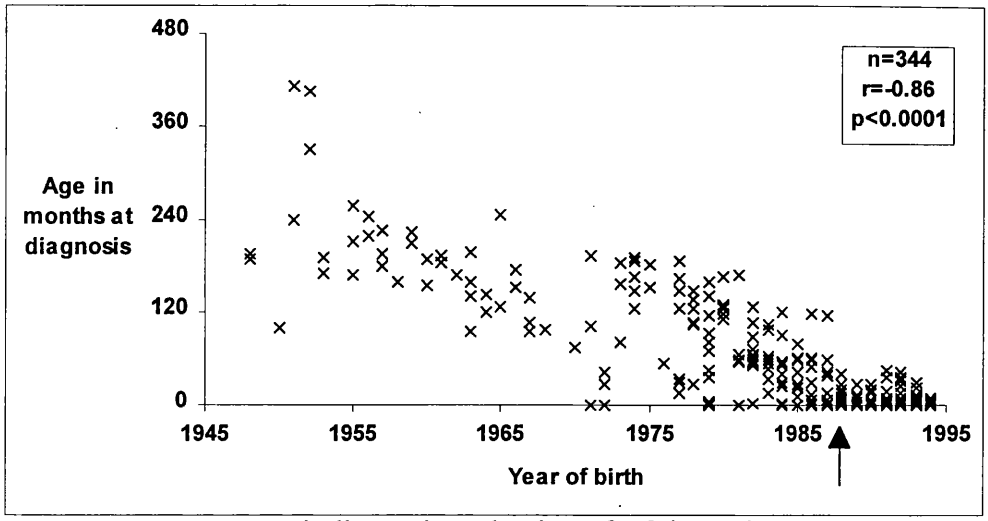
Year	1945-1954	1955-1964	1965-1974	1975-1984	1985-1994
Mild CHD					
By 1 week	0	0	8	4	19
By 1 month	0	0	8	4	34
By 3 months	0	0	8	7	52
By 6 months	0	0	8	11	67
By 9 months	0	0	8	11	74
By 1 year	0	0	8	11	79
By 4 years	0	0	17	30	96
By 10 years	11	9	42	76	100
n=344	n=9	n=23	n=24	n=70	n=218
Severe CHD					
By 1 week	0	0	0	18	35
By 1 month	0	1	0	26	53
By 3 months	0	1	1	35	71
By 6 months	0	2	4	36	80
By 9 months	0	2	4	40	84
By 1 year	0	3	5	44	88
By 4 years	1	11	23	67	98
By 10 years	17	50	80	91	100
n=609	n=81	n=92	n=83	n=141	n=212
All CHD					
By 1 week	0	0	2	13	27
By 1 month	0	1	2	18	43
By 3 months	0	1	3	26	61
By 6 months	0	2	5	28	73
By 9 months	0	2	5	30	79
By 1 year	0	3	6	33	83
By 4 years	1	9	21	55	97
By 10 years	17	42	71	86	100
n=953	n=90	n=115	n=107	n=211	n=430

8.3.2 Age at diagnosis

The ages at diagnosis for mild and severe CHD are shown in figures 8.1 and 8.2 respectively. There was a significant negative correlation for age at diagnosis with time for both mild and severe groups (mild: n=344, r=-0.86, p<0.0001; severe: n=609, r=-0.80, p<0.0001).

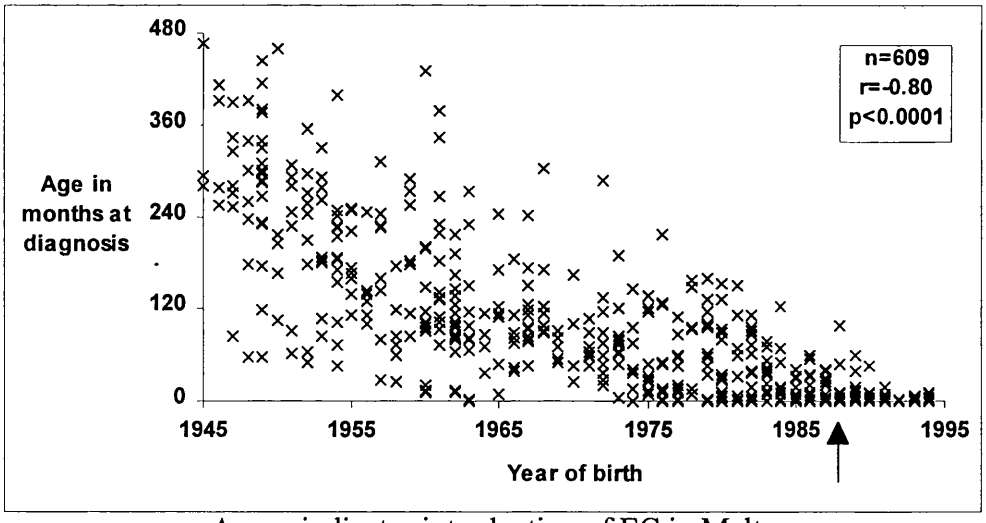
The arrow in both figures indicates 1988, the year when EC services for CHD first became widely available in Malta. There was a further significant downward trend over the period 1989-1994 for the severe group only (n=131, r=-0.25, p=0.003).

Figure 8.1: Age in months at diagnosis of mild CHD



Arrow indicates introduction of EC in Malta

Figure 8.2: Age in months at diagnosis of severe CHD

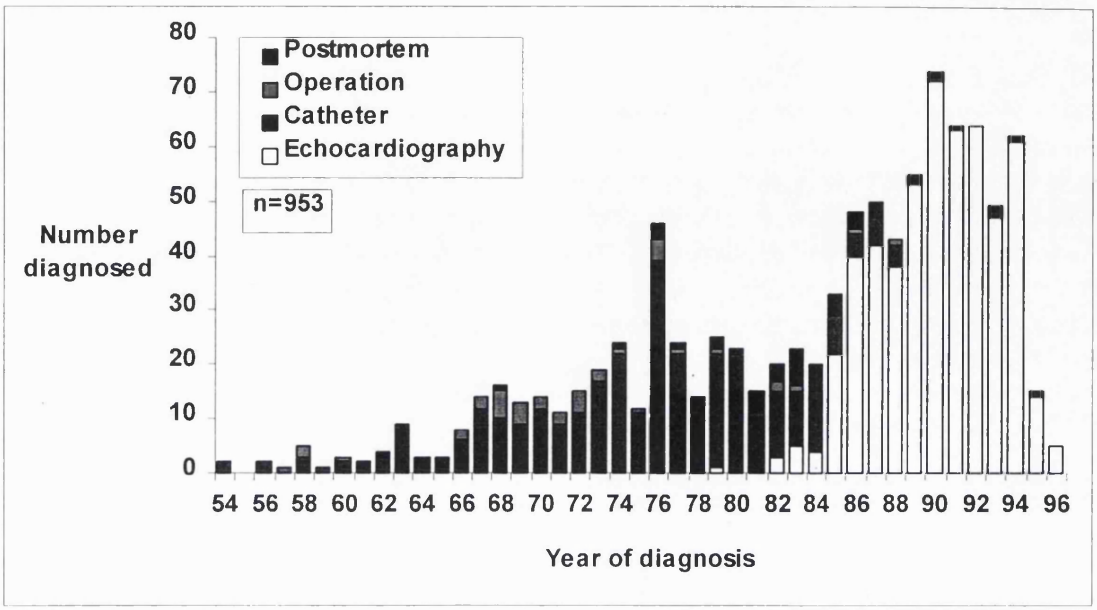


Arrow indicates introduction of EC in Malta

8.3.3 Mode of diagnosis

The mode of diagnosis for all of the above patients is shown in figure 8.3. Diagnosis had been determined primarily by CC up to the early 1980s. From the mid-1980s, EC rapidly became established as the most common diagnostic technique. In addition, the number of cases diagnosed definitively at post-mortem has declined progressively since the introduction of EC and no cases were definitively diagnosed at surgery after 1988.

Figure 8.3: Mode of diagnosis of CHD for patients born between 1945-1994



8.3.4 Diagnosis at surgery

94% of operated patients were operated in the UK while 6% were operated in Malta. 40 patients from the pre-EC era were diagnosed definitively at surgery (see table 8.2). The major haemodynamic problem was known in all cases preoperatively. The reasons for intraoperative diagnosis were twofold:

1. Preoperative CC omitted as the clinical findings were unequivocal. Two lesions were represented: uncomplicated PDA and uncomplicated coarctation.

2. Preoperative CC carried out with incomplete or incorrect diagnosis. These were comprised almost entirely of lesions in which the predominant haemodynamic feature was intracardiac left to right shunting. One case of SAS was believed to be AS preoperatively.

In all 40 cases, the surgical outcome was uncomplicated and successful despite incorrect/incomplete preoperative diagnosis. No patients were diagnosed definitively at surgery after 1988.

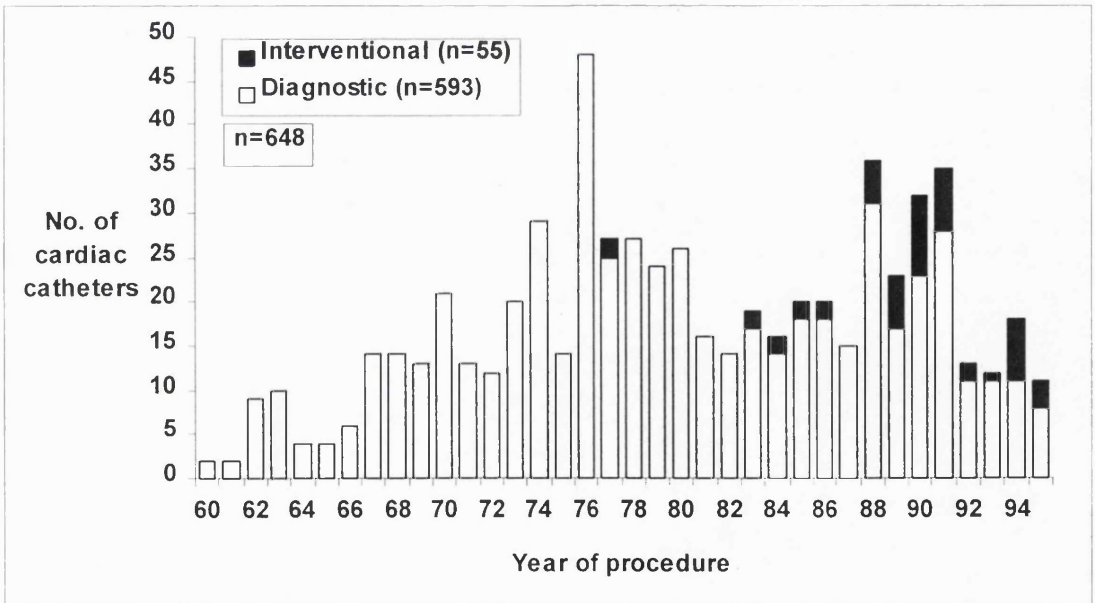
Table 8.2: Lesions definitively diagnosed at surgery - era and reason for operative diagnosis

Lesion	n	Year/s of operation	Reason for operative diagnosis
Coarctation	17	1966-1983	Catheter not done
PDA	15	1957-1975	preoperatively
ASD	2	1970-1977	One incorrectly diagnosed as partial AVSD, other missed PAPVD
SVD	2	1982-1986	PAPVD was missed.
Partial AVSD	2	1966-1979	Believed to be ASD
Complete AVSD	1	1971	Believed to be VSD
SAS	1	1988	Believed to be AS
Total	40	1957-1988	

8.3.5 Catheterisation for CHD

The annual numbers of diagnostic and interventional CC performed on Maltese patients with CHD are shown in figure 8.4. The annual number of CC peaked at 48/annum in 1976. The total annual number of CC then slowly declined to 11/annum in 1995 with an ever-increasing proportion of interventional CC. Interventional CC increased from none prior to 1977 to 24% (n=26) of all CC for 1990-1995 (n=110).

Figure 8.4: Diagnostic and interventional cardiac catheters carried out on Maltese patients with CHD from 1960-1995



Interventional catheters (n=55) were subdivided as balloon dilatation of PS (47%), balloon atrial septostomy for TGA (35%), PDA occlusion (11%), balloon dilatation of AS (4%) and balloon dilation of coarctation (4%). There was no associated morbidity or mortality for these interventions.

The reasons for diagnostic CC after 1988 were:

Preoperatively for the delineation of coronary arteries (e.g. TOF) and for further clarification of anatomy in addition to EC. This was occasionally required not only in complex lesions but also in relatively simple conditions such as multiple VSD.

Postoperatively if the immediate postoperative course did not proceed as expected and no explanation was found by EC.

8.4 Discussion

8.4.1 Declining trend in age at diagnosis

The decline in age at diagnosis of CHD predates the introduction of EC. This may be attributed to improvements in social and medical circumstances over the period under study. These include better parent education, better medical training in general with higher awareness of CHD and the then evolving means of treatment (Rashkind 1979), and the availability of increasing numbers of local paediatricians.

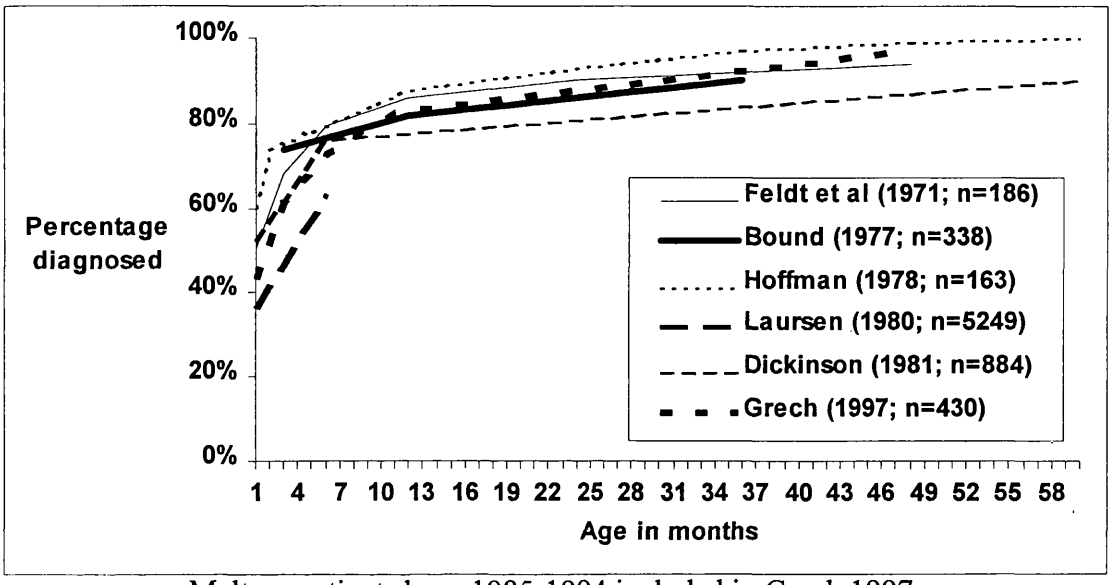
In addition, clear referral routes to a central hospital service were established with referral to visiting cardiologists in non-urgent cases since 1966 or to tertiary referral centres in the UK in cases of CHD where treatment was urgently required. Review of figures 8.1 and 8.2 indicate that the visiting consultant clinics may have been a major factor.

Services were further improved by access to accurate EC from 1988. This is a relatively easy, rapid and non-invasive diagnostic technique which allowed diagnoses to be established by trained paediatricians without access to an on-site paediatric cardiologist. Appropriate medical treatment could then be started with or without further advice over the telephone from a UK paediatric cardiologist until intervention (if required) could be organised.

8.4.2 Cumulative age at diagnosis compared with previous studies

The cumulative percentage diagnosis for 1985-1994 is compared with earlier studies in figure 8.5. For this decade, the cumulative percentage diagnosis curve closely follows that of earlier studies.

Figure 8.5: Cumulative percentage age at diagnosis: present and previous studies.



Maltese patients born 1985-1994 included in Grech 1997.

8.4.3 Impact of EC

The availability of non-invasive imaging has also allowed more cases of CHD to be diagnosed, particularly mild CHD, which resolves spontaneously (Evans et al 1960) or which in the pre-EC era would have been diagnosed on clinical grounds alone. CC would not have been undertaken if a patient was strongly suspected to have only a mild form of CHD as a definitive diagnosis by CC, an invasive procedure, would not have changed conservative management while subjecting the patient to an intervention with some associated morbidity and mortality (Fyler et al 1980).

The total number of CC carried out for CHD has declined not only because EC has taken over as the primary diagnostic tool in virtually all cases of CHD including preoperatively (Sreeram et al 1990a, Marek et al 1995), but also because this imaging technique is increasingly used for follow-up of cases of CHD. This decline coincided with the introduction of Doppler EC in the early 1990s.

The role of diagnostic CC pre- and post-operatively may decline further with refinement of 3-dimensional EC (Vogel et al 1995) while the role of CC in the early post-operative period has already been diminished by TOE (O' Leary et al 1995).

8.5 Conclusion

Diagnosis of CHD has occurred at progressively earlier ages for patients born between 1945-1994. In small countries such as Malta, EC is an essential tool for the early diagnosis of CHD and its complications, and for further follow-up, supplanting CC as the primary diagnostic tool. It is a non-invasive technique and the cost of an EC machine and operator training is less expensive than the cost of setting up and maintaining CC facilities.

Moreover, even in small countries, CC facilities are likely to be available for adult cardiology practice and can easily handle the relatively few cases of CHD that require CC. The number of paediatric patients catheterised are too few for even a single local cardiologist to gain experience in or even maintain proficiency, particularly with constantly evolving interventional techniques (Stark 1994). Our present system whereby visiting consultant paediatric cardiologists perform the necessary CC in batches appears to be the most suitable arrangement of all, not only financially, but also in terms of patient safety.

9. Surgical trends

9.1 Introduction

CHD is a label for a heterogeneous group of lesions with varying haemodynamic consequences and hence, varying need for medical/surgical intervention/s. Treatment of these conditions is expensive. All operations on Maltese patients with CHD were analysed for the period 1947 to 1995 to examine past trends and determine likely future requirements in a population based model.

9.2 Methods

CHD requiring surgery was graded pathologically to allow broad classification into two groups (Abu Harb et al 1994).

Severe CHD included those lesions with all valves and chambers present. Severe lesions can usually be completely repaired with a biventricular circulation i.e. with one ventricle supporting the systemic circulation and another ventricle supporting the pulmonary circulation.

Complex CHD included those lesions with valve and/or chamber atresia and/or hypoplasia. Generally, complex lesions can only achieve extended palliation via extensive surgery with a univentricular circulation i.e. with one ventricle supporting the systemic circulation and no ventricular support to the pulmonary circulation. Flow across the lungs is achieved by passive flow from the venae cavae (Fontan and Baudet 1971, de Leval et al 1988).

Only patients born up to the end of 1995 inclusive and operated up to end of 1995 inclusive were included in this study. Age at diagnosis by 1 year of age was not an exclusion criterion.

Operations were classified into those with preoperative CC and those without preoperative CC. CC was divided into two types: diagnostic and interventional. CC included in this study were pure diagnostic procedures, and interventional CC in which BAS was performed. CC prior to operation was defined in the following way:

For 1st operation-	CC performed any time prior to operation.
For 2nd operation-	CC performed after 1st and before 2nd operation
For 3rd operation-	CC performed after 2nd and before 3rd operation
For 4th operation-	CC performed after 3rd and before 4th operation.

Results for preoperative CC were analysed using χ^2 test for trends.

9.3 Results

The database included 1137 patients diagnosed as having CHD born up to 1995. 538 were operated at least once (47.3 %). There were a total of 671 operations for CHD.

9.3.1 Diagnoses

The primary diagnoses in the operated patients are shown in table 9.1. The commonest diagnosis was TOF (n=102, 19%) followed by ASD (n=90, 16.7%) and VSD (n=79,14.7%).

Table 9.1: Primary diagnosis of Maltese patients operated for CHD - 1947-1995

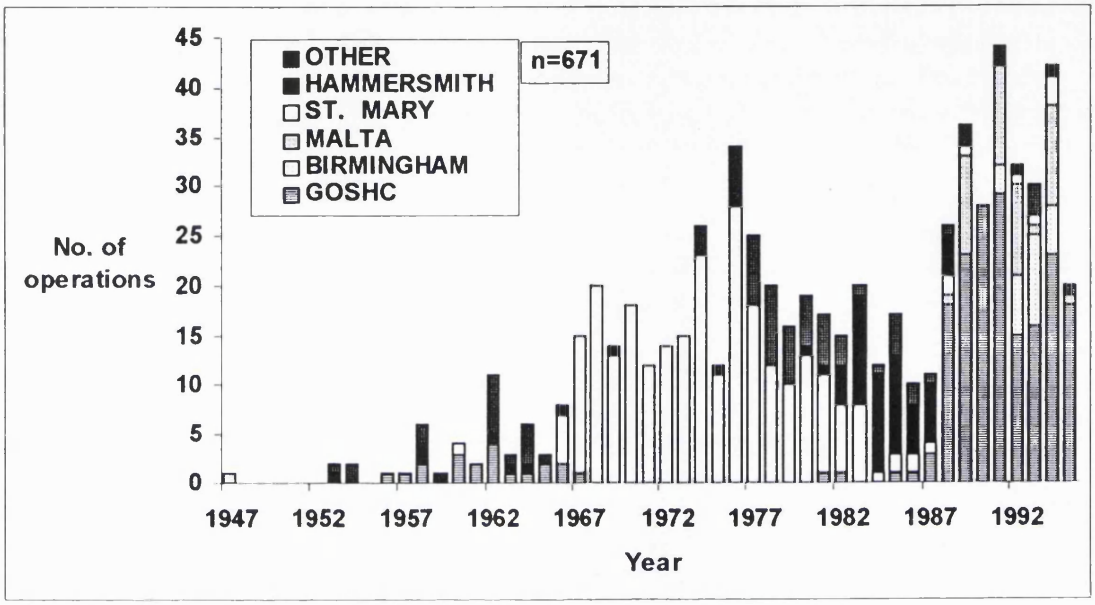
Lesion	n	Percentage	Severity
TOF	102	19.0%	severe
ASD	90	16.7%	severe
VSD	79	14.7%	severe
Coarctation	60	11.2%	severe
PDA	45	8.4%	severe
PS	36	6.7%	severe
TGA	18	3.3%	severe
SAS	17	3.2%	severe
PAVSD	12	2.2%	severe
TA	11	2.0%	complex
Sinus venosus defect	10	1.9%	severe
CAVSD	10	1.9%	severe
DORV	8	1.5%	complex
PA	8	1.5%	complex
AS	5	0.9%	severe
DILV	4	0.7%	complex
Isolated RVOTO	4	0.7%	severe
TAPVD	4	0.7%	complex
Gerbode defect	3	0.6%	severe
Congenitally corrected transposition	2	0.4%	severe
DIRV	2	0.4%	complex
Interrupted aortic arch	2	0.4%	severe
Truncus arteriosus	1	0.2%	complex
AVSD-isolated ventricular component	1	0.2%	severe
Congenital mitral stenosis	1	0.2%	severe
Congenital mitral incompetence	1	0.2%	severe
Anomalous origin of left coronary artery	1	0.2%	severe
PAPVD	1	0.2%	severe
HLHS	0	0%	complex
Total	**538**		

Of the 538 operated patients, 101 were operated on 2 occasions, 29 patients were operated 3 times and 3 patients were operated 4 times.

9.3.2 Annual operations totals and operative centres

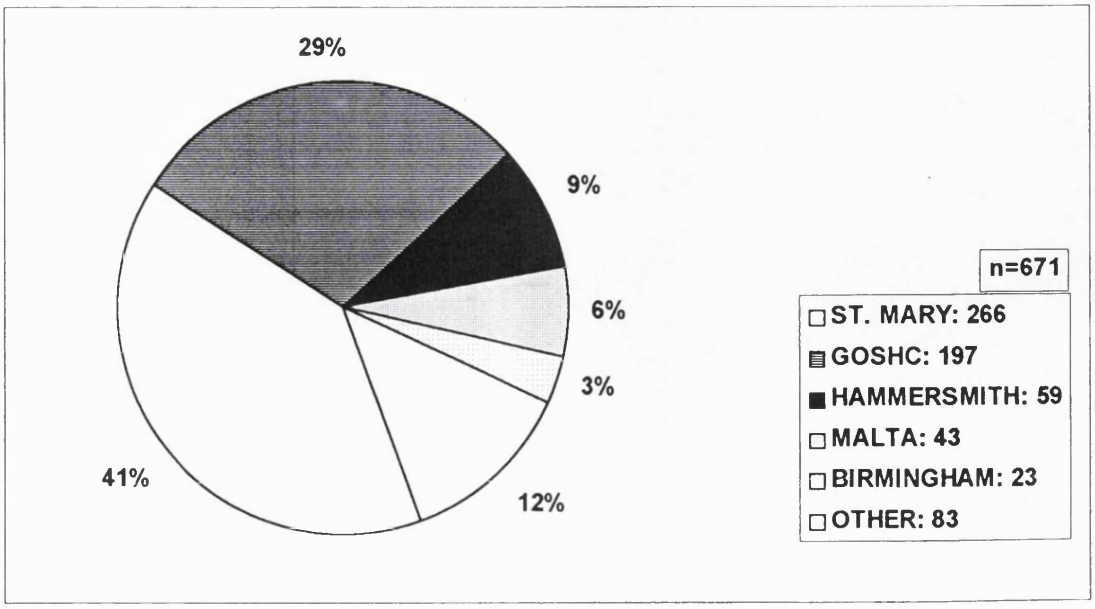
The annual number of operations increased from the first case in 1947 to 34 cases in 1976. This then decreased over the next decade, peaked again to 44 cases in 1991 and decreased to 20 cases in 1995 (figure 9.1).

Figure 9.1: Annual operation totals and operative centre for Maltese patients with CHD



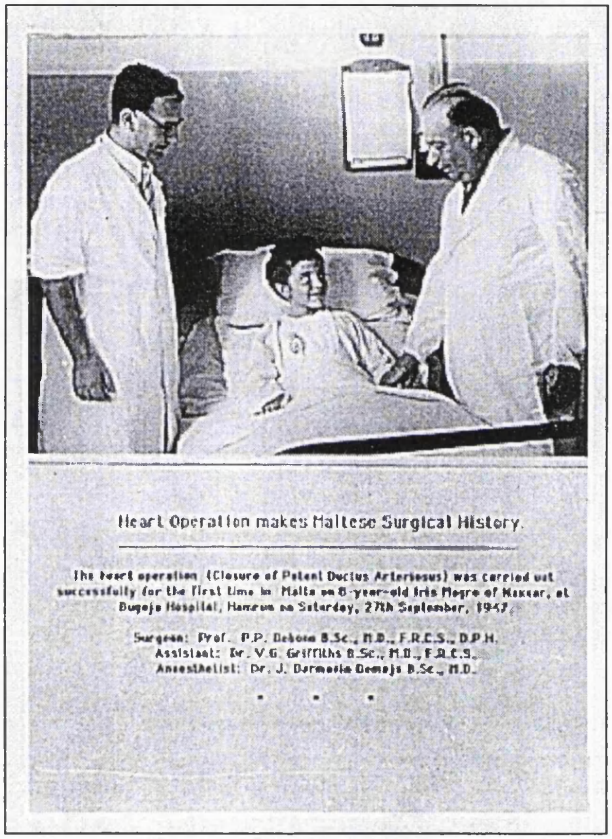
The vast majority of operations were carried out in UK while 6% were carried out in Malta. The majority of operations overall were performed at St. Mary's Hospital (figure 9.2).

Figure 9.2: Operative centres for Maltese patients with CHD: 1947-1995



The very first operation for CHD on a Maltese patient was performed locally. This was ligation of a PDA in 1947 (figure 9.3). There was a 5 year hiatus after which patients began to be referred to GOSHC and to Guy's Hospital. Cases began to be referred to St. Mary's from 1966 up to the early 1980s. Referrals then began to be sent to Hammersmith and reverted principally back to GOSHC in 1988.

Figure 9.3: First Maltese patient operated for CHD (PDA ligation)



Heart Operation makes Maltese Surgical History.

The heart operation (Closure of Patent Ductus Arteriosus) was carried out successfully for the first time in Malta on 8-year-old Iris Mogre of Naxxar, at Bugeja Hospital, Hamrun on Saturday, 27th September, 1947.

Surgeon: Prof. P.P. Debono B.Sc., M.D., F.R.C.S., D.P.H.
Assistant: Dr. V.G. Griffiths B.Sc., M.D., F.R.C.S.
Anaesthetist: Dr. J. Dermosia Demajo B.Sc., M.D.

Times of Malta 1947

501 patients with severe CHD and 37 patients with complex CHD were operated (ratio 13.5:1). A 593 operations were carried out on significant CHD and 78 operations on complex CHD (ratio 7.6:1).

Of these, 8 were reoperations on the same day as the previous operation. 7 were for significant CHD and 1 for complex CHD.

An increasing proportion of complex cases has been operated (figure 9.4). In 1990-1994, 142 and 34 operations were carried out on severe and complex CHD respectively (total=176, ratio 4.2:1). No complex lesions have been operated in Malta (figure 9.5). Over the same period, 30 of 176 operations were carried out in Malta (17%).

Figure 9.4: Yearly surgery for severe and complex CHD

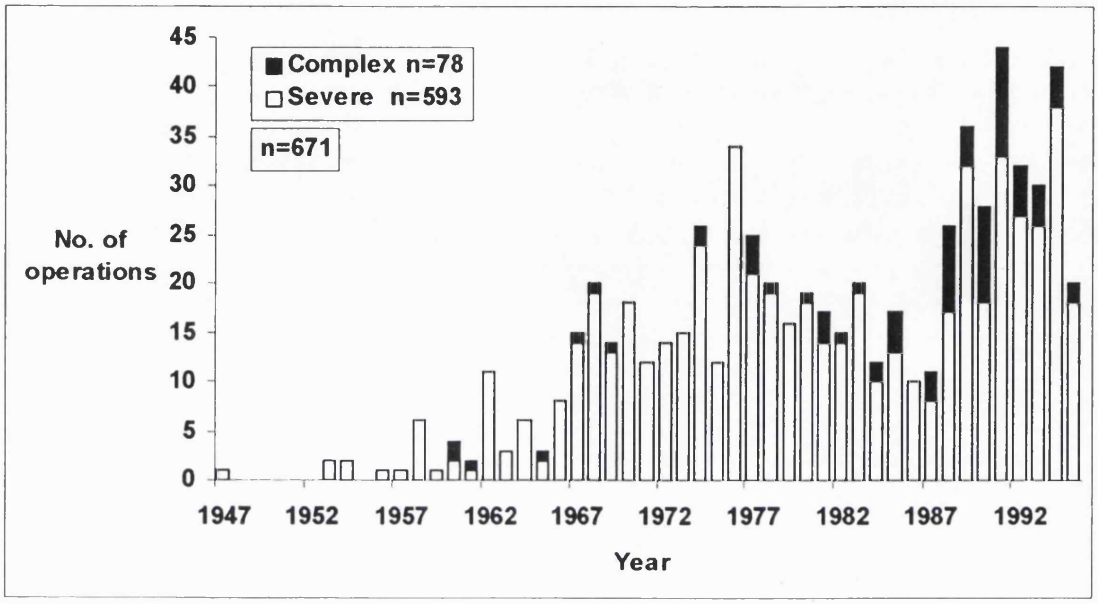
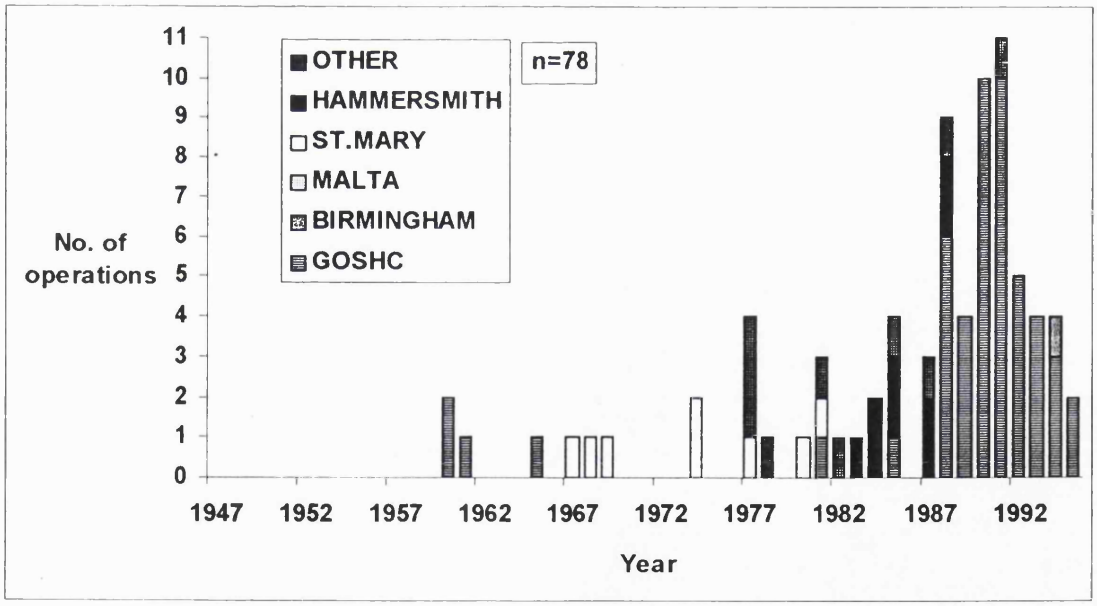


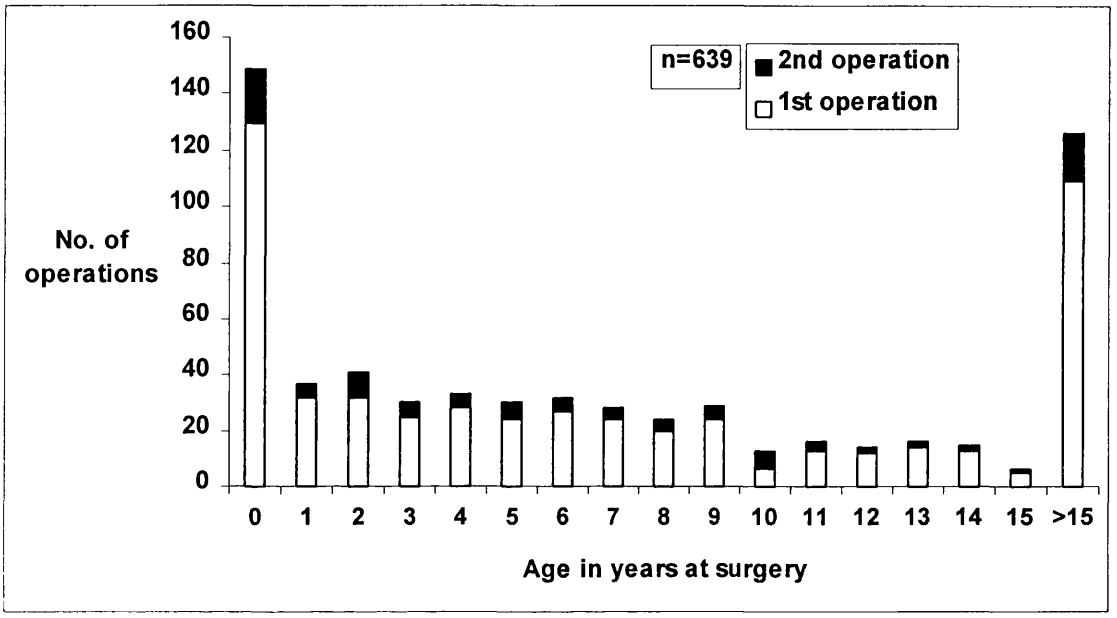
Figure 9.5: Operative centre for complex CHD



9.3.3 Age at surgery and perioperative mortality

Overall, 1st and 2nd operations for CHD were performed early in life (figure 9.6) with 24% and 19% of 1st operations and 2nd operations respectively being undertaken under 1 year of age. 80% and 83% of 1st operations and 2nd operations respectively were undertaken under 15 years of age. 3rd and 4th operations were evenly distributed throughout the childhood age group.

Figure 9.6: Age at 1st and 2nd surgical interventions for CHD - 1947-1995



Minimum age at first surgery and mean age at first surgery have decreased progressively since 1960 (table 9.2).

Table 9.2: Mean age and age range at first operation for CHD

Year	1960-1969	1970-1979	1980-1989	1990-1995
Severe CHD				
n	67	152	130	138
Mean (years)	12.7	14.3	9.9	4.5
Minimum (months)	9.9	1	0.2	0.1
Maximum (years)	31.7	56.8	58.7	50.3
n<1 month of age	0 (0%)	1 (1%)	15 (12%)	12 (9%)
n<1 year of age	2 (3%)	6(4%)	39 (30%)	61 (44%)
Complex CHD				
n	5	4	17	11
Mean (years)	5.7	8.4	1.6	0.4
Minimum (months)	14.4	14	0.1	0.1
Maximum (years)	9.2	27.6	8.9	2.7
n<1 month of age	0 (0%)	0 (0%)	8 (47%)	4 (36%)
n<1 year of age	0 (0%)	0 (0%)	12 (71%)	10 (91%)

The proportion of cases of severe and complex CHD operated under 1 month of age and under 1 year of age has increased from the 1960s to the 1990s.

There was a significant negative correlation of age at 1st operation with time for both severe (r=-0.27, p<0.0001) and complex (r=-0.42, p=0.01) CHD (figures 9.7 and 9.8).

Figure 9.7: Age at first operation for severe CHD

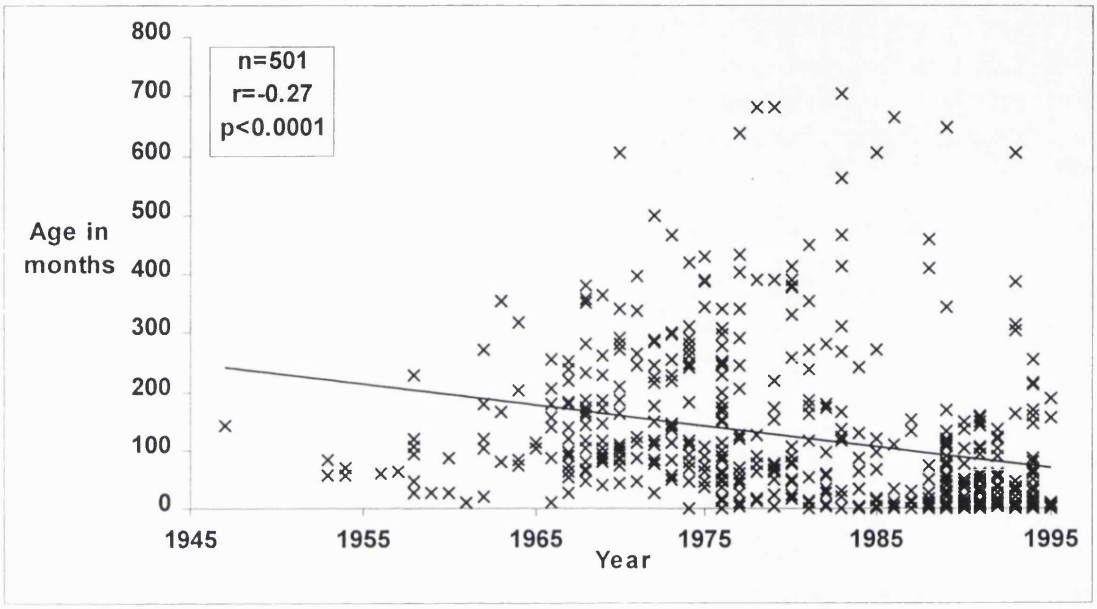
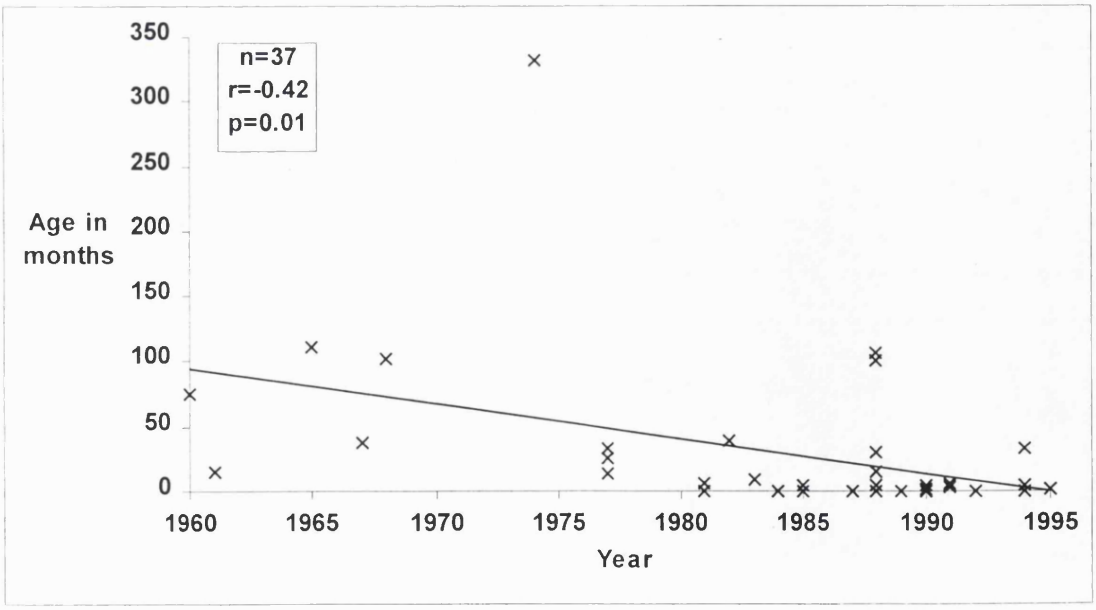
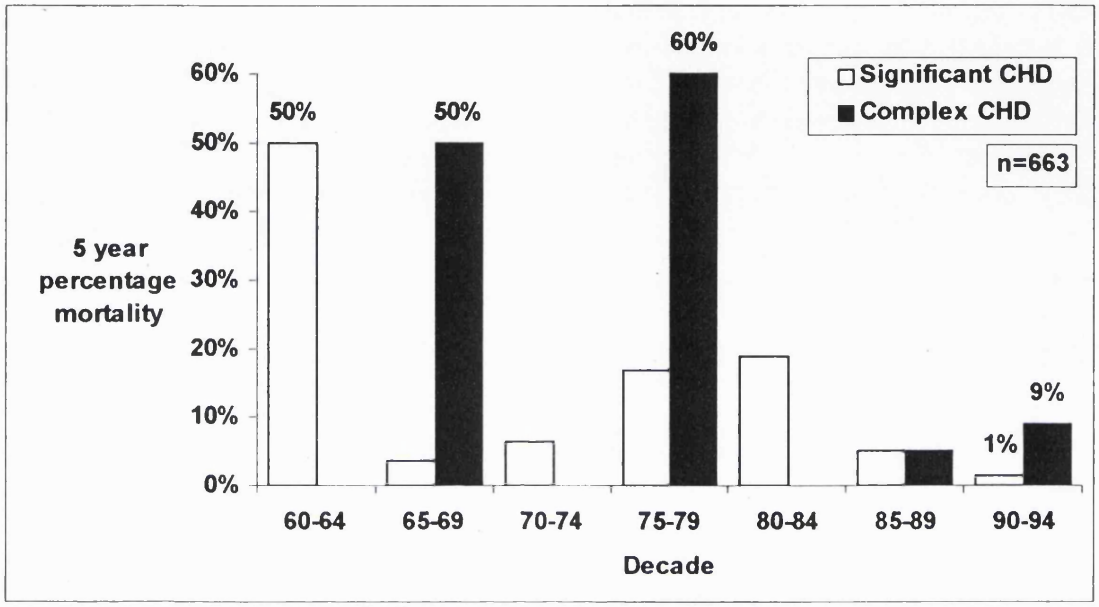


Figure 9.8: Age at first operation for complex CHD



The percentage 5-year PM decreased significantly throughout the period under study for both severe and complex CHD (figure 9.9 and table 9.3).

Figure 9.9: 5-year percentage perioperative mortality



Excluding 8 reoperations on same day

Table 9.3: Declining mortality for surgery for CHD: 1960-1994 (χ^2 for trend)

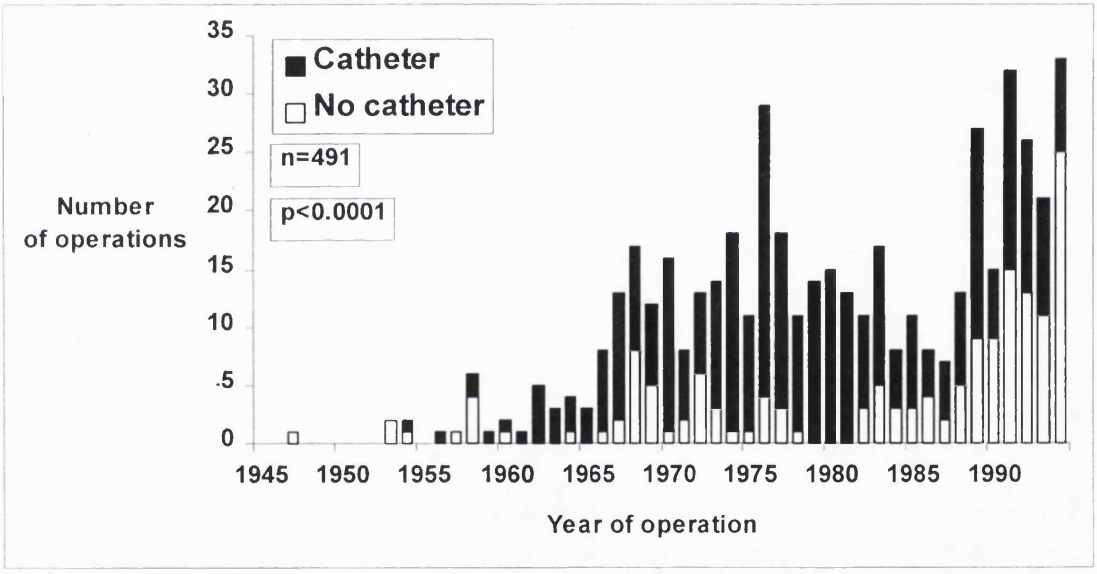
Type of surgery	χ^2	p
Overall	15.15	0.00010
Severe	14.03	0.00018
Complex	4.3	0.037

9.3.4 Cardiac catheterisation prior to surgery

There was a significant trend towards an increase in the ratio of uncatheterised to catheterised patients (non CC:CC) from 0.5 in 1960-64 to 1.1 in 1990-94 (χ^2 for trend 12.21 - p=0.0004). 1st operations for significant CHD constituted 75% of all operations for CHD. The numbers of uncatheterised and catheterised operations for 1st operation for significant CHD are shown in figure 9.10. The ratio of non CC:CC operations increased significantly from 0.2 in 1960-64 to 1.4 in 1990-94 (χ^2 for trend 21.03 - p<0.0001).

The ratio of non CC:CC operations for 2nd, 3rd and 4th operations for severe CHD failed to display any trends (appendix 12). Similarly, there were no significant trends in operations for complex CHD (appendix 13).

Figure 9.10: Catheterisation prior to 1st operation for severe CHD



Of the patients requiring intervention born in 1990-1994 (by surgery or interventional catheter), 12 (11%) required urgent transfer for intervention i.e. within 1 week of the diagnosis being established, with subsequently increased financial transfer costs.

9.4 Discussion

9.4.1 Age at surgery and mortality

There has been a significant decline in age at surgery for CHD in Malta. This was paralleled with a significant reduction in perioperative mortality. Many factors were involved including surgical learning curves and the utilisation of new techniques such as deep hypothermia and cardiopulmonary bypass (Lilehei 1955, Barrat-Boyes et al 1971).

9.4.2 Preoperative catheterisation

CC was formerly the only reliable diagnostic test available to the paediatric cardiologist. However, it is an invasive procedure and is not without some risk of morbidity and mortality (Fyler et al 1980). For this reason, CC was frequently omitted in cases where a diagnosis could be established clinically due to clear physical signs, as in coarctation and PDA. Definitive diagnosis would then be established at surgery.

The introduction of EC in the mid-1980s allowed diagnosis to be established non-invasively, and the addition of Doppler measurements and colour-Doppler flow-mapping further augmented the value of this investigation by increasing the information that could be obtained during the procedure. This led to a gradual decline in the need for preoperative CC for severe CHD which began in the mid-1980s (Sreeram et al 1990a, Marek et al 1995). However, CC is still used for the performance of balloon atrial septostomy in TGA with inadequate intracardiac mixing, and to delineate the coronary arteries as in tetralogy of Fallot where complete repair in the region of the RVOT may damage an aberrant coronary artery.

Reoperations frequently require CC as these may need to be undertaken to redo the original operation which may have been partially or wholly unsuccessful. In these situations, it is natural to attempt to gather all the information possible by any means available prior to reoperation.

In complex CHD, although EC is often sufficient for surgery to be undertaken, some details may not be sufficiently clear. This is particularly the case when details of intrapulmonary vasculature are required such as in PA, as ultrasound cannot penetrate air.

9.4.3 Cost of surgery

176 operations were carried out in the 5 year period 1990-1994 with an annual mean of 32.7 operations. For 1995-1999, the total number of operations is extrapolated to be 163.

Surgery for CHD is expensive. The current (1997) open-market cost of neonatal open heart surgery for CHD is quoted at £16,000 (stg) for a 2 week hospital stay which includes up to 1 week of intensive care stay, and £15,000 for the older child (GOSHC and Harley Street Clinic). Extra costs will be incurred for longer hospital stays and insertion of homograft valves/conduits etc.

A crude calculation based on £15,000/operation gives an estimate of the 5 year surgical cost. However, of the 176 operations expected to take place in 1995-1999, some will not be open heart procedures, resulting in lower costs than open heart operations. On the other hand, factors which will increase the overall cost include neonatal surgery and prolonged intensive care stay.

With the above provisos, the true total cost of surgical treatment of Maltese patients with CHD for 1995-1999 will be approximately £2,500,000.

Surgery performed in 1990-94 will be determined not only by new cases of CHD born in this period, but also 'knock-on' effects from previous years. These include elective cases awaiting surgery and operations which were preplanned such as multistage repairs for complex conditions initiated in earlier years (Gutgesell and Massaro 1995) and reoperations for failed procedures or worsening conditions (Delius et al 1996).

Assuming that Maltese patients with CHD have been managed in the same way as patients in the UK (chapter 2), the above data can be used to extrapolate these costs to larger countries such as the UK.

Simple proportion shows that if a country with a live birth rate of approximately 5200/annum (birth rate stable at this rate for 20 years prior to 1994-figure 5.1-page 30) generates surgical costs of £2,500,000/5 years, surgical costs for the UK with a live birth rate of around 750,000/annum are approximately £360,000,000/5 years.

If the entire world population of CHD had been managed as were Maltese patients with CHD, the global 5 year cost of surgical treatment of CHD would be approximately £70,000,000,000. However, surgery for CHD costs Malta far less for several reasons.

There is a bilateral health agreement between Malta and the UK which caters for the free emergency treatment of each country's nationals while on holiday in the other country. This agreement also allows up to 180 Maltese patients per annum to be treated in the UK as NHS patients at no charge. Cases of CHD almost invariably tend to be included within this category due to the high cost of surgery.

In addition, a visiting team from GOSHC has operated on 10 cases of CHD over a 1 week period on a biennial basis since 1989. 14 patients were operated during the last visit in 1996. The majority of cases were ASDs and over the years, with increasing confidence in post-operative care, cases of ASD ± PAPVD, PDA, PS, VSD ± acquired RVOTO, SAS and coarctation have also been operated locally. In 1990-1994, 17% of all operations for CHD were performed in Malta. This further reduces the overall cost of treatment for CHD in Malta.

However, surgery incurs other financial costs including air-fares and board and lodging costs for accompanying relatives and friends if surgery is not carried out locally. Furthermore, patients operated abroad are usually accompanied by both parents who then return to Malta when the child is discharged. These losses in production and earnings are minimised if surgery is carried out in Malta with working parents probably returning to work soon after patient transfer from intensive care to the general wards.

Non-financial costs are difficult to quantify but stress to the family is certainly minimised if surgery is carried out in Malta in a familiar hospital with the support of family, friends and local medical staff who often follow the patient for years prior to surgery.

9.4.4 Future trends

The ratio of operations for severe:complex conditions has decreased over the years (4.2:1 or less) and in future may decline further if the current trend continues with more surgery being carried out on more complicated lesions. For example, the policy so far has been not to operate on neonates with HLHS (table 9.1). This may yet change with Norwood staged series (Norwood et al 1980) or heart transplantation (Bailey et al 1986) being undertaken.

Another factor which may change this ratio is interventional cardiology. Such procedures are more usually performed on severe rather than complex CHD, reducing the number of operations for severe CHD. For example, 24 of the operations performed in 1990-1994 were for closure of ASD. The choice of transcatheter ASD occlusion devices has increased dramatically in recent years (King et al 1976, Das et al 1993, Rao et al 1994, Hausdorf et al 1996). If current ASD occlusion systems are proven to be viable, most of these defects may not come to surgery but will be closed via CC. Similarly, there were 20 operations for VSD in 1990-1994 with no other associated cardiac anomalies except for 9 with ASD. Should an effective transcatheter closure system be developed, similar cases may not come to surgery.

All of these factors may change the pattern of surgery world-wide, and therefore also in Malta.

10. Ventricular septal defect

10.1 Introduction

VSD is the commonest form of CHD. This chapter outlines historical trends in diagnosis and surgery for VSD, and analyses epidemiological aspects of VSD for the period 1990-94.

10.2 Methods

10.2.1 Definitions

VSD was defined as a defect in the interventricular septum. Patients with a primary diagnosis of VSD were graded by severity into 2 groups. Mild VSDs were those which did not require surgical intervention while severe VSDs were those which required intervention.

VSDs were also subdivided into perimembranous and muscular defects. Perimembranous defects were those localised in the upper, membranous portion of the interventricular septum adjacent to the TV on the RV side of the heart, and situated under the AV on the LV side of the heart. Muscular VSDs were those located in the lower, muscular part of the interventricular septum.

10.2.2 Patients

Follow-up was to the end of December 1996, when all mild VSDs born in the period 1990-1994 had EC performed to document whether spontaneous closure had occurred, if this event had not already been documented by EC.

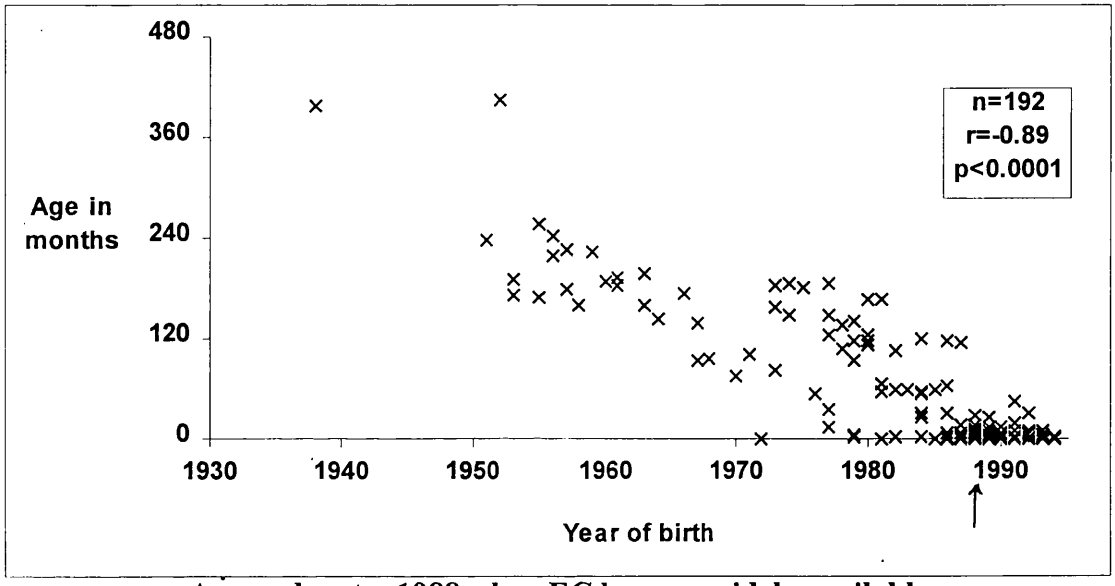
10.3 Results

There were 279 identified cases of VSD born between 1930 and 1994. The male:female ratio was 0.88. 194 had mild VSD (70%) and 85 had severe VSD (30%).

10.3.1 Age at diagnosis

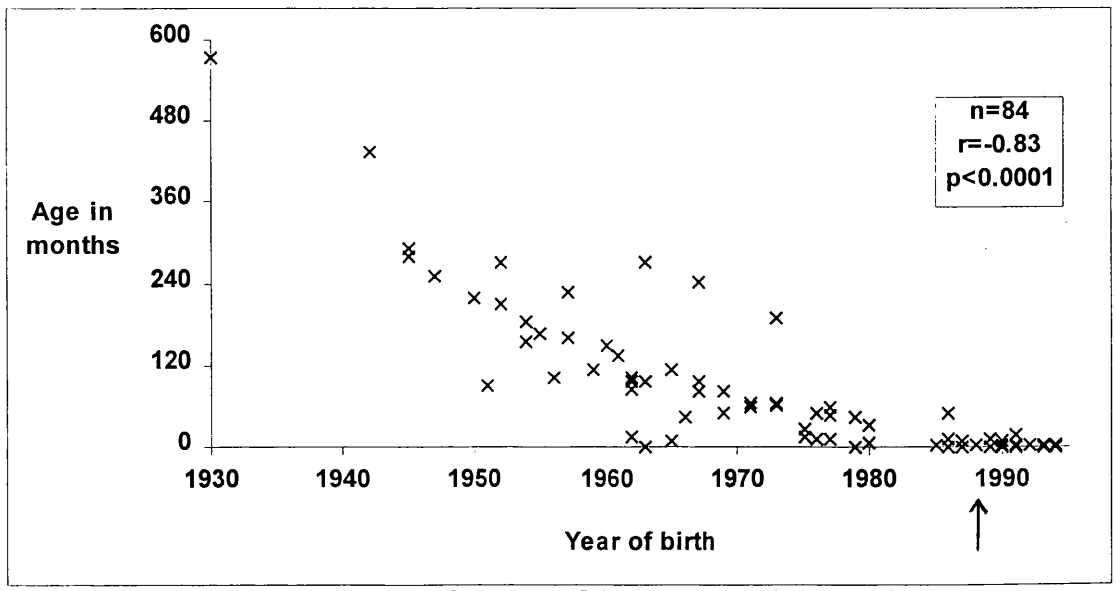
The age and mode of initial diagnosis were uncertain in 2 cases of mild VSD and 1 case of severe VSD. There was a significant decline in age at diagnosis for both mild VSD and severe VSD (figures 10.1 and 10.2 respectively).

Figure 10.1: Age in months at diagnosis of mild VSD



Arrow denotes 1988 when EC became widely available

Figure 10.2: Age in months at diagnosis of severe VSD



Arrow denotes 1988 when EC became widely available

There was also a significant trend towards earlier age at diagnosis for mild VSD since introduction of EC in Malta in 1988 (table 10.1). This trend was also present but not statistically significant for severe VSD.

Table 10.1: Correlation between year of birth and age at diagnosis of VSD for patients born 1988-1994

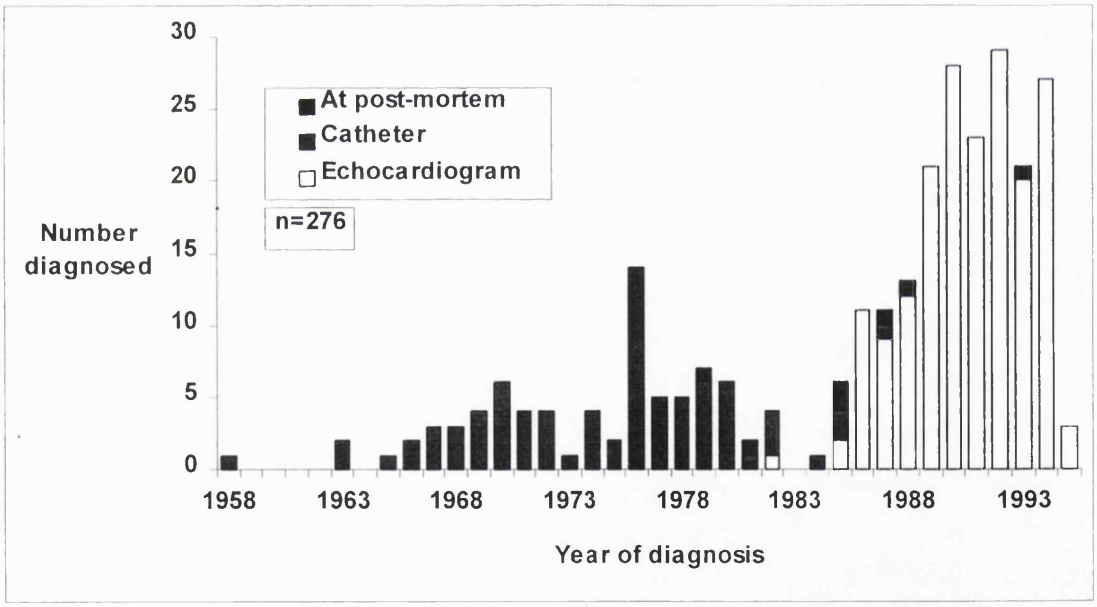
	n	r	p
Mild VSD	111	-0.22	0.02
Severe VSD	26	-0.28	0.16

There was no significant difference between the ages at diagnosis of mild and severe VSDs born 1930-1987, prior to the EC era. For patients born between 1988 and 1994, the mean age at diagnosis of severe VSD was less than that of mild VSD, but this was not statistically significant.

10.3.2 Mode of diagnosis and severity of VSD

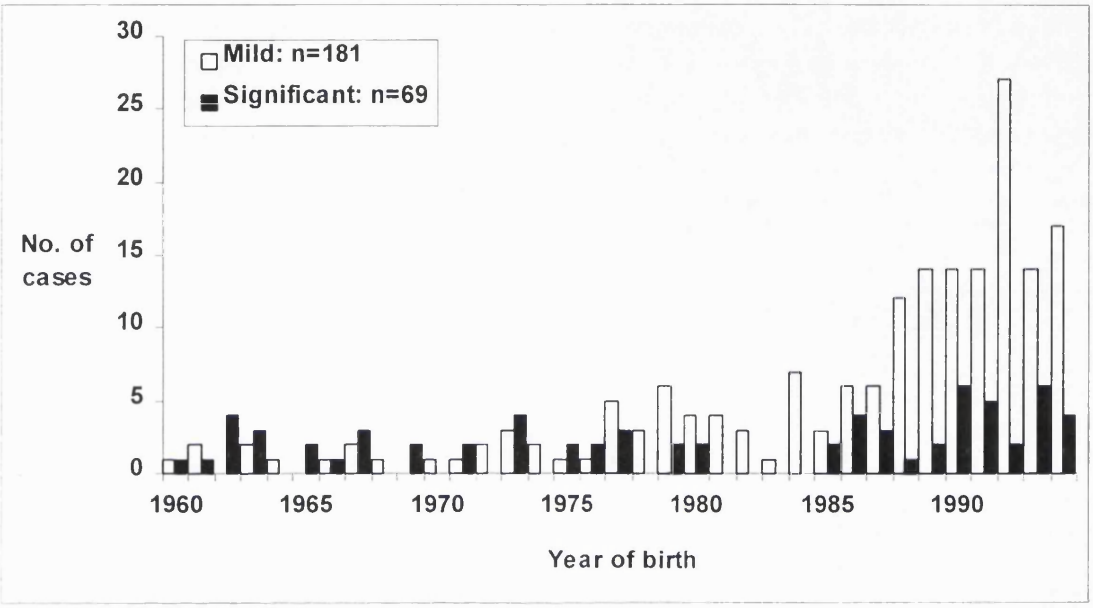
Prior to the mid-1980s, the predominant mode of diagnosis of VSD was by CC (figure 10.3). After the mid-1980s, this changed to EC.

Figure 10.3: Mode of diagnosis of VSD



Prior to 1988, the pattern of severity of VSD showed an approximately equal proportion of mild and severe lesions. After 1988, the total number of cases of VSD increased, with more mild VSD diagnosed and little increase in the number of severe VSD (figure 10.4).

Figure 10.4: Spectrum of mild and severe VSDs for patients born 1960-1994



10.3.3 Surgery for VSD

Non-operation of severe VSD

Of the 85 severe defects, 75 were operated while 10 were not (table 10.2).

Table 10.2: Non-operation for severe VSD

Year of birth	n	Reason for non-operation
1930-1986	5	Irreversible pulmonary hypertension
1967-1973	3	Down's syndrome
1979-1991	2	Multiple malformations

Reoperation for VSD

10 of the 75 operated VSDs were reoperated (13%-table 10.3).

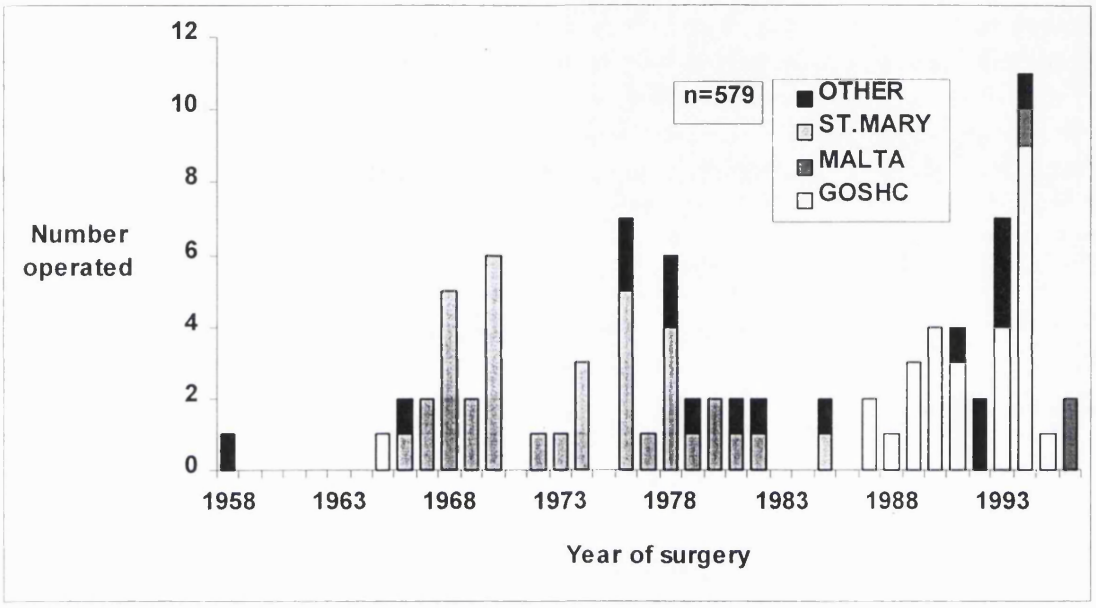
Table 10.3: Reoperation for VSD

Year of 1st operation	n	Reason for reoperation
1976-1993	4	Redo
1966-1993	3	Debanding of PAB and closure of multiple VSDs
1968	1	Pacemaker insertion for iatrogenic heart block
1976	1	AVR for associated, progressive AS
1987	1	Re-exploration early postoperatively for tamponade

Operative centre

Referral centre for surgery for VSD followed the overall pattern described in chapter 9. Patients were initially referred to St. Mary's Hospital, and later began to be referred to GOSHC (figure 10.5).

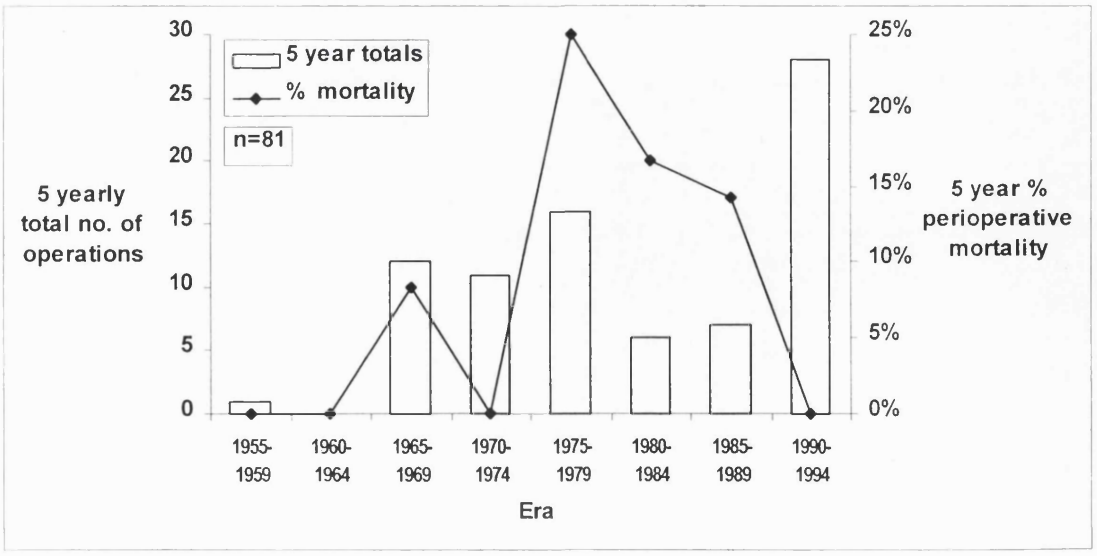
Figure 10.5: Operative centre for VSD



10.3.4 5-yearly operation totals and perioperative mortality

The 5-yearly total number of operated VSDs has increased progressively from 1 case in 1955-1959 to 28 cases in 1990-1994 (figure 10.6). The yearly number of operations for VSD has levelled out at 5.6 cases per annum in 1990-1994. 5 yearly perioperative mortality decreased steadily from 25% in 1975-1979 to nil in 1990-1994.

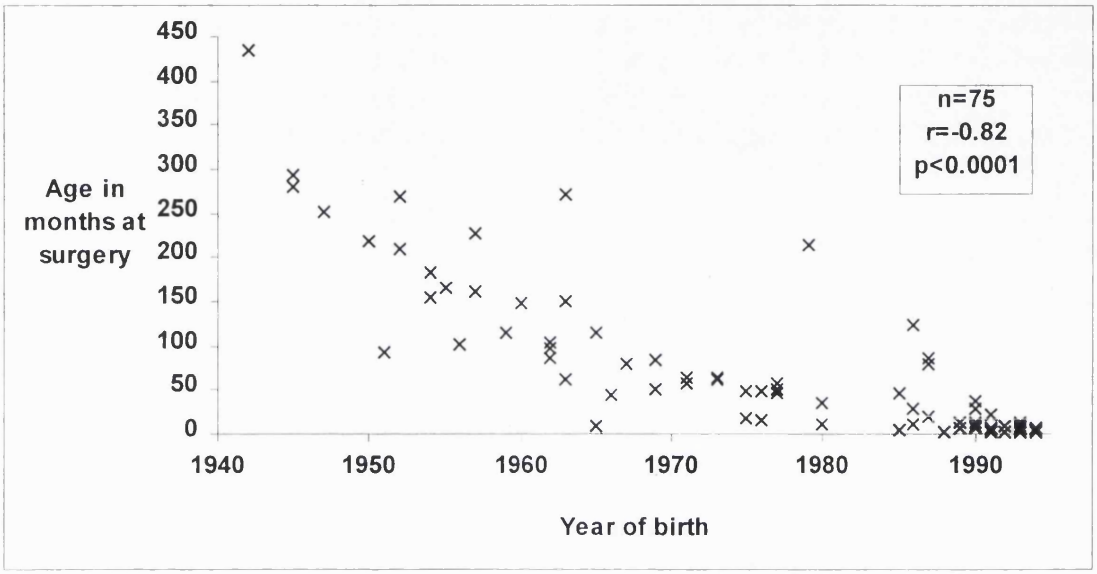
Figure 10.6: 5 year percentage perioperative mortality for VSD operations



10.3.5 Age At Surgery

There was a significant trend towards earlier age at surgery (figure 10.7). This trend was also present but not statistically significant over the period 1988-1994 (n=25, r=-0.36, p=0.07).

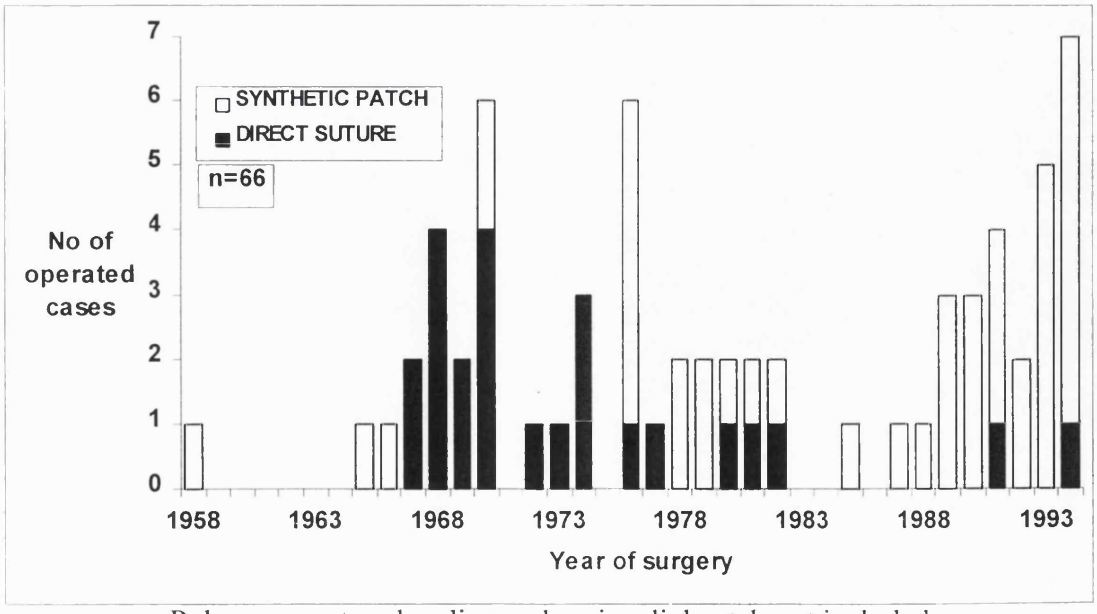
Figure 10.7: Age in months at first operation for VSD



Method of surgery

The method of VSD closure has changed from predominantly direct suture up to the late 1970s to closure almost exclusively by synthetic patch thereafter (figure 10.8).

Figure 10.8: Method of VSD closure



Pulmonary artery banding and pericardial patch not included

10.3.6 VSD associated with left/right ventricular outflow tract obstruction

6 cases of VSD were associated with eventual development of SAS (2% of VSD), 7 with RVOTO (3%) and 1 with both (table 10.4).

Table 10.4: VSD associated with ventricular outflow tract obstruction

LVOTO		RVOTO	
Born	**Outcome**	**Born**	**Outcome**
1978	VSD smaller→mild SAS	1960	Operated RVOT+VSD 1972
1982	VSD smaller→operated SAS 1994	1961	VSD smaller→mild RVOTO
1985	Operated VSD 1989→mild SAS	1963	Operated RVOT+VSD 1985
1989	VSD smaller→mild SAS	1973	Severe RVOTO*
1990	VSD smaller→operated SAS 1994	1977	Operated RVOT+VSD 1980
1993	Operated: VSD 1993→SAS 1994	1986	Operated RVOT 1996
		1987	Operated RVOT 1994
RVOTO and LVOTO			
Born			
1945	Operated SAS+RVOTO→AV block→permanent pacemaker insertion		

* Down's syndrome-RVOTO unoperated

10.3.7 Epidemiology - 1990-1994

In 1990-1994, 103 cases of VSD were diagnosed by 1 year of age. The birth prevalence of VSD was 3.85/1000 live births. 81 cases were mild VSD (79%) and 22 were severe VSD (21%). The birth prevalences were 3.02 and 0.83/1000 live births respectively. All cases of severe VSD were operated except for one case with multiple congenital anomalies. 3 of the severe VSD group had multiple VSDs (0.11/1000 live births). Only 1 of these required 2-stage repair with pulmonary artery banding prior to total definitive repair. The overall operation rate was 1.05 operations/1000 live-births. As already mentioned in chapter 5, a significantly higher birth prevalence of VSD in Malta was found when the above data was compared with recent studies with similar methodologies. No seasonal variation was found with Edward's method.

Age and mode of diagnosis

All of the defects were diagnosed at EC except for 1 patient with a small VSD diagnosed at post-mortem. Analysis of cumulative percentage age at diagnosis showed that 58% of mild VSDs were diagnosed in the neonatal period (up to 1 month of age) and 93% by 6 months of age (table 10.5).

Table 10.5: Cumulative percentage diagnosis of mild VSDs by age for 1990-1994

Age at diagnosis of VSD	Cumulative number diagnosed	Cumulative % diagnosed
By 1 week	26	33%
By 1 month	46	58%
By 3 months	65	81%
By 6 months	74	93%
By 9 months	79	99%
Total	81	

Location of VSD

The majority of defects were muscular (table 10.6). This is in accordance with other studies (Lewis et al 1996). The rate of surgery for perimembranous defects was twice that of muscular defects but this was not a significant difference.

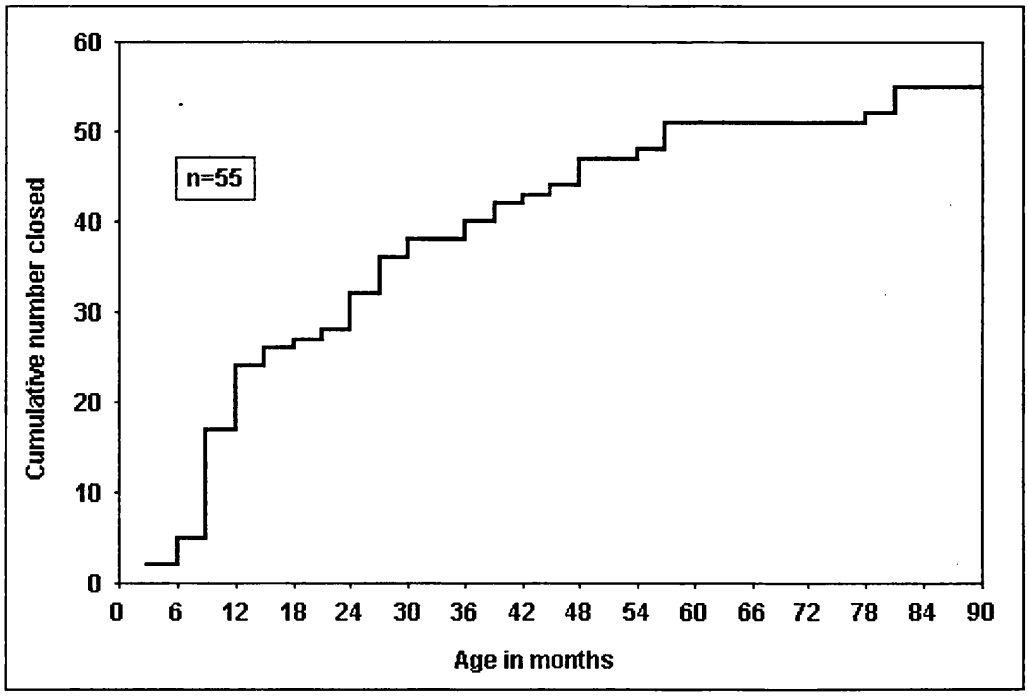
Table 10.6: Location and severity of VSD

	Mild	% of all VSD	Closed spontaneously	% of type	Severe	% of all VSD	Totals	%
Perimembranous	33	32%	21	47%	12	12%	45	44%
Muscular	48	47%	34	62%	7	7%	55	53%
Mixed	0	0%	-	-	3	3%	3	3%
Totals	81		55		22		103	

Spontaneous closure of VSD

55 of 81 (68%) of mild VSDs closed spontaneously (table 10.6). The number of muscular defects which closed spontaneously was twice that of perimembranous defects. Patients with VSD which closed spontaneously were diagnosed at an earlier age (n=55, mean age at diagnosis 1.1 months) than those which did not close (n=26, mean age at diagnosis 2.2 months). However, this difference did not quite reach statistical significance (p=0.06). Cumulative number of VSDs closed by age at diagnosis is shown in figure 10.9.

Figure 10.9: Age at echocardiography documented spontaneous closure of VSD



VSD associated with syndromes

There were 11 cases of Down's syndrome, 7 of which were in the severe group (64%-table 10.7). This was a significant deviation from the distribution of VSD severity in the non-syndromic population (p=0.001-Fisher's exact test). The location of VSD in Down's syndrome was also reversed with the majority being located in the perimembranous septum, but this was not statistically significant (p=0.21). These findings agree with earlier studies (Lewis et al 1996). There were also 1 case of Holt-Oram syndrome with severe multiple muscular VSDs, successfully operated for CHD and 1 case of VACTER syndrome who died of prematurity and was found to have a small VSD at post-mortem.

Table 10.7: Severity of VSD in Down's syndrome and non-Down's syndrome

	Mild		Severe		Total
Non-Down's	77	85%	14	15%	91
Down's	4	36%	7	64%	11

1 case of Holt-Oram syndrome excluded

10.4 Discussion

10.4.1 Historical trends

Diagnosis of VSD

Mild and severe VSDs have been diagnosed at progressively earlier ages in the period under study. The introduction of EC led to a further decline in age at diagnosis, and the diagnosis of a larger number of patients with VSD due to a higher pick-up of mild VSD, and earlier pick-up of severe defects over mild defects. Large defects with severe left-to-right shunting cause pulmonary hypertension. This is initially reversible with surgical treatment, but gradually becomes irreversible due to damage to the pulmonary microvasculature (Wood 1958), generally at about one year of age. This study has shown that with improved medical services including the availability of EC, no severe defects have been diagnosed beyond a year of age or in the stage of irreversible pulmonary hypertension.

Surgery for VSD

Successful surgical closure of VSD was first carried out in 1955 (Kirklin et al 1955). The declining trend in age at diagnosis of VSD in Malta was paralleled by a decline in the age at first surgery. Other trends in surgical management of VSD include a predominance of synthetic patch closure of defects rather than direct suture since the late 1970s.

These changes along with other evolutions in surgical management and experience, intensive care supervision and ever more sophisticated equipment have led to a striking fall in the 5-year perioperative mortality.

Down's syndrome

All severe VSD associated with Down's syndrome have been operated since 1973. This reflects a world-wide trend towards more aggressive treatment of CHD in Down's syndrome in order to ameliorate quality of life and functional capacity.

10.4.2 Epidemiology

Birth prevalence

The clinical diagnosis of a spontaneously closed VSD was reported early in this century (French 1918). Subsequently, closure of VSD was documented by CC studies (De Carvalho et al 1958). CC later also showed that defects which were large enough to cause heart failure could also become smaller and even close, thereby avoiding surgery (Evans et al 1960). It also became evident that VSDs could close after infancy, including at school age (Morton et al 1966).

Earlier studies quoted birth prevalence of VSD of 1.7-2.6/1000 live births (Carlgren 1959, Hoffman 1978) with spontaneous closure rates of approximately 30% (Mitchell et al 1971). This study showed a birth prevalence of VSD of 3.9/1000 live births, a significantly higher prevalence than previously reported in a non-screening study. In addition, a higher rate of spontaneous closure of 50% was found. Screening studies (by EC) have shown birth prevalences of VSD of 200-530/1000 live births. The defects detected in excess are not only asymptomatic, but clinically undetectable (Hiraishi et al 1992, Roguin et al 1996). The 75% spontaneous closure rate found in these studies was also higher than that reported for spontaneous closure of routinely detected defects.

Unfortunately, the present study was not prospective, and there was no form of systematic follow-up to document spontaneous closure of defects. In addition, there had been no consistent attempt at EC reporting to document size of defects in more than one scanning plane, and mechanism of spontaneous closure.

A prospective study regarding the natural history of ASD, VSD and PS is currently underway in Malta. This will include structured follow up by EC with standardised measurements of chamber sizes and flow until intervention/spontaneous resolution.

10.5 Conclusion

VSDs are relatively benign with a high rate of spontaneous closure. These lesions can be detected very early in life and should surgery be deemed necessary, this can be done at a very early age with a very low surgical risk. VSD can probably be used as an audit tool for a region's diagnostic cardiac services as the rate of detection of small VSDs would appear to depend largely on an early age at diagnosis prior to spontaneous closure.

11. Atrial septal defect

11.1 Introduction

This chapter outlines trends in diagnosis and surgery of ASD in Malta and analyses epidemiological aspects of this condition for live births in 1990-1994.

11.2 Methods

11.2.1 Definitions

ASD was defined as a defect in the fossa ovalis of the interatrial septum which allows blood to flow from one atrium to another due to the pressure differences between the two chambers. Sinus venosus defects, atrioventricular septal defects and unroofed coronary sinus defects were excluded.

Patients with a primary diagnosis of ASD were graded by severity into 2 groups. Mild defects were those which did not require surgical intervention and PFO was included in this group. Severe defects were those which required intervention, or are expected to require intervention in future.

Due to the constant improvement in non-invasive diagnostic imaging, mild and asymptomatic ASDs with no clinical signs whatsoever are increasingly diagnosed. In order to avoid over-inflation of the birth prevalence of ASD, only those lesions which required intervention, or are planned to undergo intervention were used for the calculation of birth prevalence of ASD.

11.2.2 Patients

Follow-up was to the end of December 1996, when all mild ASDs born in the period 1990-1994 had EC performed to document whether spontaneous closure had occurred, if this event had not already been documented previously.

11.3 Results

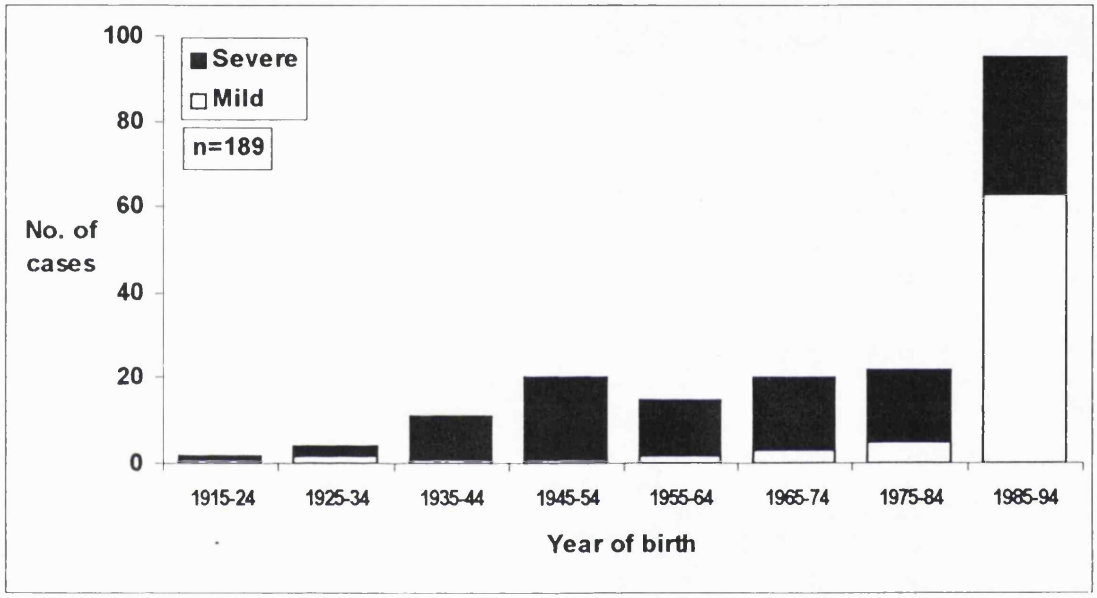
189 individuals born between 1910 and 1994 were diagnosed as having ASD. The male:female ratio was 0.88. 78 had mild ASD (42%) and 111 had severe ASD (58%).

11.3.1 Diagnostic trends

Spectrum of severity

Prior to 1988, the spectrum of ASD showed a higher proportion of severe lesions. After 1988, the total number of cases of ASD increased, with higher proportion of mild ASD and little increase in the number of severe ASD diagnosed (figure 11.1).

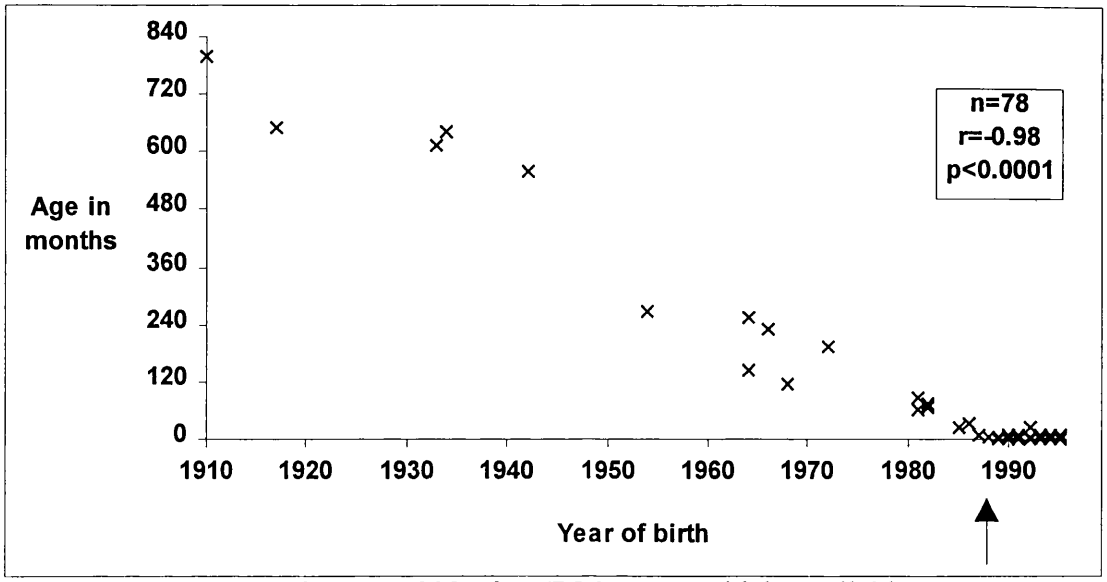
Figure 11.1: 5-yearly totals of mild and severe ASD by year of birth



Age at diagnosis

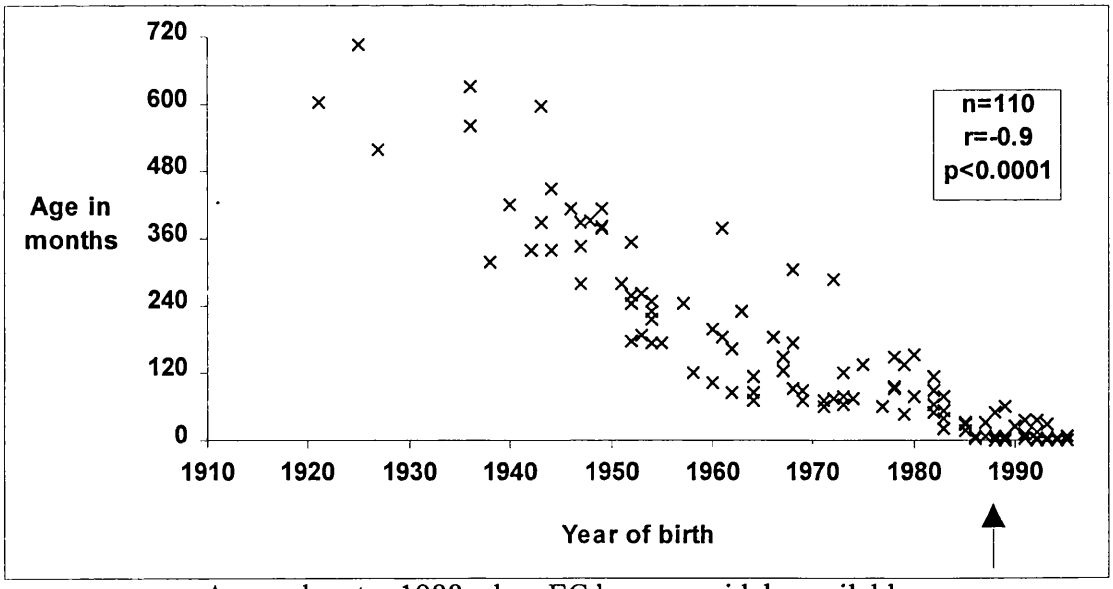
The age and mode of initial diagnosis was uncertain in 1 patient with mild ASD and 1 patient with severe ASD. There was a significant decline in age at diagnosis for both mild ASD and severe ASD (figures 11.2 and 11.3 respectively). There was no trend towards earlier age at diagnosis for either group since the introduction of EC in Malta (patients born 1988-1994).

Figure 11.2: Age in months at diagnosis of mild ASD



Arrow denotes 1988 when EC became widely available

Figure 11.3: Age in months at diagnosis of severe ASD



Arrow denotes 1988 when EC became widely available

No significant difference was found in age at diagnosis of mild and severe ASDs born prior to the EC era (table 11.1). However, the mean age at diagnosis of mild ASD born after the availability of EC was significantly less than that of severe ASD.

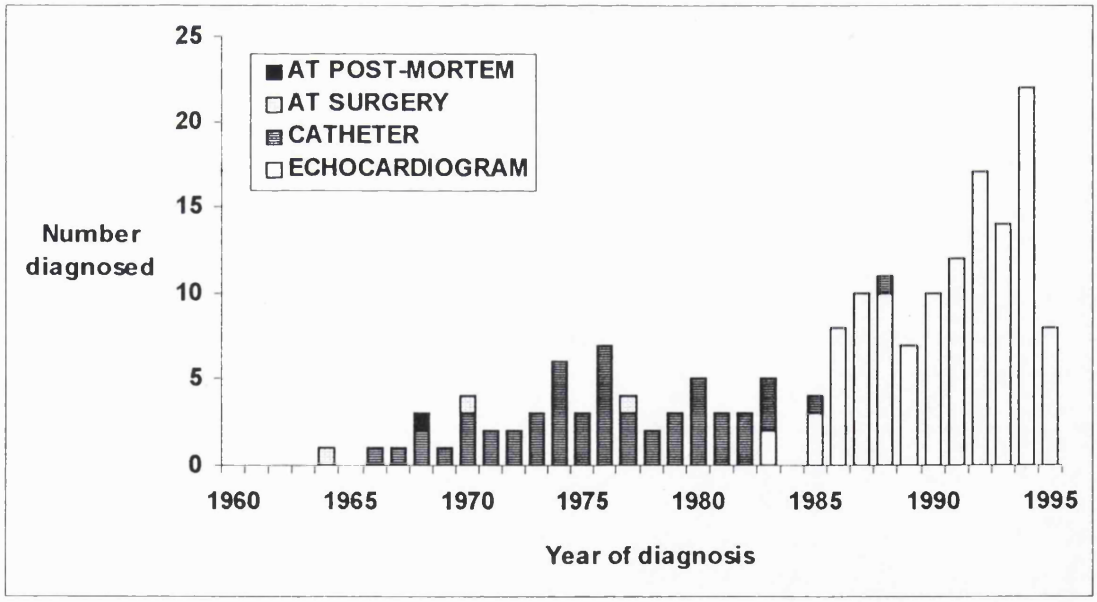
Table 11.1: Mean age in months at diagnosis of mild and severe ASD, pre- and post-EC

	n	Mean age in months at diagnosis
Born ≤ 1987		
Mild ASD	19	257.9
Severe ASD	86	201.1
		p=NS
Born 1988-94		
Mild ASD	59	3.1
Severe ASD	24	13.8
		p=0.006

Mode of diagnosis

Prior to the mid-1980s, the commonest mode of diagnosis of ASD was by CC (figure 11.4). After the mid-1980s, this changed almost exclusively to EC.

Figure 11.4: Mode of diagnosis of ASD



11.3.2 Surgery

111 patients born between 1910-1994 were shown to have severe ASD. 103 patients underwent surgical closure, 8 patients are awaiting surgery and 1 patient was not offered surgery as the diagnosis was made at 43 years of age, after the onset of irreversible pulmonary hypertension. Only 1 patient required reoperation. This was for pericardial bleeding and the outcome was successful. There was no other significant morbidity.

5 yearly operation totals and perioperative mortality

The 5 yearly total number of operated ASD have increased progressively (figure 11.5) while the 5 yearly perioperative mortality has decreased steadily. This was coupled with a significant decline in age at first surgery for the period under study (figure 11.6). The same trend was also present but not significant over the period 1988-1994.

Figure 11.5: 5 year totals and percentage perioperative mortality for ASD

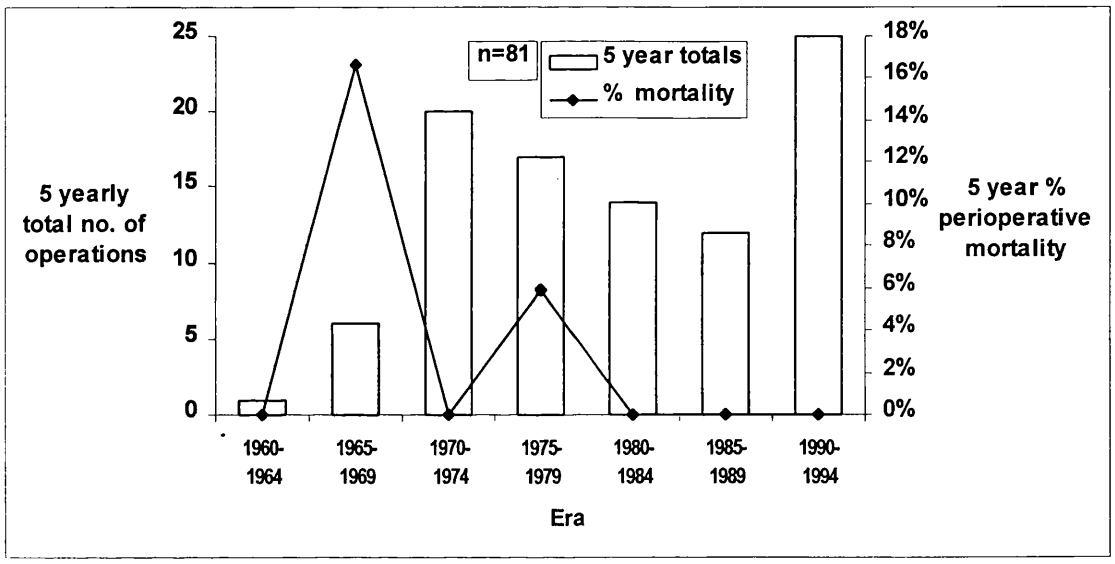
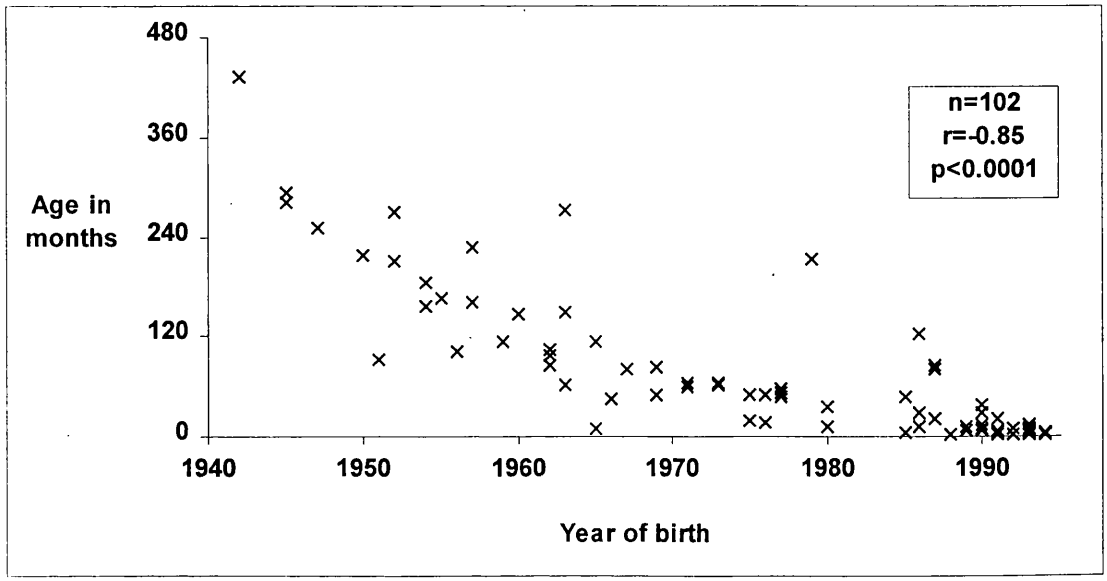


Figure 11.6: Age in months at first operation for ASD



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5-yearly operation totals and perioperative mortality

The 5-yearly total number of operated ASD have increased progressively (figure 11.5) while the 5-yearly perioperative mortality has decreased steadily. This was coupled with a significant decline in age at first surgery for the period under study (figure 11.6). The same trend was also present but not significant over the period 1988-1994.

Figure 11.5: 5-year totals and percentage perioperative mortality for ASD

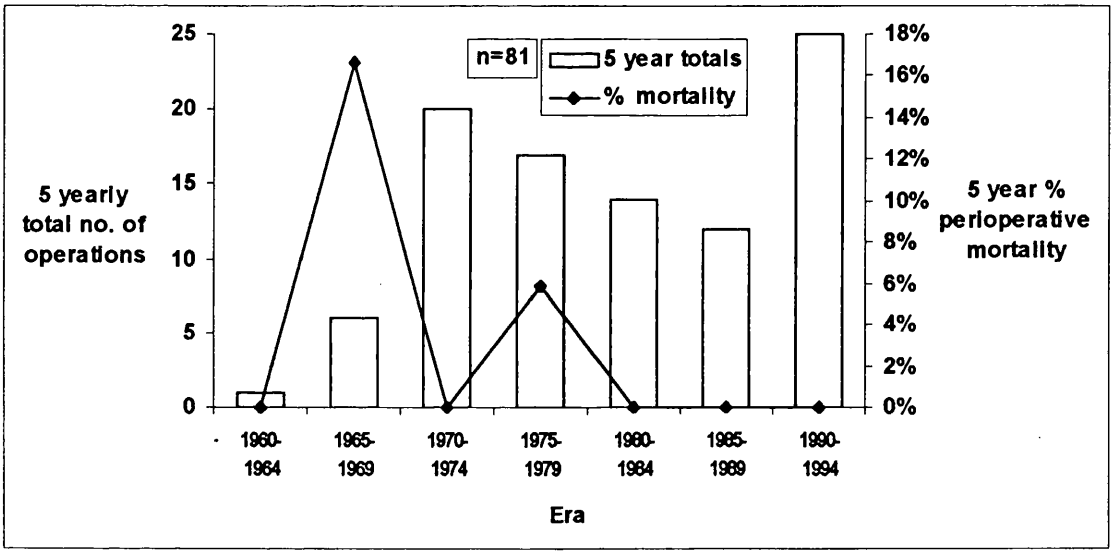
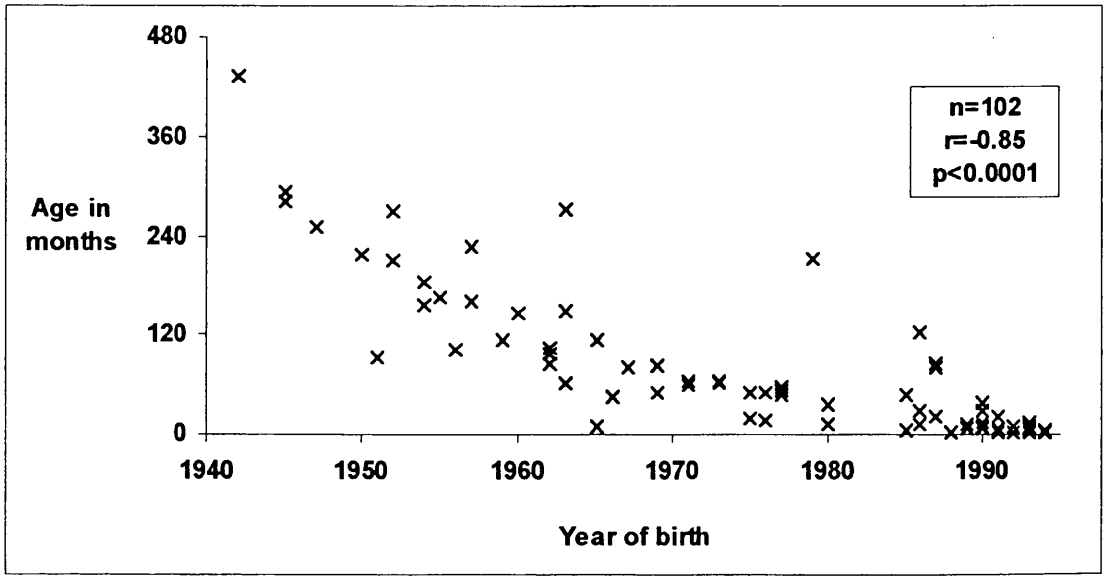


Figure 11.6: Age in months at first operation for ASD



Method of closure and operative centre

The commonest method of ASD closure has always been that of direct suture (figure 11.7). To date, no Maltese patients have had transcatheter ASD closure. Surgery for ASD is increasingly being carried out locally (figure 11.8) by a visiting surgical team from GOSHC. In 1990-1994, 74% (n=30) of all operations for ASD were carried out locally.

Figure 11.7: Method of ASD closure

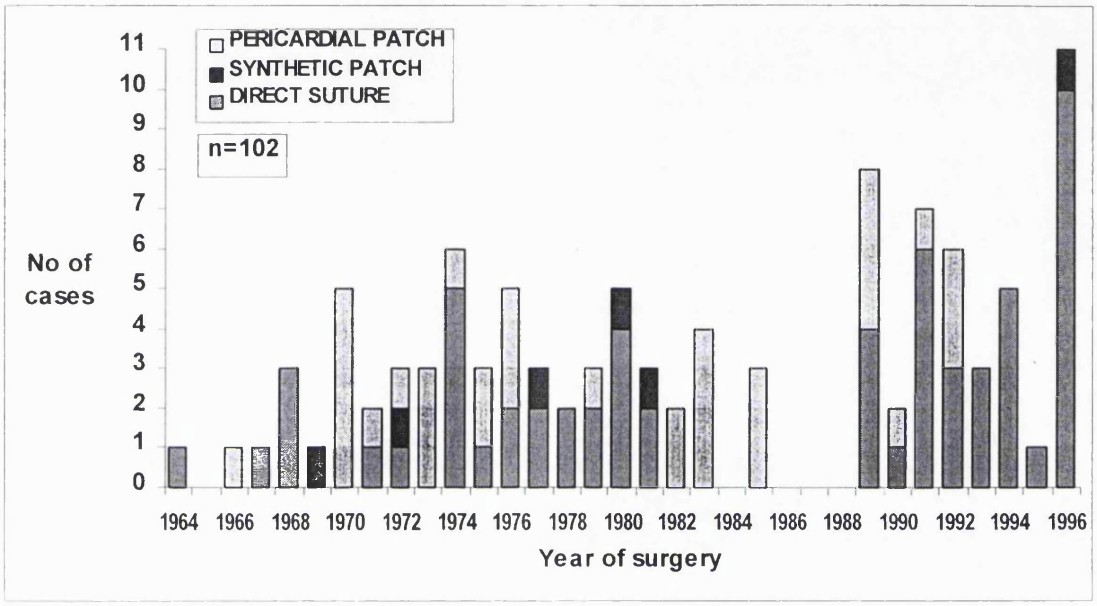
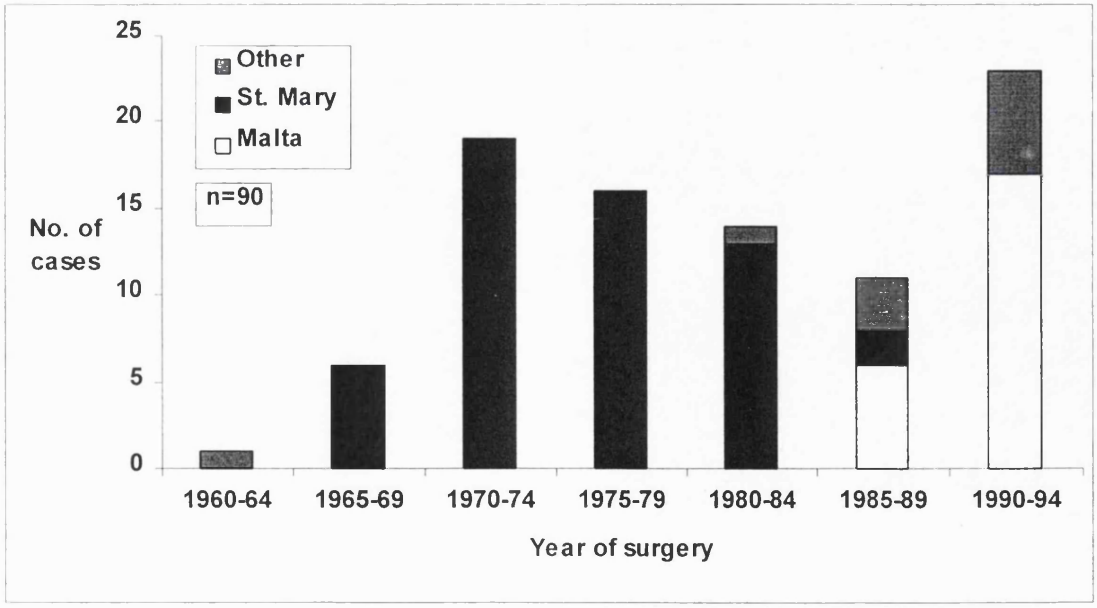


Figure 11.8: Operative centre for Maltese patients with ASD



11.3.3 Epidemiology

64 cases of ASD born in 1990-1994 were diagnosed by 1 year of age. All of the defects were diagnosed by EC (figure 11.4). These were distributed as 53 mild (83%) and 11 severe defects (17%). Of the latter group, 8 have not yet undergone intervention. This gave a birth prevalence of 0.42/1000 live-births for severe ASD, within the reported range for birth prevalence of ASD (chapter 5).

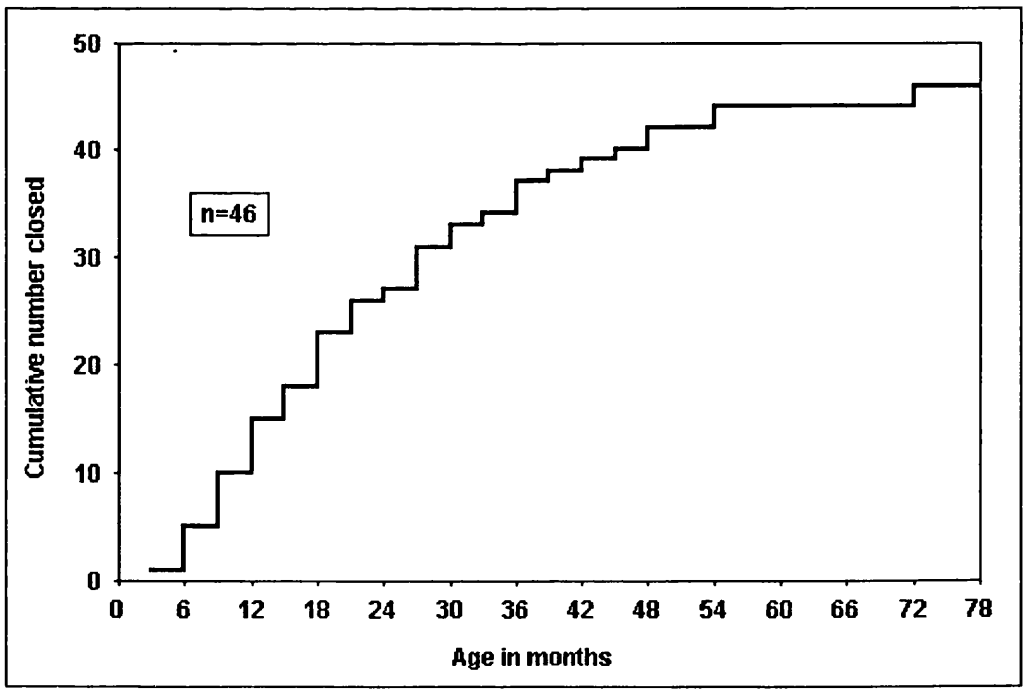
The yearly number of operations for ASD for 1990-1994 was 5 cases per annum, resulting in a rate of 0.19 operations for ASD per 1000 live births. However, 8 more patients are planned to undergo intervention which will result in 0.5 operations for ASD per 1000 live births for the period 1990-1994.

Only one case of severe ASD was associated with Down's syndrome. No other syndromes were represented with ASD as the primary cardiac malformation.

Spontaneous closure of ASD

3 of 53 mild ASD were lost to follow-up. 46 of the remaining 50 mild defects (92%) closed spontaneously and the remaining 4 had grown smaller at follow-up EC. The maximum recorded ASD diameters for both groups ranged from 2-12 mm. There was no apparent relationship between initial size and rate or timing of spontaneous closure, probably due to the small numbers involved and the lack of EC documentation of details such as diameter of defect in 2 planes. Such a relationship had been described in a prospective study (Radzig 1993). Age at EC recorded closure varied from 2 months to 5-years (figure 11.9) and there was no residual right heart volume overload.

Figure 11.9: Age at echocardiography documented spontaneous closure of ASD



11.4 Discussion

The findings overall are similar to those described for VSD in the previous chapter. A decline was found in age at diagnosis, age at surgery and perioperative mortality since the first operation on a Maltese patient with ASD at the Middlesex Hospital in 1964. This was a decade after the first successful reports of ASD closure using hypothermia and cardiopulmonary bypass (Lewis and Taufic 1953, Gibbon 1954).

11.4.1 Impact of echocardiography

EC has resulted in more cases of ASD being diagnosed, with a high rate of spontaneous closure. Mild and asymptomatic defects can be considered to be variations of the norm. Unfortunately, a high pick-up rate of these innocuous lesions causes severe parental anxiety once it is revealed that their child has a 'hole in the heart'. This naturally carries ominous overtones, despite extensive explanation by the child's physician that the defect is a normal variation which will almost certainly close spontaneously, in any case. Some degree of reassurance can also be given in cases where defects are significantly large with mild to moderate right heart volume overload, as even these may occasionally close (Ghisla et al 1985).

11.4.2 Surgery

ASD closure under total cardiopulmonary bypass was first carried out in 1954 (Gibbon 1954). Closure of ASD is traditionally carried in the pre-school period in order to prevent functional impairment in middle age due to chronic right heart volume overload (Konstantinides et al 1995). In rare instances, closure may need to be carried out in infancy due to early onset of heart failure (Bull C et al 1981). However, an ongoing controversy persists as to which defects actually need to be closed (Shah et al 1994).

Surgery for ASD is increasingly being carried out locally. This trend began in 1989 with the first of a series of 1 week visits of a surgical team from GOSHC on a biennial basis. The bulk of cases operated consist of ASDs due to the relative simplicity of technique, low expectation of complications and short duration of intensive care stay. The proportion of ASD closed locally is expected to continue to rise due to the establishment of a local adult cardiac surgery programme, although in future, the method of closure may change from surgery to transcatheter occlusion (King et al 1976) once these techniques are further refined (Hausdorf et al 1996).

11.5 Conclusion

ASD is a relatively benign form of CHD, with an excellent chance of spontaneous closure or reduction in size resulting in no residual right ventricular volume overload. Diagnosis can be achieved at an early age with relatively inexpensive and non-invasive techniques. Should surgery be required, the operative mortality is extremely low.

12. Pulmonary Stenosis

12.1 Introduction

This chapter identifies trends in diagnosis and intervention of pulmonary stenosis and calculates birth prevalences for 1990-94.

12.2 Methods

12.2.1 Definitions

PS was defined as flow acceleration across the pulmonary valve orifice ≥ 2m/s in the Doppler EC era (Wilson et al 1985).

Patients with a primary diagnosis of PS were graded by severity into 2 groups. Mild PS were those cases who did not require any intervention. Severe PS were those who underwent or are planned to undergo surgical or CC intervention.

Due to the constant improvement in non-invasive diagnostic imaging, very mild PS with few physical signs is increasingly diagnosed. In an attempt not to artificially inflate the birth prevalence of PS, rates were calculated for all PS and for mild and severe PS separately

Critical PS was defined as PS severe enough to require intervention in the neonatal period (≤28 days of age).

12.3 Results

12.3.1 Birth prevalences and gender differences

142 individuals born between 1943 and 1994 were diagnosed as having PS.

1990-1994

For this period, the birth prevalences of PS overall, and for mild and severe PS were 1.65, 1.1 and 0.54 /1000 live births respectively. The overall prevalence is in excess of that reported in earlier studies (Samanek et al 1989, Jackson et al 1996-table 5.4) but the prevalence of severe PS is similar to previously quoted figures. This suggests that the increased Maltese prevalence of PS is due to higher pickup of mild PS.

Two cases of severe PS were associated with Noonan's syndrome (0.08/1000 live births). Four of the severe PS group had critical PS (0.15/1000 live births). The number of females was significantly higher (M:F ratio 0.48-table 12.1). Analysis of minor and severe groups by sex again showed no significant differences in the severe group but a significantly higher proportion of females in the mild group (M:F ratio 0.56).

There were 15 interventions for PS for patients born in 1990-1994. In addition, 1 patient is awaiting balloon valvuloplasty. These interventions were comprised of 4 operations and 11 balloon valvuloplasties which gave rates of 0.15 and 0.42/1000 live births respectively. Overall, the number of interventions will be at least 0.6/1000 live births. All 4 patients with critical PS underwent balloon valvuloplasty as the initial procedure. 2 of these also required surgical relief of PS shortly afterwards. All 4 patients survived and are well.

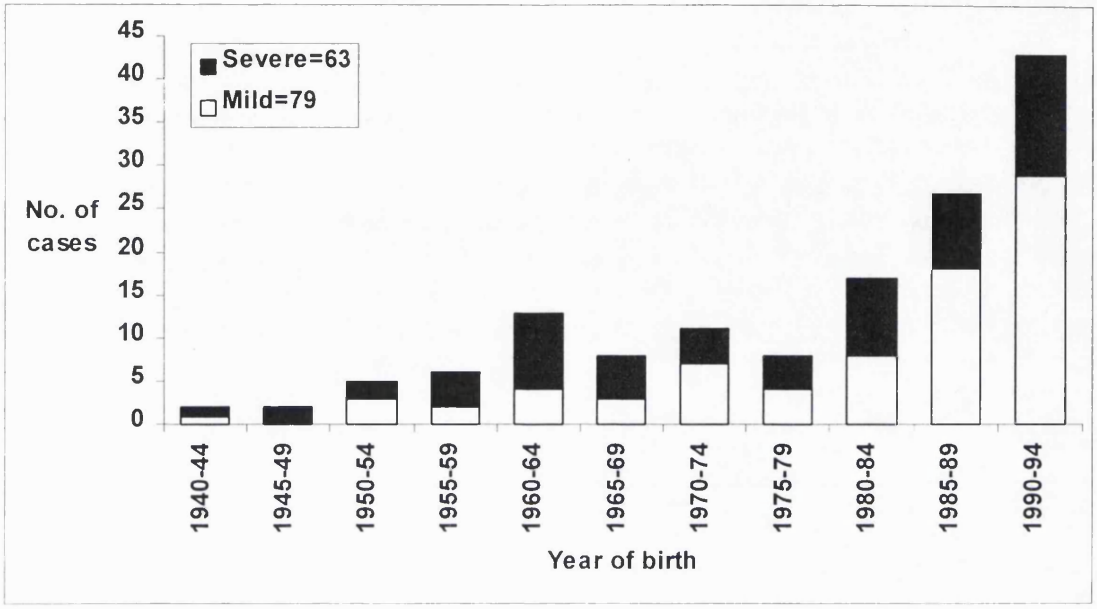
Table 12.1: PS subdivided by severity and sex for patients, born between 1990-94 diagnosed by 1 year of age

	PS born 1990-94 diagnosed by 1 year of age		
	Mild	Severe	Totals
Female	20	9	29
Male	9	5	14
Total	28	14	42
%	67%	33%	
p	0.04	NS	0.019

12.3.2 Pattern of severity of PS

Prior to 1988, the spectrum of PS showed a higher proportion of severe lesions. After 1988, the total number of cases of PS diagnosed increased, with higher proportion of mild PS and little increase in the number of severe PS diagnosed (figure 12.1). Prior to 1990, 8 patients were diagnosed as having critical PS and all 8 died. 2 were diagnosed at post-mortem, 2 died due to complications arising after diagnostic CC, and 4 died after surgery.

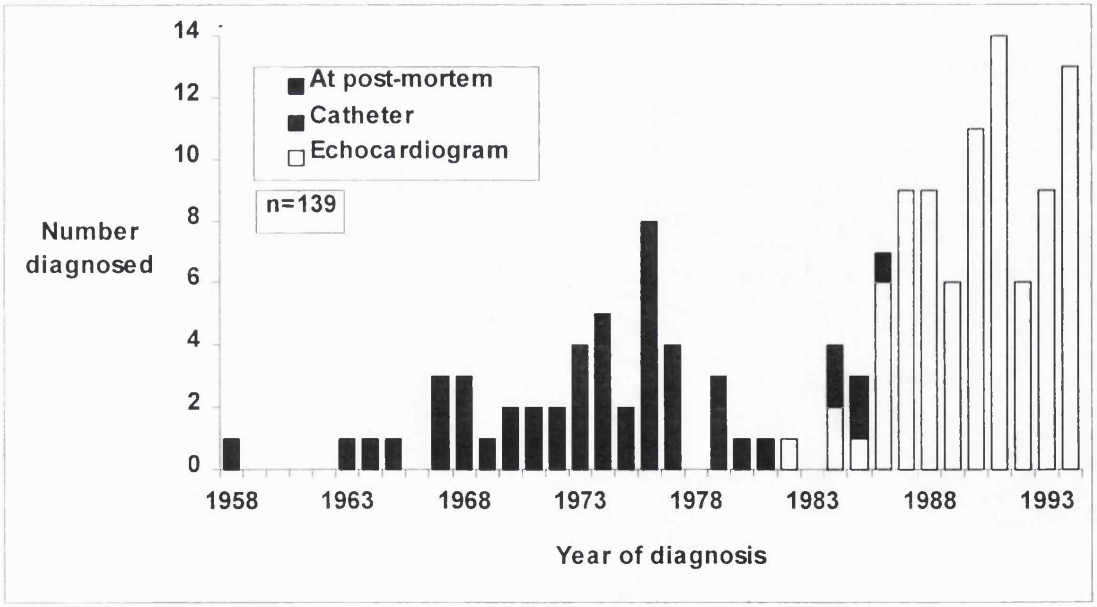
Figure 12.1: 5-yearly totals of mild and severe PS by year of birth



12.3.3 Mode of diagnosis

Prior to the mid-1980s, the commonest mode of diagnosis of PS was CC (figure 12.2). After the mid-1980s, this changed exclusively to EC. No definitive diagnoses of PS were first made at surgery.

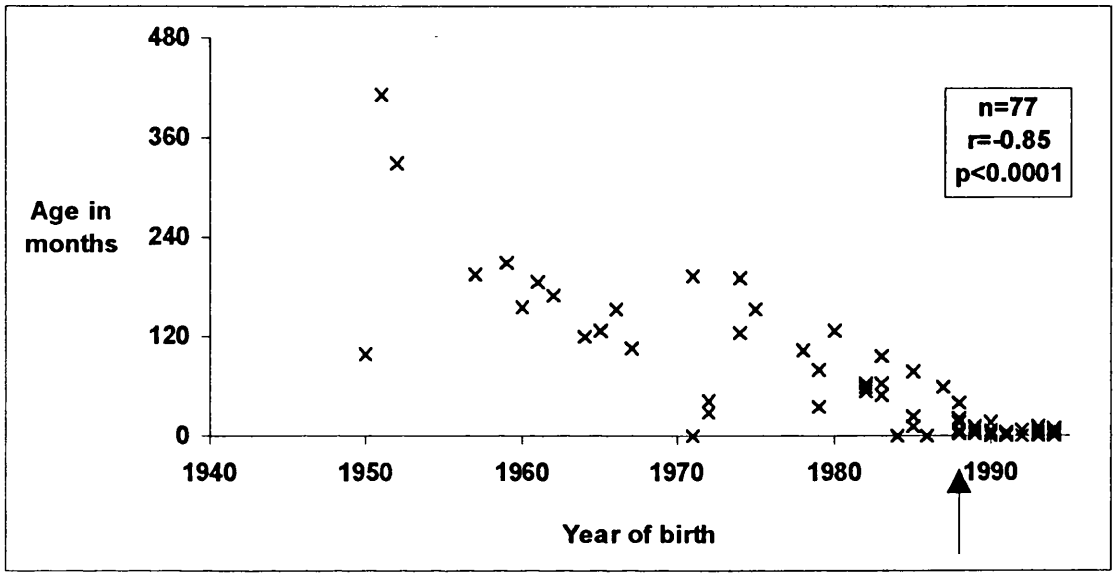
Figure 12.2: Mode of diagnosis of PS



12.3.4 Age at diagnosis

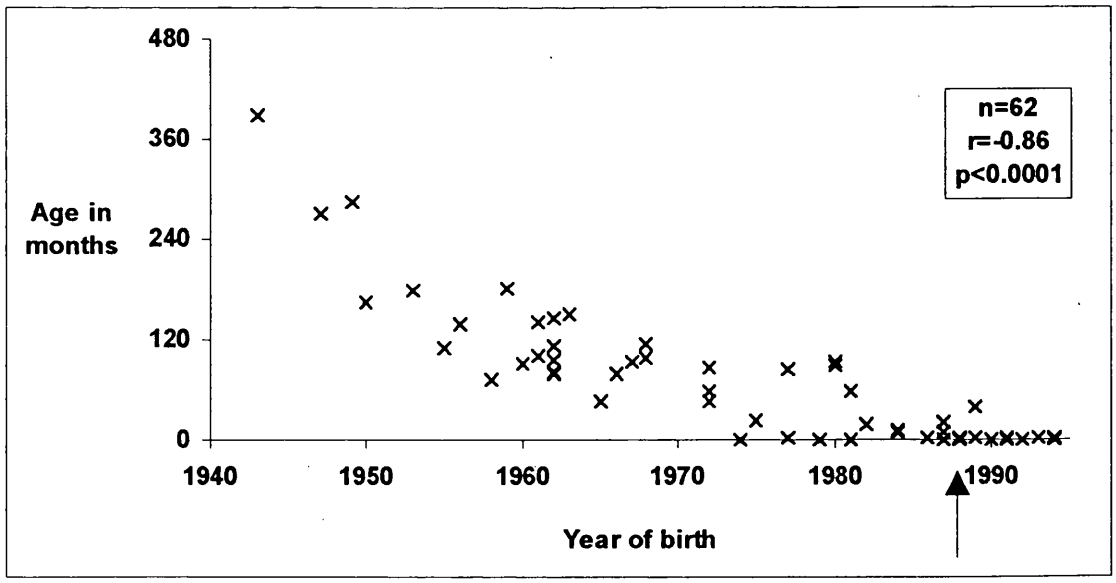
The age and mode of initial diagnosis were uncertain in 2 patients with mild PS and 1 patient with severe PS. There was a significant decline in age at diagnosis for both mild and severe PS (figures 12.3 and 12.4 respectively). There was no significant trend towards earlier age at diagnosis for either group since the introduction of EC (patients born 1988-1994).

Figure 12.3: Age in months at diagnosis of mild PS



Arrow denotes 1988 when EC became widely available

Figure 12.4: Age in months at diagnosis of severe PS



Arrow denotes 1988 when EC became widely available

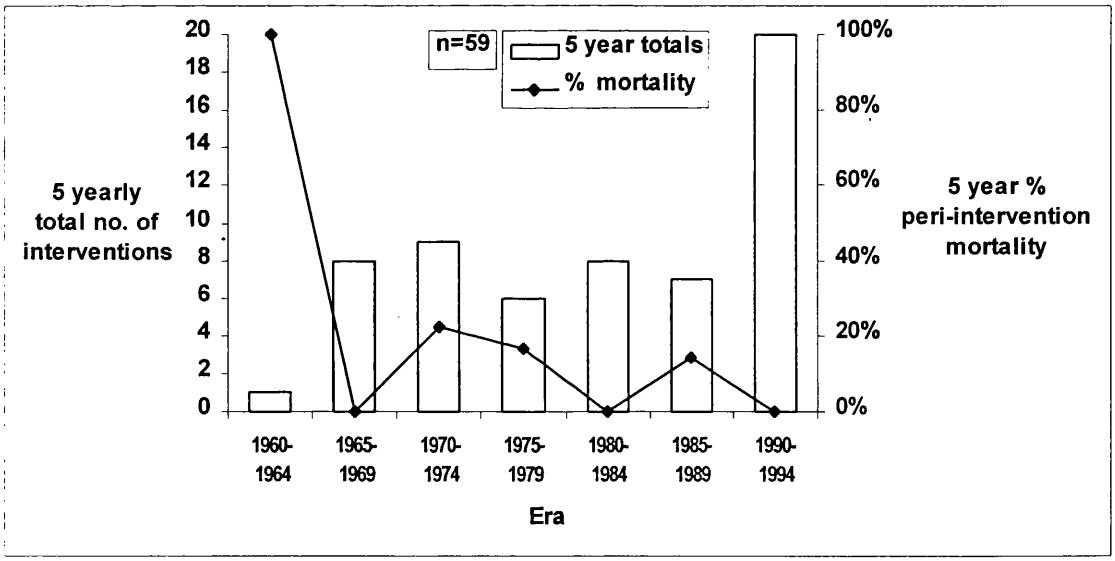
12.3.5 Severe PS

63 patients born over between 1943-1994 had severe PS. 40 underwent surgical correction and 22 underwent balloon valvotomy. 34 had surgery only, 16 had CC only and 6 had both. 2 patients underwent reoperation, 1 as an urgent procedure due to post-operative mediastinal bleeding and 1 patient with Noonan's syndrome had a second operation for recurrent PS necessitating pulmonary valve excision. In both cases, the outcome was successful. There was no other severe morbidity.

12.3.6 5-yearly intervention totals

The 5-year total number of interventions for PS has increased from 2 cases in 1960-1964 to 9 cases in 1990-1994 (figure 12.5). The 5-yearly perioperative mortality decreased steadily from 20% in 1970-1974 to 0% in 1990-1994. In addition, there were 4 other deaths associated with PS. One patient died after diagnostic CC due to inhalation of stomach contents (year of death 1975), one died inexplicably with severe (not critical) PS with post-mortem findings that tallied with the premortal diagnosis (1994), and 2 died of critical PS which was diagnosed at post-mortem (1975 and 1981).

Figure 12.5: 5-year percentage perioperative mortality for patients undergoing intervention for PS



12.3.7 Age at intervention

There was a significant trend towards earlier age at first operation and earlier age at first balloon valvuloplasty for severe PS (figures 12.6 and 12.7 respectively).

Figure 12.6: Age in months at first operation for PS

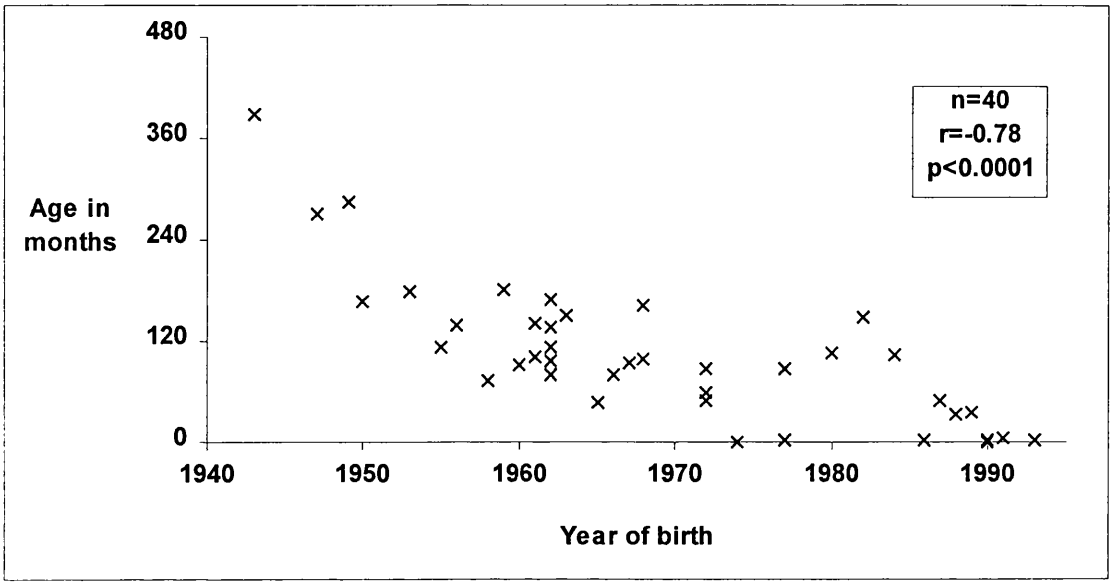
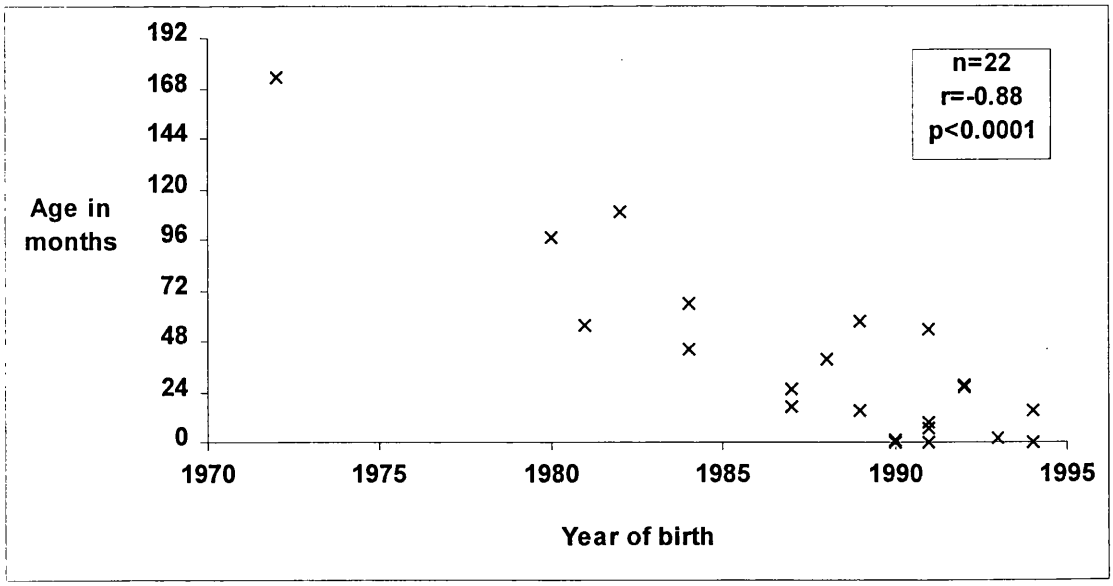


Figure 12.7: Age in months at first balloon valvotomy for PS



12.3.8 Method and centre of intervention

Initially, the commonest form of intervention for severe PS was open valvotomy. This has changed to balloon valvuloplasty (figure 12.8). No pulmonary valve replacements have been carried out. Surgery for this condition was carried out predominantly at St. Mary's Hospital, but is this increasingly being carried out locally with the first patient operated in Malta in 1989 (figure 12.9). Similarly, balloon valvuloplasty is increasingly carried out locally by visiting paediatric cardiologists.

Figure 12.8: Method of PS intervention

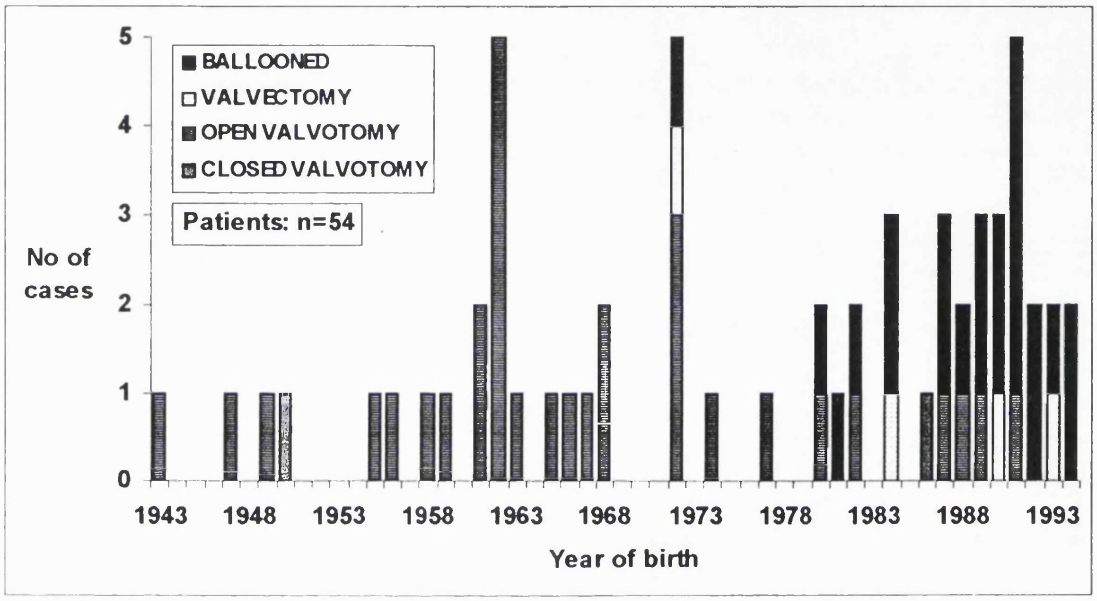
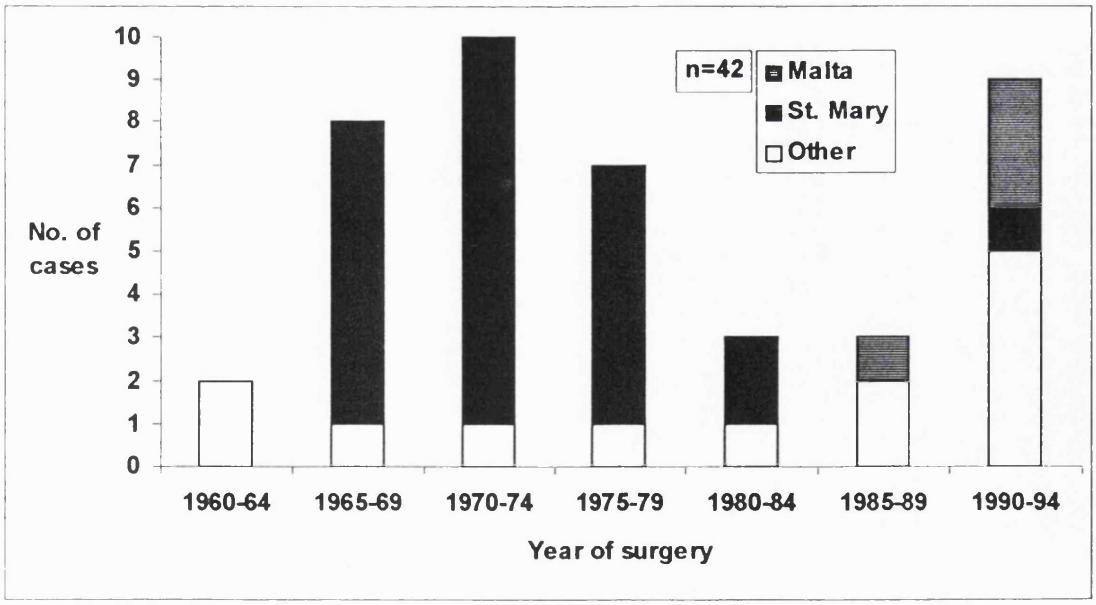


Figure 12.9: Operative centre for Maltese patients with PS



12.4 Discussion

12.4.1 Spectrum and diagnosis

PS has been diagnosed at progressively earlier ages in the period under study, as was found for VSD and ASD (chapters 10 and 11 respectively). Prior to EC, more cases of severe PS were diagnosed definitely, almost certainly due to the more striking physical signs in severe PS and the greater likelihood of the development of symptoms. EC has had the effect of increasing the number of cases of definitively diagnosed PS and inverting the ratio of mild:severe PS diagnosed.

12.4.2 Intervention

The first operation on a Maltese patient with PS was a closed valvotomy by Mr. Brock at Guys Hospital in 1963, 15 years after this procedure was first described in the literature (Brock 1948). The delay to application of balloon valvotomy was far less, just 4 years after this technique was pioneered (Kan et al 1982). The first CC balloon dilatation for a Maltese patient with PS took place the UK in 1986 (Dr. K.A. Hallidie-Smith and Dr. P. Rees).

Surgery for PS is increasingly being carried out locally. This trend began in 1989 with the visits of a surgical team from GOSHC. However, the proportion of PS operated locally may not continue to rise as the preferred mode of intervention has become that of balloon dilatation. Surgery is being reserved for more severe cases of PS, resistant to balloon dilatation, which might potentially be more safely carried out in a tertiary referral centre in the paediatric age group.

12.5 Conclusions

PS is a relatively benign malformation in which diagnosis can be achieved at an early age by EC, which has caused an increase in prevalence due to increased diagnosis of mild defects. Should intervention be required, mortality is very low.

13. Tetralogy of Fallot

13.1 Introduction

In this study, TOF constituted the most frequently operated lesion (chapter 9). This chapter reviews trends in diagnosis and treatment, and further analyses the epidemiological differences discussed in chapter 5.

TOF was defined as anterior aortic displacement over a malaligned, outlet VSD resulting in RVOTO.

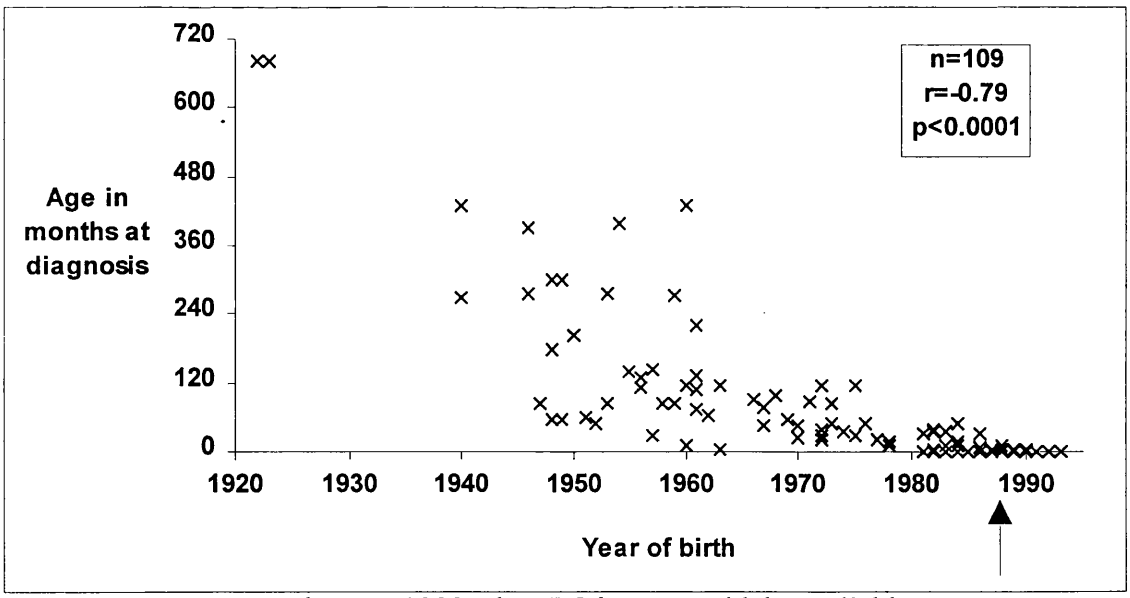
13.2 Results

13.2.1 Patients and diagnosis

109 individuals born between 1922 and 1994 were diagnosed as having TOF. The male:female ratio was 1.37 (p=NS).

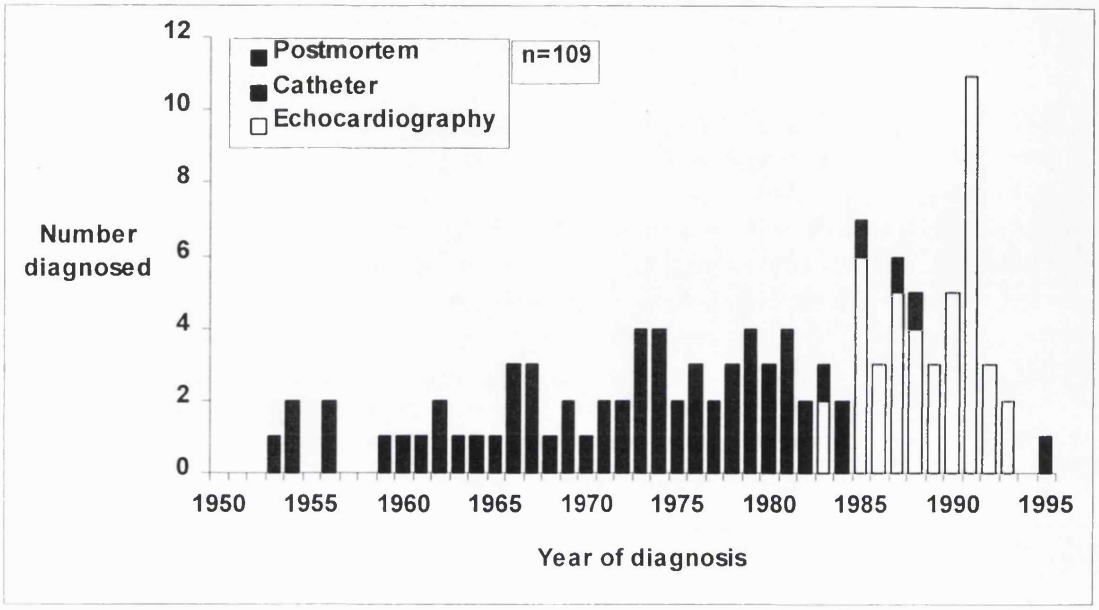
The age and mode of initial diagnosis were known in all patients. There was a significant decline in age at diagnosis over the period studied (figure 13.1). Prior to the mid-1980s, the commonest mode of diagnosis of TOF was CC (figure 13.2). After the mid-1980s, this changed almost exclusively to EC.

Figure 13.1: Age in months at diagnosis of tetralogy of Fallot



Arrow denotes 1988 when EC became widely available

Figure 13.2: Mode of diagnosis of tetralogy of Fallot



13.2.2 Surgery

101 patients underwent surgery. Reasons for non-operation in the remaining 8 patients are shown in table 13.1.

Table 13.1: Reason for non-operation in TOF

Reason	Year of birth	n
Syndromic/multiple anomalies	1990	2
Diagnosed post-mortem	1983-1989	3
Lost to follow-up	1989	1
Awaiting surgery	1983-1989	2

13.2.3 5-yearly operation totals, perioperative mortality and age at surgery

The 5-yearly operation totals for TOF have increased progressively from the 1950s (figure 13.3). There was a significant trend towards earlier age at surgery (figure 13.4) coupled with a progressively lower perioperative mortality (figure 13.3). The operation rate for TOF born in 1990-94 was 1/1000 live births.

Figure 13.3: 5-year percentage perioperative mortality for TOF operations

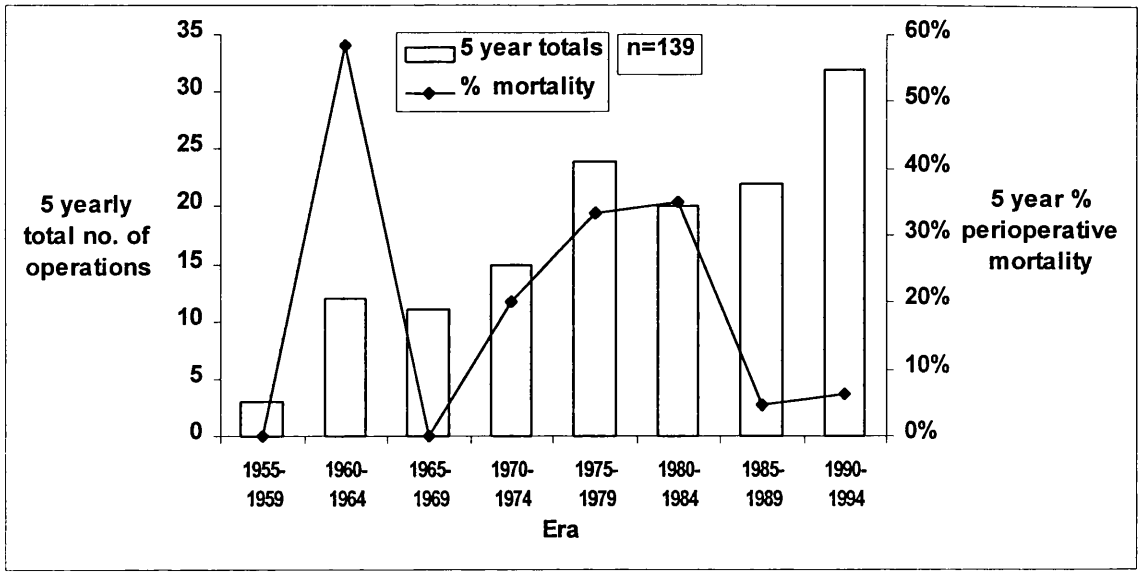
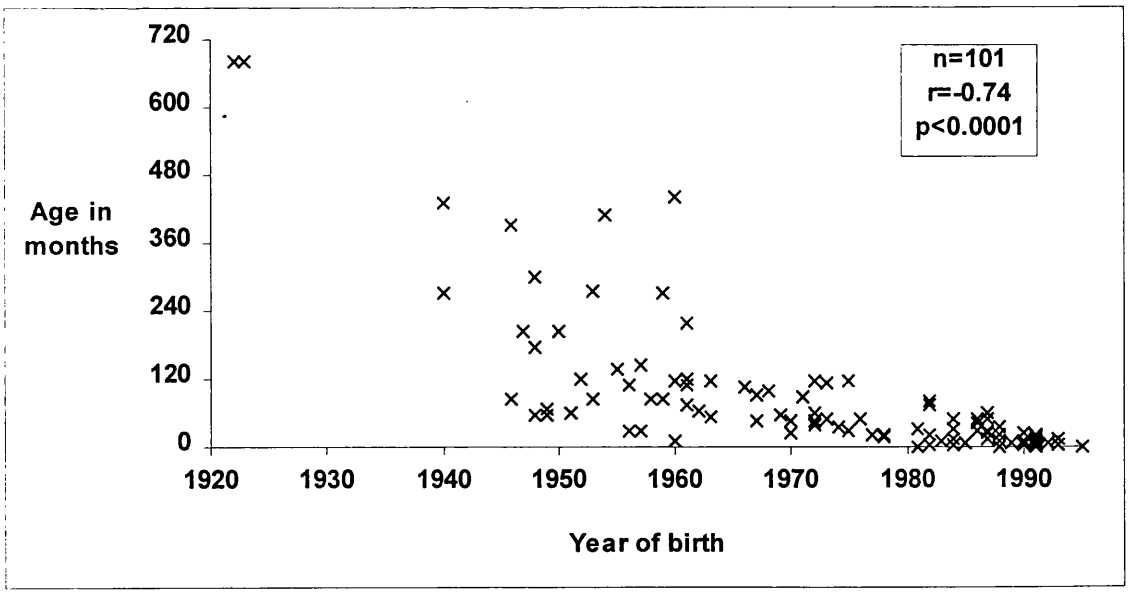


Figure 13.4: Age in months at first operation for tetralogy of Fallot



13.2.4 Method of surgery and operative centre

The first operation for the early patients in the series was invariably a shunt procedure (figure 13.5). The first classical BTS on a Maltese patient with TOF was carried out in 1953, 8 years after the first report of a successful shunt (Blalock and Taussig 1945). The change to a MBTS rather than a classical BTS in the event of shunt being needed prior to total repair came about in the early 1980s (McKay et al 1980). The first total correction was carried out in 1959, only 4 years after the first reported case (Lillehei 1955). Primary repair became the preferred mode of treatment in the mid-1970s. The youngest patient to undergo primary repair had surgery at 10 weeks of age (year of operation 1992). To date, all operations for TOF have been carried out in UK tertiary referral centres (figure 13.6).

Figure 13.5: Initial operation for tetralogy of Fallot

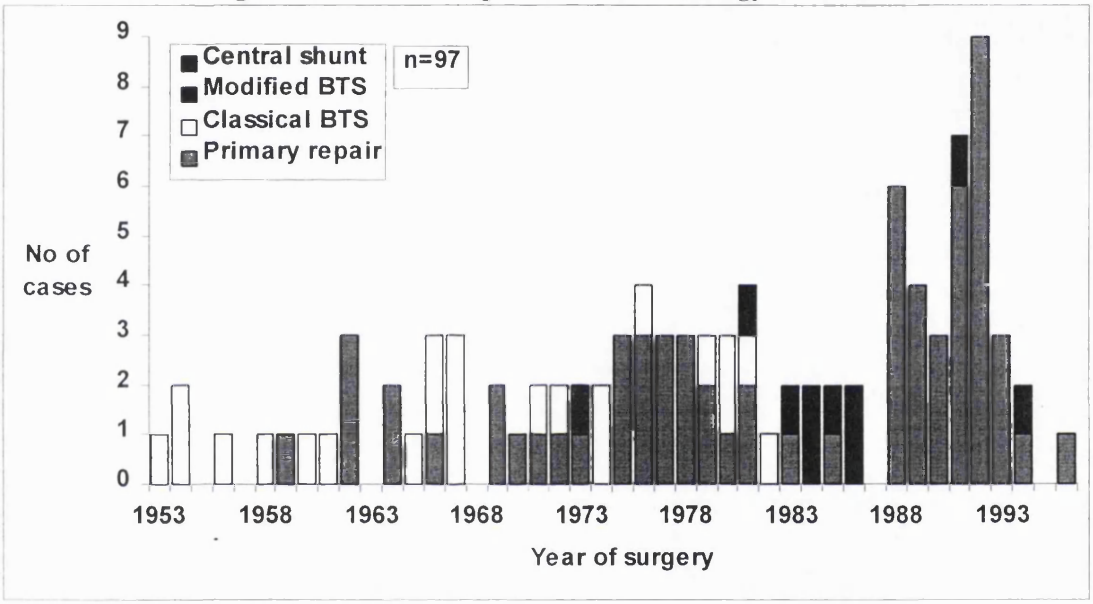
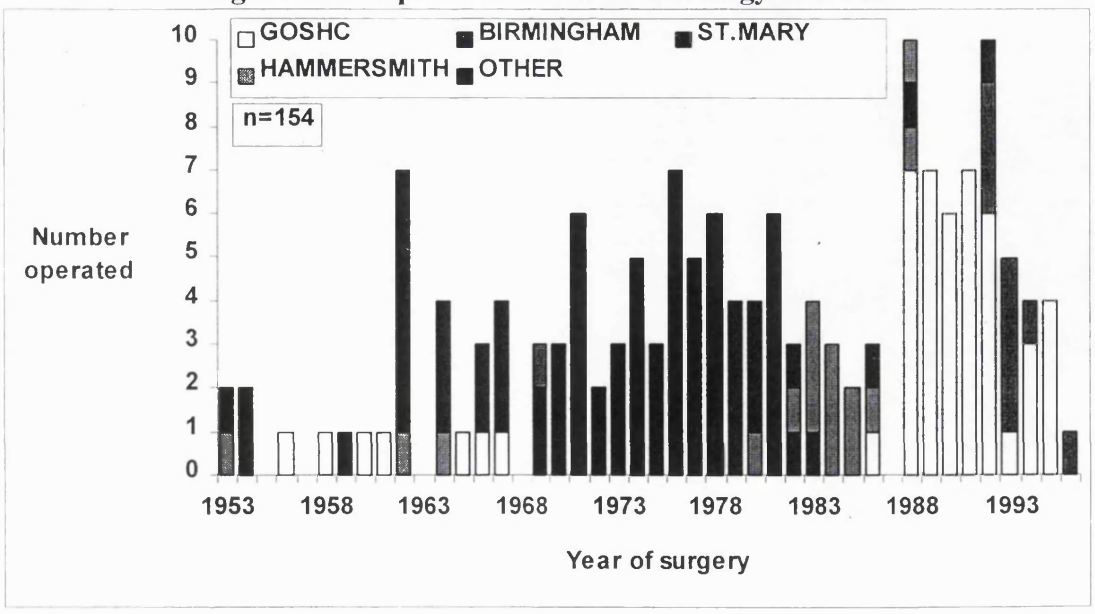


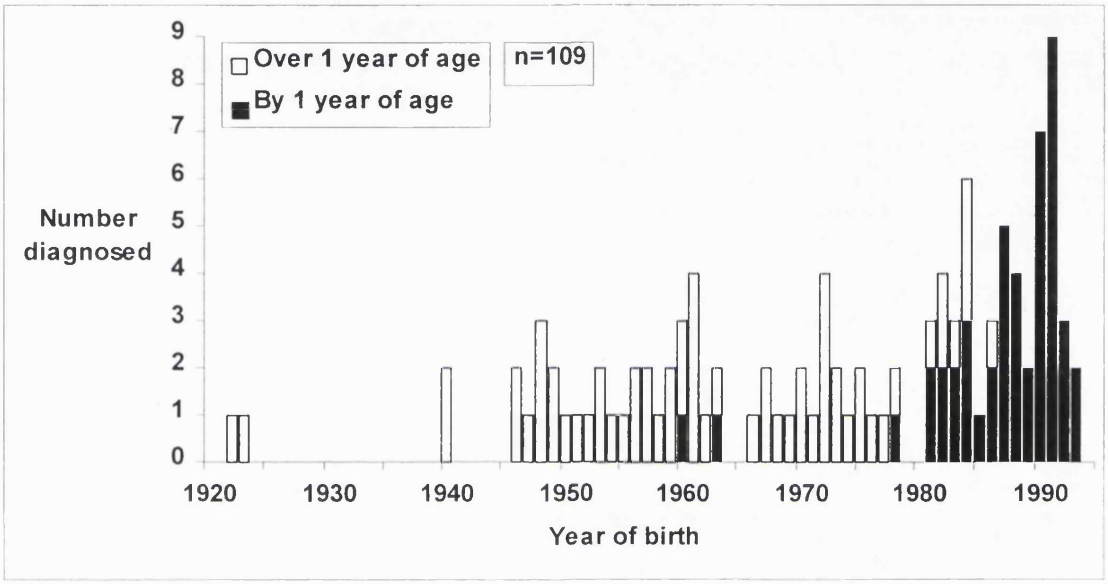
Figure 13.6: Operative centre for tetralogy of Fallot



13.2.5 Epidemiology: 1980-1994

Recent studies dealing with the epidemiology of CHD have only included cases diagnosed by 1 year of age. The annual number of live births with TOF is shown in figure 13.7, subdivided into those cases detected in infancy and those detected after infancy. Due to the historical nature of this study, cases diagnosed after 1 year of age have also been included for calculations of prevalence for 1980-1989. No cases were diagnosed beyond infancy after 1990.

Figure 13.7: Patients diagnosed in infancy and beyond



The annual number of live births with TOF prior to 1980 suggest incomplete ascertainment with fewer cases being diagnosed (figure 13.7). The decade 1980-89 was therefore used to calculate baseline birth prevalence of TOF along with 95% CI (table 13.2). A peak of TOF cases was noted for 1990-1. The above rates were calculated for the period 1990-91. There was a significant difference in birth prevalences of TOF between these 2 periods (p=0.0018-Yates continuity correction).

Table 13.2: Birth prevalences and 95% CI for TOF for 1980-89 and 1990-91

	Total live births	TOF	Birth prevalence per 1000 live births	95% CI	
1980-89	55133	31	0.56	0.39	0.81
1990-91	10670	16	1.50	0.89	2.49

Seasonal breakdown of TOF for the period 1990-91 showed a TOF peak for the 3rd quarter (appendix 14) but statistical analysis by Edwards' method (Edwards 1961a) and by standard 2 by 2 χ^2 test for the 2 halves of the year failed to show any significant seasonal variation, due to the small numbers involved.

The prevalences of TOF for the period with relatively low birth prevalence of TOF (1980-1989) and for the entire period under discussion (1980-1994) were compared with two recent studies with similar methodologies (Samanek et al 1989, Jackson et al 1996) using the χ^2 test. The Maltese prevalence was significantly higher than that reported in both studies (table 13.3). Comparison was also made between Maltese births diagnosed by 1 year of age for 1980-94 and the above 2 studies. The Maltese prevalence of TOF remained significantly higher ($p \leq 0.01$).

Table 13.3: Comparison of birth prevalence of tetralogy of Fallot with 2 recent studies with similar methodologies

Reference	Samanek 1989	Jackson 1996	Present study	Present study
Locality	Bohemia	Merseyside	Malta	Malta
Years studied	1980	1979-88	1980-94	1980-89
Total livebirths	91823	203880	81250	55133
With TOF	21	66	52	21
Birth prevalence	0.23	0.32	0.64	0.56
Upper 95% CI	0.36	0.41	0.86	0.54
Lower 95% CI	0.15	0.25	0.68	0.22
p	<0.0001	0.0003	vs. Malta 1980-94	
p	0.015	0.001	vs. Malta 1980-89	

13.3 Discussion

TOF has been diagnosed and operated at progressively earlier ages in the period under study. These trends were paralleled by a declining perioperative mortality.

The birth prevalence of TOF in Malta was significantly higher than that previously reported in the literature. A genetic predisposition to conotruncal anomalies has been reported in association with 22q11 microdeletion, including TOF (Wilson et al 1992). A genetic tendency towards the development of TOF may be inherent in the Maltese gene pool.

A peak in live births with TOF was noted in 1990-1991. Closer inspection of figure 13.7 shows approximately 10-yearly peaks above the slowly increasing baseline prevalence of TOF for the years 1948, 1960-61, 1973 and 1983-1985. Due to the retrospective nature of this study, it is not possible to identify causative factors for these peaks (chapter 5) but a relationship may exist between epidemics of viral infections in the last quarter of the year and live births with TOF 6-9 months later, in the 3rd quarter of the year.

14. Patent ductus arteriosus

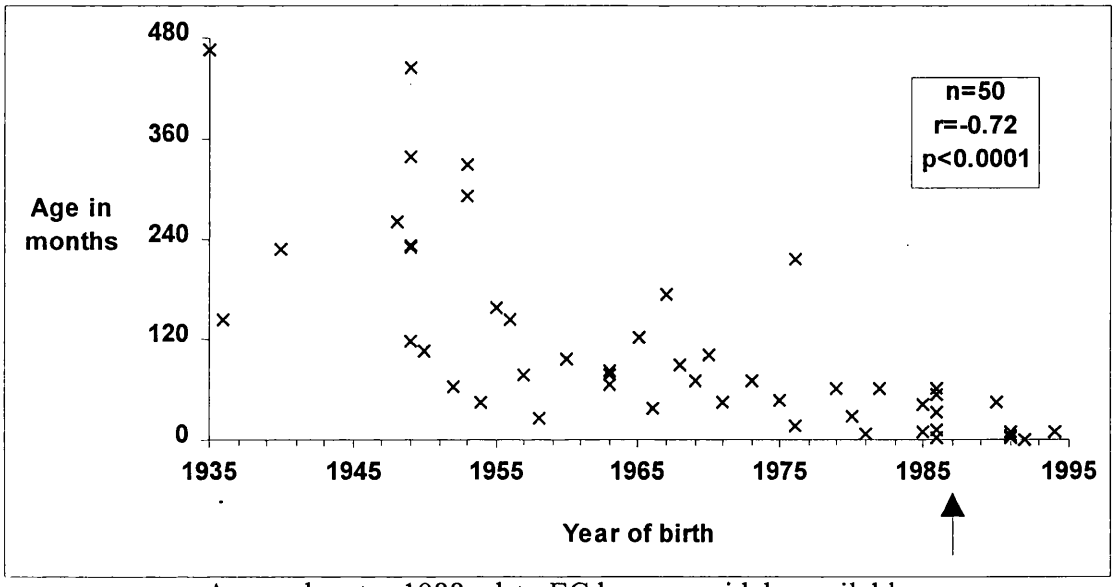
14.1 Introduction

PDA is a relatively common form of CHD causing left to right shunting. This chapter outlines trends in diagnosis and treatment of this condition.

14.2 Results

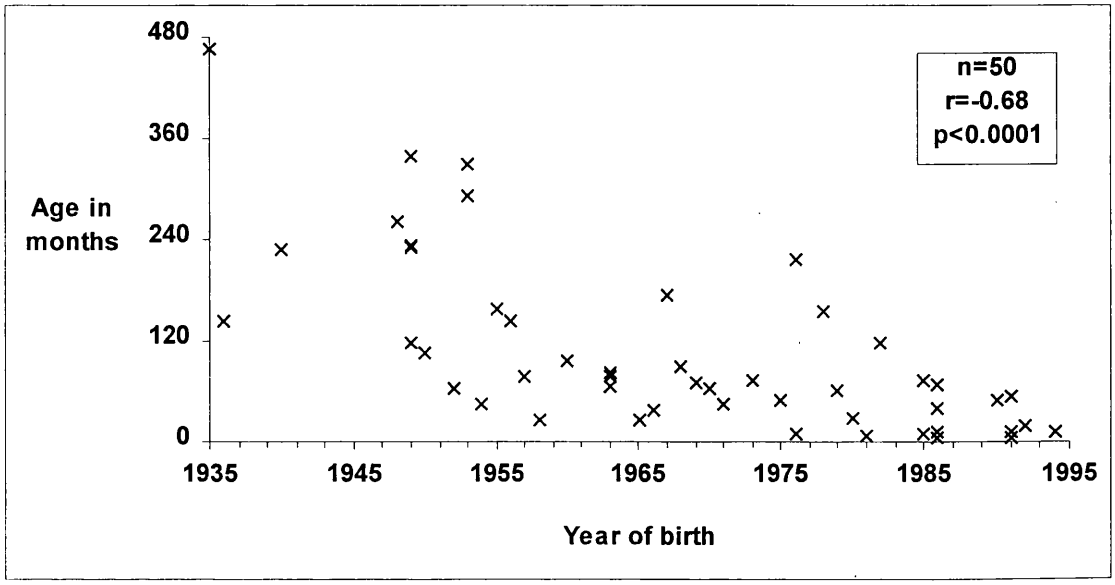
There were 51 live births with PDA born up to 1994. Age at diagnosis was uncertain in 1 case. Age at diagnosis and at catheter/surgical intervention for PDA have declined significantly in the period under study (figures 14.1 and 14.2 respectively).

Figure 14.1: Age at diagnosis of PDA



Arrow denotes 1988 when EC became widely available

Figure 14.2: Age at intervention for PDA



The mode of diagnosis and type of intervention are related to the year of diagnosis, with patients being diagnosed by CC or at surgery prior to 1988 and having the duct closed surgically (figures 14.3 and 14.4 respectively). More recently, patients with PDA have been diagnosed by EC and an increasing proportion have had the duct occluded by interventional CC. One patient did not undergo any form of intervention due to irreversible pulmonary hypertension at diagnosis (born 1945, diagnosed in 1985). No mortality was associated with any of the interventions.

Figure 14.3: Mode of diagnosis of PDA

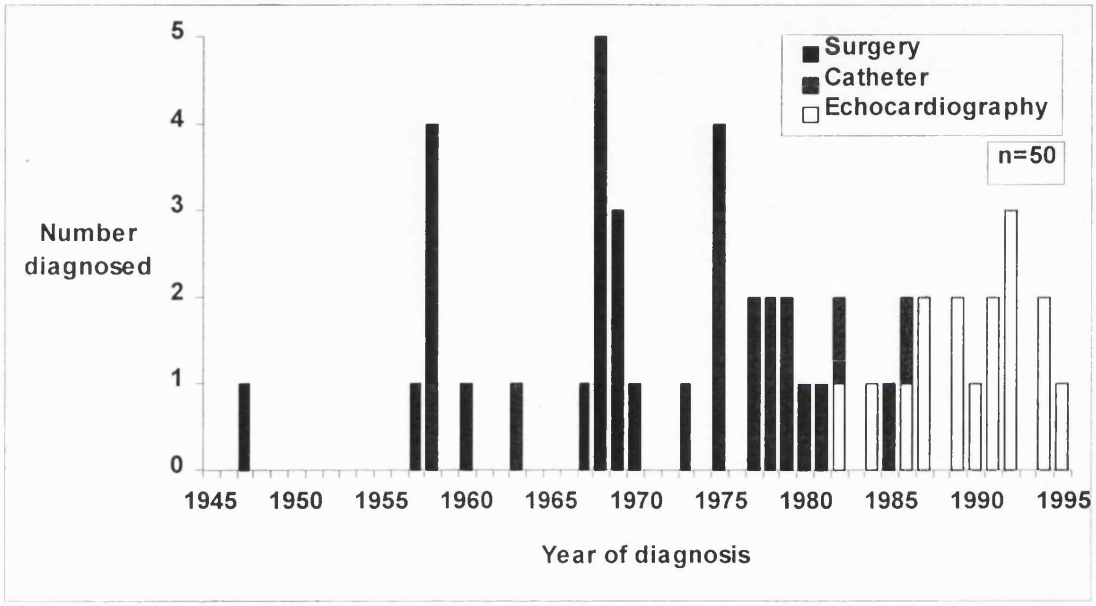
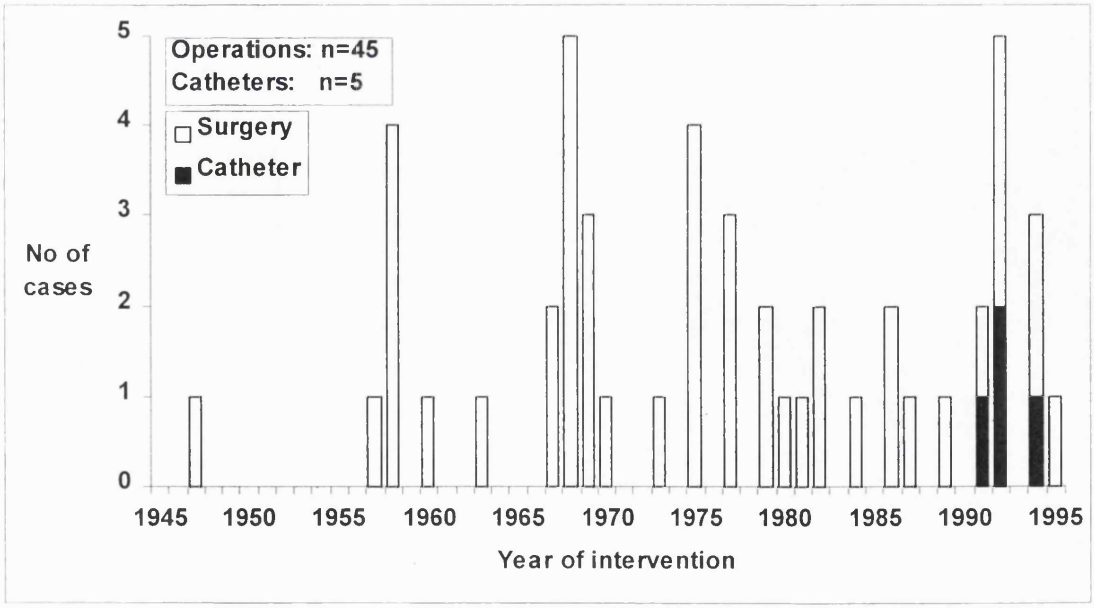


Figure 14.4: Type of intervention for PDA



14.3 Discussion

PDA was the first type of CHD which was treated surgically (Gross and Hubbard 1939). This was also the first CHD lesion for which a Maltese patient underwent intervention in 1947 - in Malta. Similarly, the first CC device occlusion (Porstmann et al 1971) for a Maltese patient with PDA took place in Malta in 1991 by Dr. J.DeGiovanni.

Patent ductus is a benign form of CHD which can be diagnosed and treated surgically at a very young age with very low risk. Older children and adults can undergo CC occlusion of PDA by means of various devices (Rashkind 1983).

15. Coarctation of the aorta

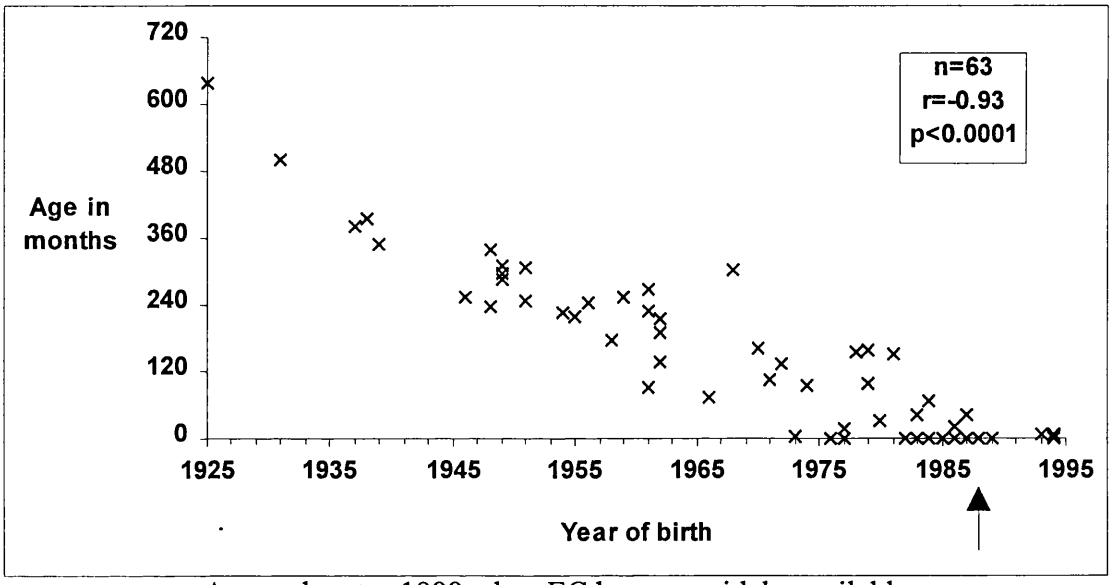
15.1 Introduction

This chapter outlines trends in diagnosis and treatment of coarctation.

15.2 Results

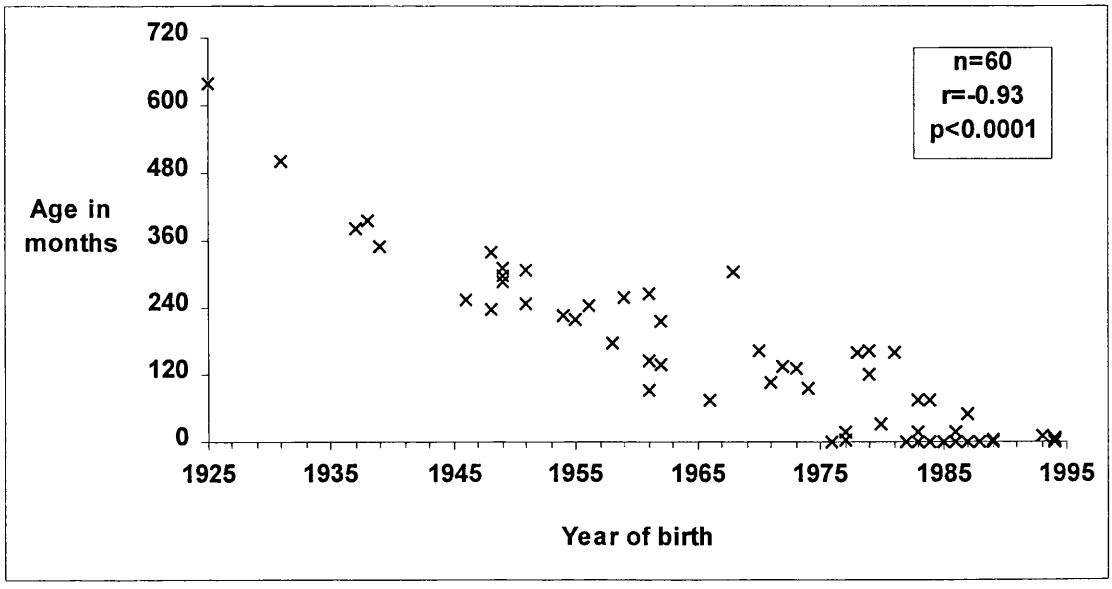
There were 64 live births with coarctation born up to 1994. Age at diagnosis was unknown in 1 case. Age at diagnosis and age at surgery for coarctation have declined significantly in the period under study (figures 15.1 and 15.2 respectively).

Figure 15.1: Age at diagnosis of coarctation



Arrow denotes 1988 when EC became widely available

Figure 15.2: Age at intervention for coarctation



As with other forms of CHD age, mode of diagnosis and type of intervention are related to the year of diagnosis (figures 15.3 and 15.4 respectively). Different surgical techniques relate to surgeons' attempts to reduce the risk of recoarctation, with resection and end-to-end anastomosis (Crafoord 1945) giving way to patch aortoplasty (Reul et al 1974), which in turn fell out of favour to be replaced by subclavian flap aortoplasty (Waldhausen and Nahrwold 1966), and back to resection and end-to-end anastomosis. To date, 3 patients have had recoarctation. The first 2 patients had redo surgery but the last patient who developed recoarctation underwent successful balloon dilation. To date, no native coarctations have been ballooned (Kan et al 1983).

Figure 15.3: Mode of diagnosis of coarctation

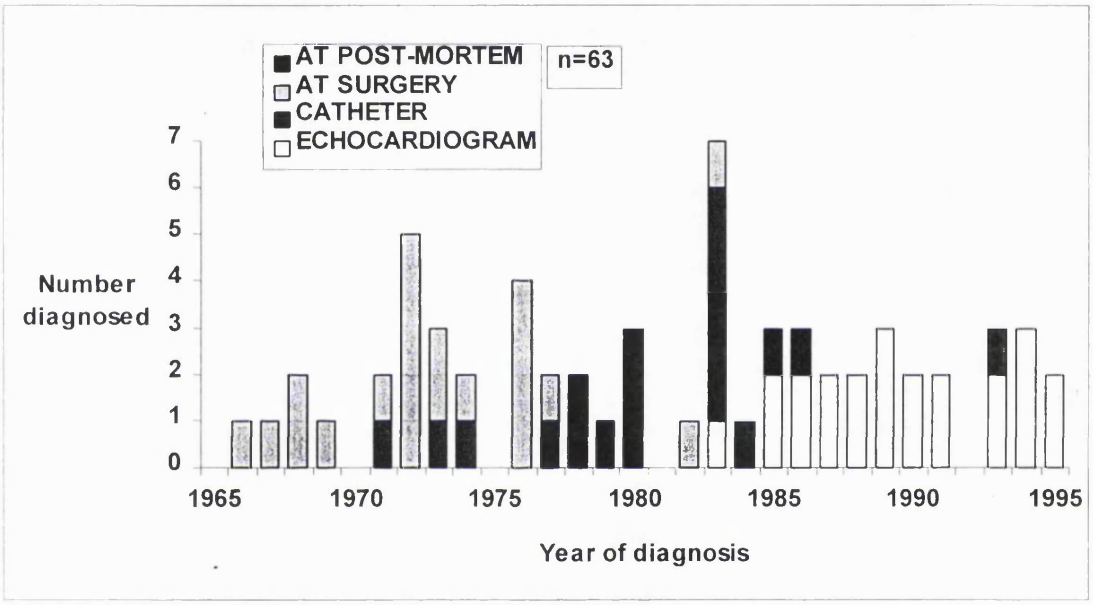
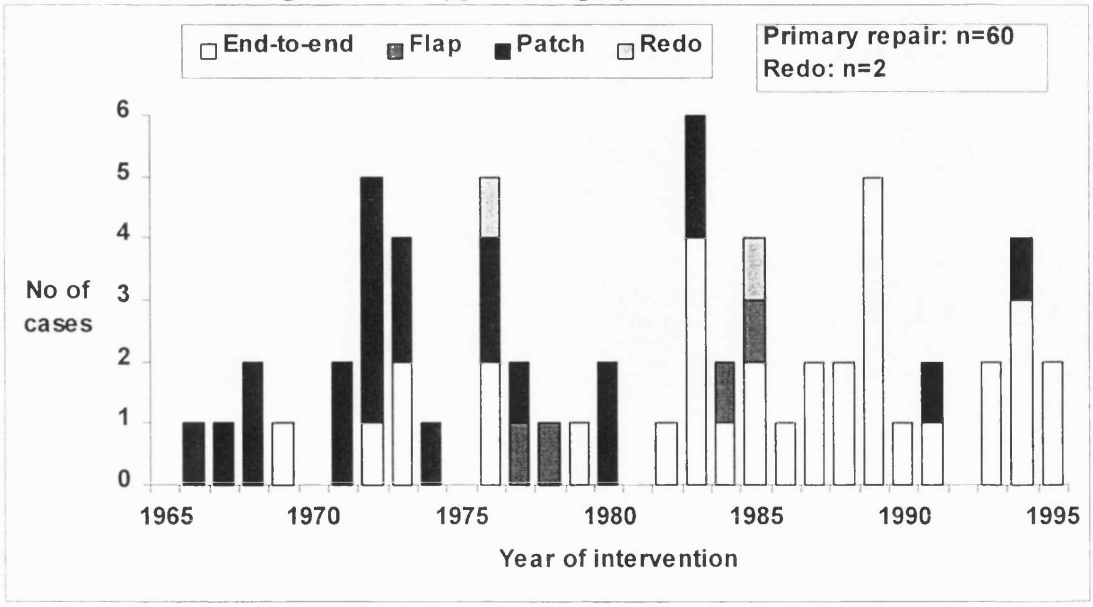


Figure 15.4: Type of surgery for coarctation



End-to-end: Resection and end-to-end anastomosis Patch: Patch aortoplasty
Flap: Subclavian artery flap aortoplasty

4 patients were unoperated (table 15.1) and 10 were reoperated (table 15.2). The operative centre changed from St. Mary's to Hammersmith to GOSHC with a few older children having been done electively in Malta since 1989 (figure 15.5).

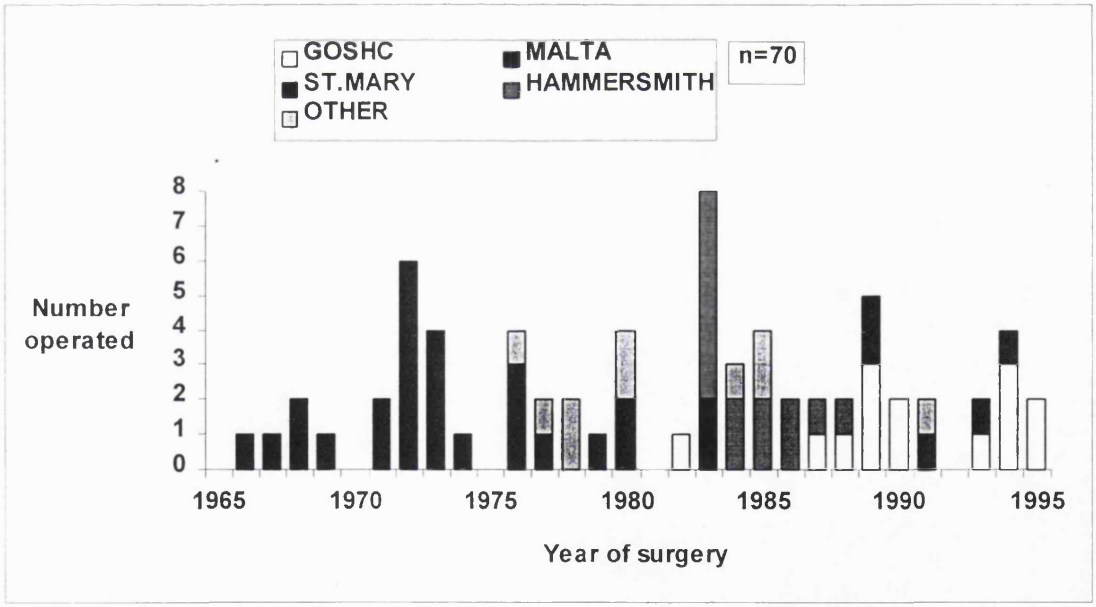
Table 15.1: Reason for non-operation in coarctation of aorta

Year of birth	n	Reason for non-operation
1985 and 1986	2	Diagnosed at post-mortem
1987	1	Mild coarctation variant
1962	1	Coarctation associated with hypoplastic descending aorta in a case of neurofibromatosis

Table 15.2: Reason for reoperation in coarctation of aorta

Date of 2nd operation	n	Reason for reoperation
1978-1990	4	PAB debanding and closure of associated VSD
1984 and 1985	2	Redo (after patch repair-1 Dacron and 1 Goretex)
1980 and 1983	2	Ligation of leaking thoracic lymphatic channels
1972	1	Mediastinal reexploration for haemothorax
1980	1	Open valvotomy for associated, progressive AS

Figure 15.5: Operative centre for coarctation



The perioperative mortality for this condition showed no mortality in the early 1970s, followed by a period of increased mortality which peaked in the early 1980s and then decreased steadily (figure 15.6). The differences which could be identified between the first decade of surgery (1965-1974) with no mortality, and the following 15 years (1975-1989) with increased mortality were operative centre, technique of repair and age at surgery (table 15.3).

The mean age at surgery for patients who did not survive surgery in 1975-1989 was lower than patients surviving in the same period or in the previous decade. Furthermore, the youngest operated patient in 1965-1974 was aged 75.8 months at the time of surgery, in contrast with 1975-1989 where the youngest survivor of surgery was aged 0.3 months. The move to lower age at surgery was associated with operative centre change from St. Mary's Hospital to the Hammersmith Hospital and operative technique change from primarily patch aortoplasty to end-to-end resection (figures 15.4 and 15.5).

Figure 15.6: 5-year percentage perioperative mortality for coarctation repair

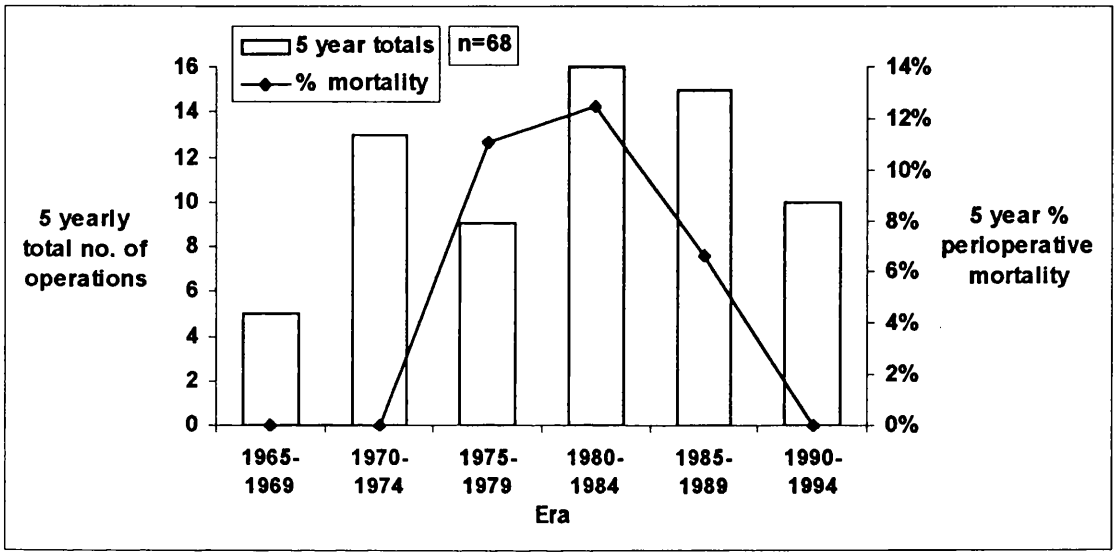


Table 15.3: Age at surgery for coarctation

Era	1965-1974	1975-1989		1990-1994
Outcome	Alive	Alive	Deceased	Alive
n	18	36	4	10
Age in months at surgery				
Mean	268.3	107	4.7	93.2
Range	424.7	637	13.6	302.3
Minimum	75.8	0.1	0.9	0.2
Maximum	500.5	637	14.5	302.5
Confidence Level (95%)	57.3	46	6.5	62.2

15.3 Discussion

Coarctation repair carries a low perioperative mortality. A surgical learning curve for early age at surgery is clearly evident in the mortality data and in the reasons for reoperation (recoarctation and leaking lymphatic channels).

16. Transposition of the great arteries

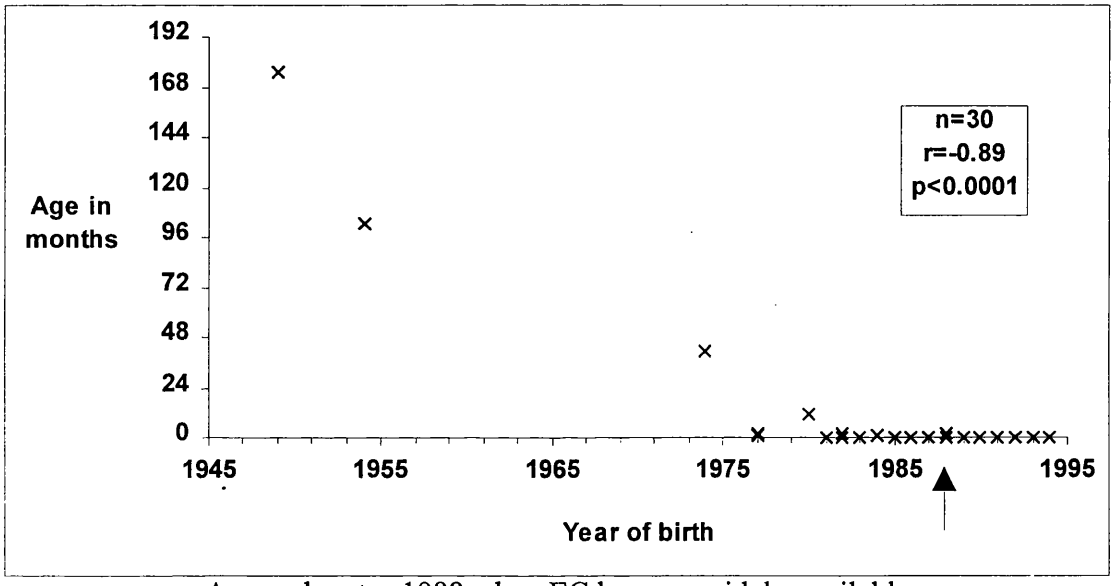
16.1 Introduction

TGA is commonest form of cyanotic CHD presenting in infancy (Scott et al 1984). This chapter outlines trends in diagnosis and treatment of TGA in Malta.

16.2 Results

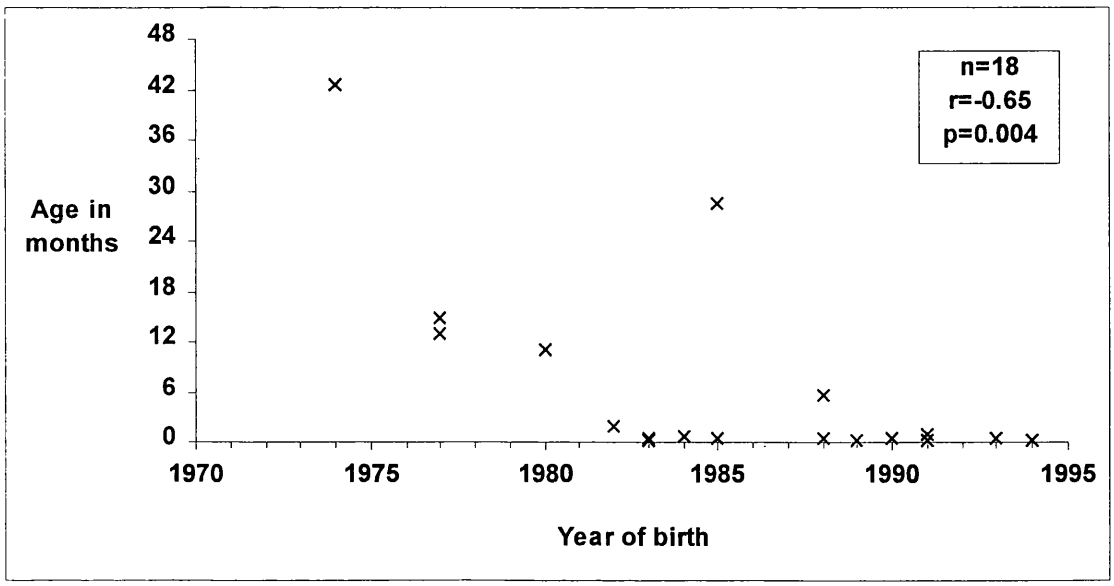
There were 30 diagnosed live births with TGA born up to 1994. Age at diagnosis and age at first operation for TGA have declined significantly (figures 16.1 and 16.2 respectively).

Figure 16.1: Age at diagnosis of transposition of the great arteries



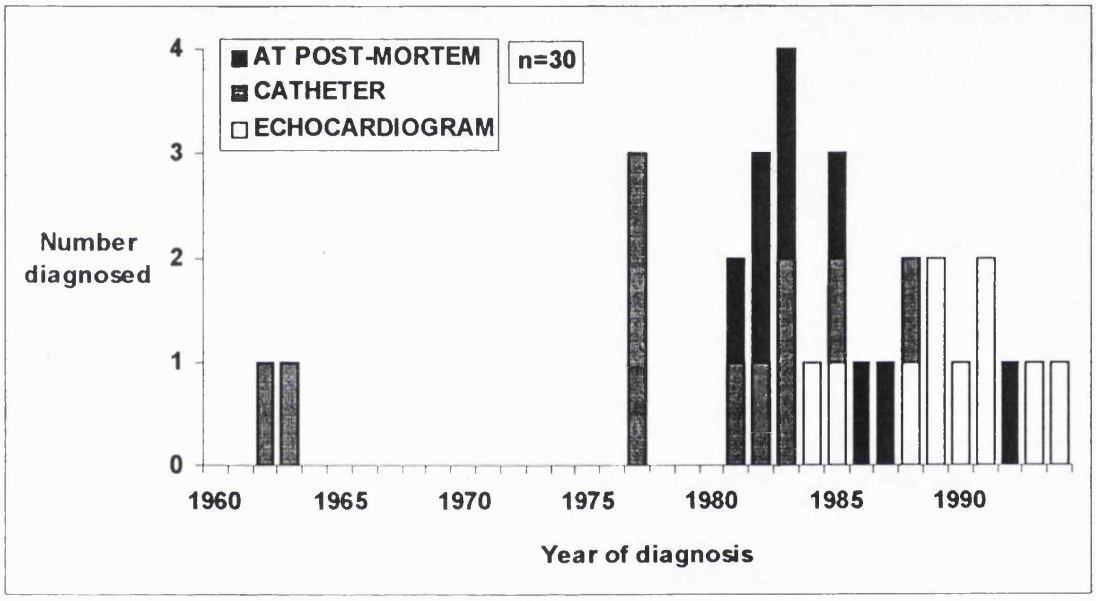
Arrow denotes 1988 when EC became widely available

Figure 16.2: Age at first surgery for transposition of the great arteries



Mode of diagnosis in a condition which usually presents acutely with cyanosis in the neonatal period reflects not only the diagnostic techniques available, but also the quality of medical services in place (figure 16.3). Only 2 patients were diagnosed prior to 1975 (at 8 and 14 years of age by CC). This suggests that not only were infants dying of TGA undiagnosed, but also that post-mortem services failed to recognise cases dying of TGA prior to 1980. The quality of post-mortem improved before diagnostic services, with a substantial proportion of cases diagnosed at post-mortem in the early 1980s. Diagnostic services improved shortly afterwards with more cases being diagnosed (and treated) early in infancy (figure 16.1).

Figure 16.3: Mode of diagnosis of transposition of the great arteries



18 patients were operated and 12 were not (table 16.1). 3 patients were operated twice (table 16.2).

Table 16.1: Reason for non-operation in TGA

Year of birth	n	Reason for non-operation
1981 - 1992	9	Diagnosed at post-mortem
1989	1	Died before transfer could be accomplished
1949 and 1954	2	Diagnosed in 1963 and 1962 respectively

Table 16.2: Reason for reoperation in TGA

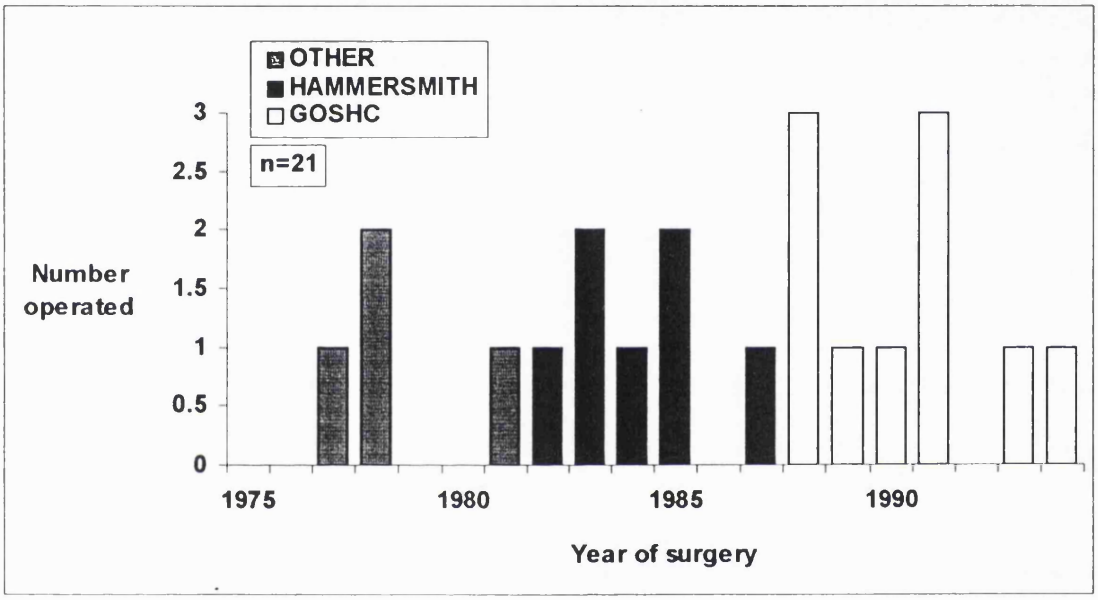
Year of birth	1st operation	2nd operation	Year of 2nd operation
1983	BAS→BHS	Mustard	1985
1985	BAS→PAB (+ VSD, ASD)	Arterial switch	1988
1982	BTS and BHS (+ VSD, LVOTO)	Rastelli	1991

BAS: Balloon atrial septostomy
BHS: Blalock-Hanlon septectomy
PAB: Pulmonary artery band
BTS: Blalock-Tuassig shunt

As in coarctation, surgery for TGA was dependent on era, with a transition from delayed physiological repair at atrial level (Senning 1959, Mustard 1969) with prior surgical or balloon septostomy (Blalock and Hanlon 1950, Rashkind and Miller 1966) to anatomical repair with the arterial switch operation in the 1980s (Jatene 1972).

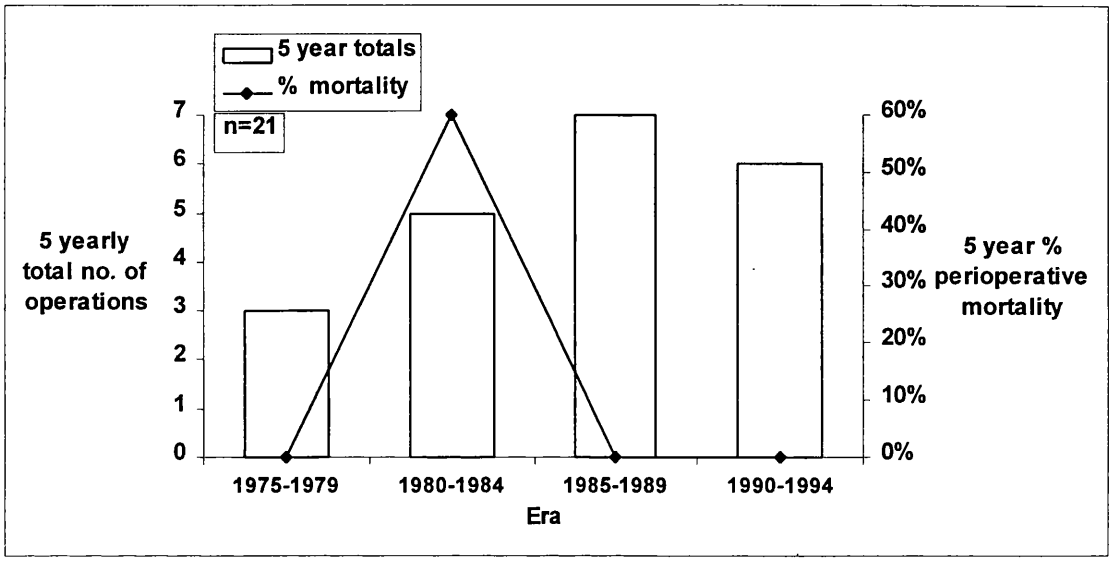
The operative centre follows the pattern described in other lesions with a sharp transition from the Hammersmith Hospital to GOSHC in 1988 (figure 16.5). No patients with TGA have undergone surgery in Malta.

Figure 16.4: Operative centre for transposition of the great arteries



As in other lesions, the 5 yearly perioperative mortality shows a sharp fall after the mid-1980s (figure 16.6).

Figure 16.6: 5 year percentage perioperative mortality for surgery for transposition of the great arteries



16.3 Discussion

Transposition of the great arteries is a condition in which a minimum level of medical expertise is necessary for early diagnosis, which is in turn essential for successful surgical repair. If intervention is not undertaken early in life, the likelihood of survival is poor.

17. Subaortic stenosis

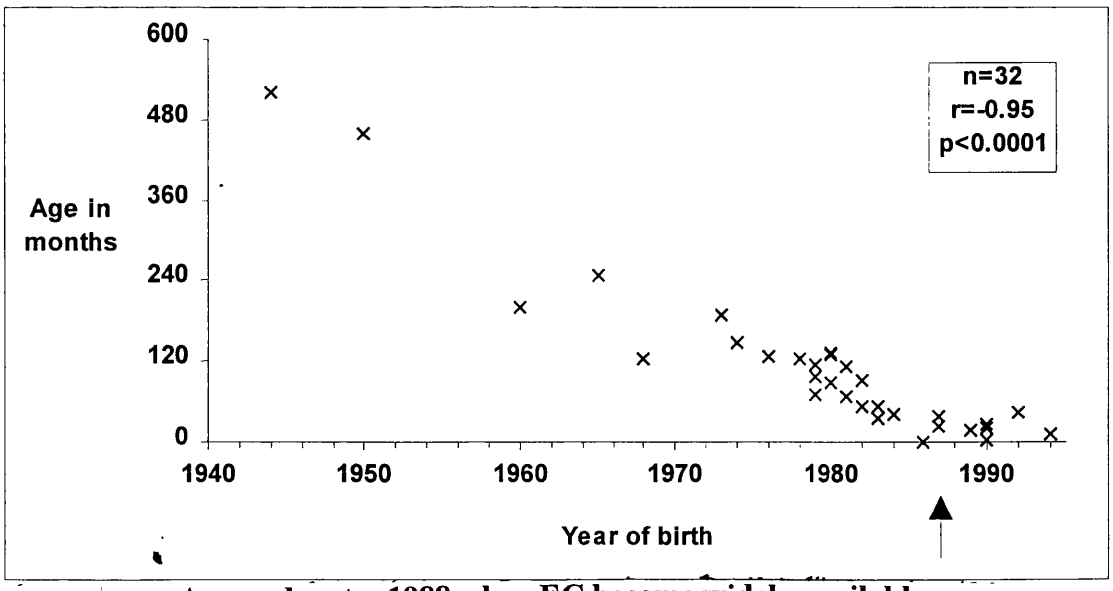
17.1 Introduction

Subaortic stenosis is one of the causes of LVOTO and is defined as obstruction in the LV outflow tract below the AV. This may be caused by a discrete ridge or by long-segment narrowing (Arnold and Kitchener 1995). It usually develops after infancy and therefore should not really be placed under the umbrella of CHD (Kitchener et al 1994a). However, about 30% of SAS develops in association with a subaortic VSD (Kitchener et al 1994b). This study looks at epidemiology of SAS, association with VSD, and outcome of treatment.

17.2 Results

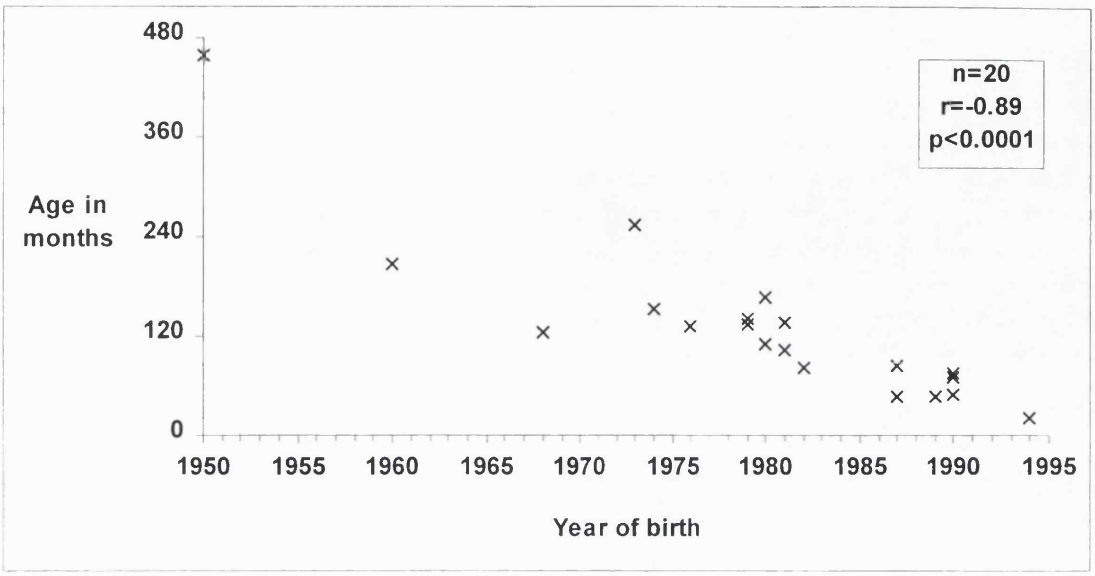
32 cases of SAS were diagnosed up to the end 1996. Age at diagnosis and surgery follow the pattern described in other lesions (figures 17.1 and 17.2 respectively). Fewer cases were diagnosed recently. This is attributed to the later age at onset of this condition which leads to incomplete ascertainment of cases born in more recent years. These cases have not yet manifested the symptoms and signs associated with SAS although they may be currently being followed up for VSD.

Figure 17.1: Age at diagnosis of SAS



Arrow denotes 1988 when EC became widely available

Figure 17.2: Age at surgery for SAS



Mode of diagnosis also follows the patterns described for other lesions (figure 17.3). An interesting peak of diagnosed cases is noted in the 1980s, diagnosed by EC. SAS is not only associated with VSD, but the clinical signs of SAS may mimic those of other conditions, particularly VSD itself. Indeed, VSDs becoming smaller or closing spontaneously predispose to the formation of SAS (Somerville 1979). The availability of EC in the 1980s showed the correct, late diagnosis to be SAS.

A progressively higher proportion of cases is being operated in Malta (Figure 17.4). This trend is expected to continue with the availability of a local cardiothoracic surgical team. There was no perioperative mortality.

Figure 17.3: Mode of diagnosis of SAS

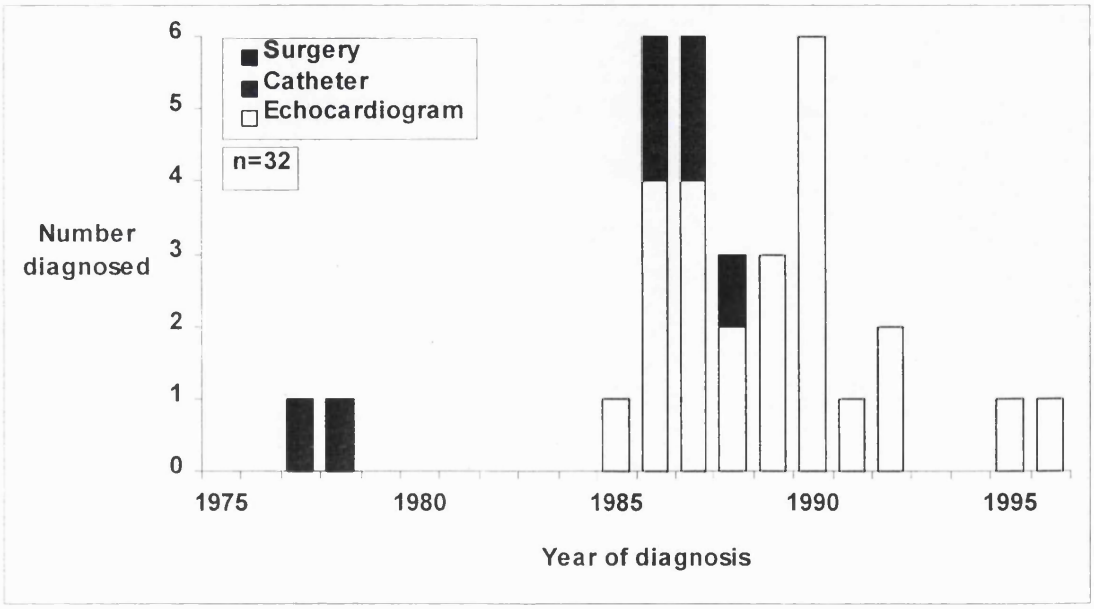
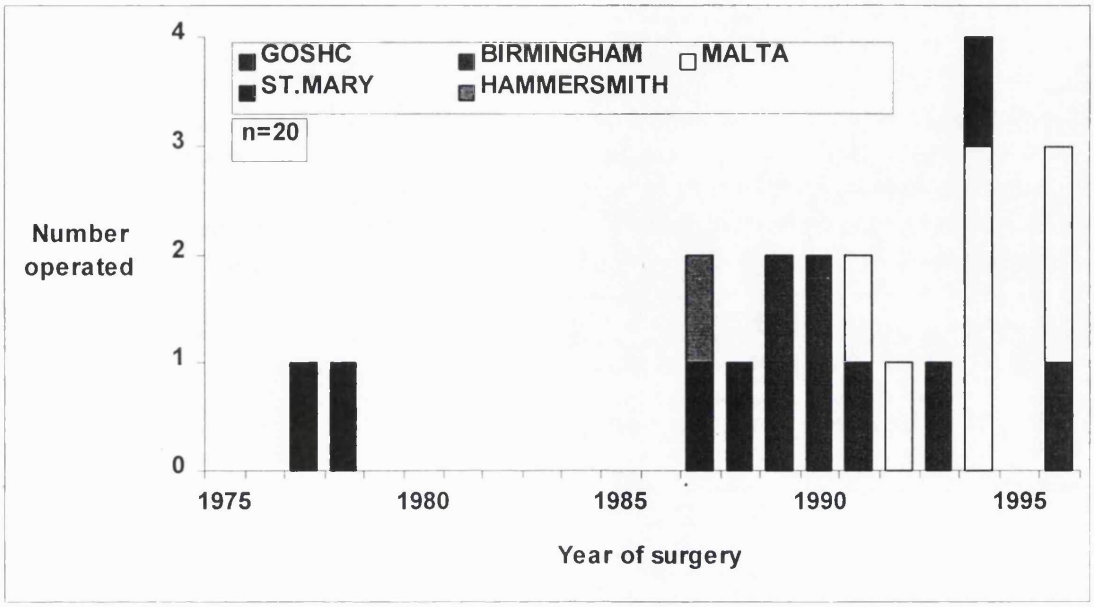


Figure 17.4: Operative centre for SAS



7 cases in this series were associated with a VSD (chapter 10), 2 cases with AS and 1 case with BAV.

The overall birth prevalence of LVOTO has been estimated at 0.6/1000 live births and SAS is believed to account for approximately 15% (Kitchener et al 1994b) of all LVOTO. This gives an estimated 0.09/1000 live births who will eventually develop SAS.

Due to the late onset of this condition (Kitchener et al 1994a), Maltese live births from the decade 1981-1990 were used for epidemiological calculations. There were 54899 live births in this period, 9 of whom eventually developed SAS. This gives a rate of 0.16/1000 (95% CI 0.08-0.32/1000) live births who develop SAS, similar to the rate calculated above. 6 of the 32 patients with SAS (19%) were associated with a VSD.

18. Atrioventricular septal defect

18.1 Introduction

This chapter examines diagnostic and operative trends, and epidemiology of AVSD (formerly known as endocardial cushion defect/atrioventricular canal defect). Due to the small numbers involved, partial and complete AVSD have been amalgamated.

18.2 Results

A total of 38 cases of AVSD were diagnosed. The proportion of Down's syndrome is shown in table 18.1.

Table 18.1: Proportion of Down's syndrome to non-Down's syndrome

Total AVSD	38
Down's	39%
Non-Down's	61%

The proportions of operated and unoperated patients with and without Down's syndrome are shown in table 18.2. Prior to the 1980s, no patients with Down's syndrome underwent surgery for AVSD, while all others underwent surgery. After 1980, the proportion of unoperated AVSD was approximately the same in both groups. This reflects a universal trend towards identical treatment strategies irrespective of the presence or absence of Down's syndrome. Reasons for non-operation were predominantly complete AVSD with small ventricular component in the Down's group, partial AVSD with a haemodynamically insignificant shunt in the non-Down's group and irreversible pulmonary hypertension at diagnosis in both groups.

Table 18.2: Operated and unoperated Down's and non-Down's syndrome with AVSD

Year of birth	Down's syndrome			Non-Down's		
	Operated	Unoperated	n	Operated	Unoperated	n
1944-1979	0%	100%	2	100%	0%	11
1980-1994	38%	62%	13	42%	58%	12

The age and mode of diagnosis were uncertain in 2 patients. The ages at diagnosis and surgery reflect the declining trends which are described in other lesions (figures 18.1 and 18.2 respectively), as does mode of diagnosis (figure 18.3). There were no perioperative deaths from this condition.

Figure 18.1: Age in months at diagnosis of AVSD

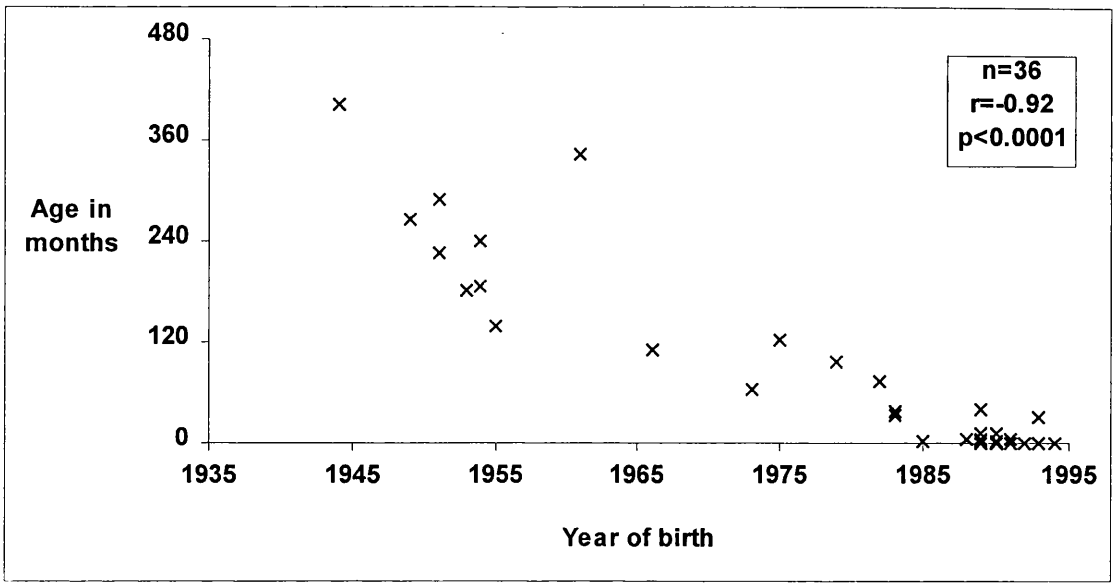


Figure 18.2: Age in months at first operation for AVSD

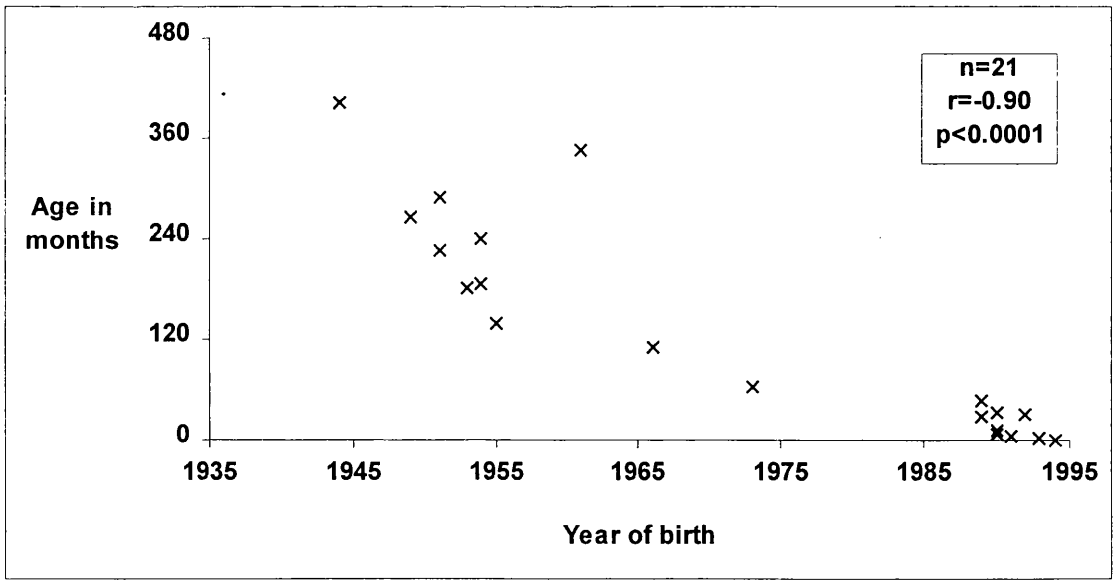
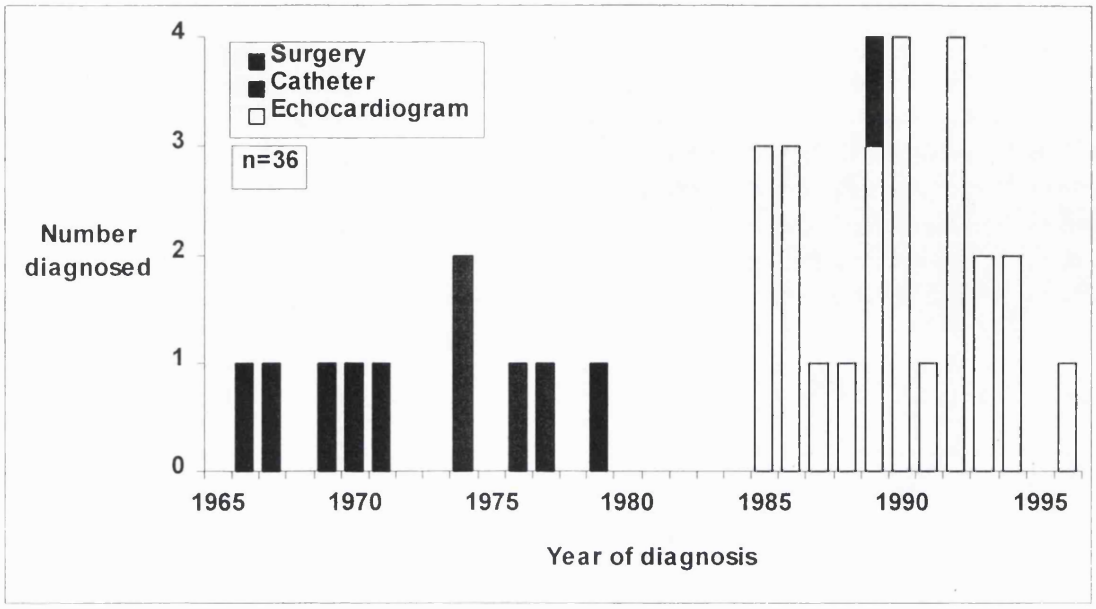


Figure 18.3: Mode of diagnosis of AVSD



18.3 Discussion

AVSD followed the same diagnostic and surgical patterns as other CHD lesions. The total number of operations for AVSD overall is expected to rise as all patients with AVSD, including Down's syndrome patients, undergo early surgery in order to avoid the onset of irreversible pulmonary hypertension (Newfeld et al 1977). A few patients may need reoperation for atrioventricular valve regurgitation (Studer et al 1982).

19. Syndromes and malformations associated with CHD

19.1 Introduction

CHD is a frequent component of syndromes. The most well known association is that with trisomies, particularly trisomy 21. In addition, neonates, especially syndromic neonates, frequently have other problems in association with CHD which require intervention of a surgical or medical nature. Management may therefore be influenced the medical and/or surgical treatment required for all of the various components of the syndrome in question.

A neonate with severe and/or multiple abnormalities may not fit into a recognised syndrome and also have CHD. For this reason, all new-borns in Malta suspected of having a syndrome or noted to have major or multiple abnormalities are scanned routinely in order to diagnose and potentially treat any form of CHD as early as possible. MAPCAD was used to list all known syndromic infants and all infants with malformations, born between 1990-1994, diagnosed as having CHD by 1 year of age.

19.2 Results

19.2.1 Syndromes

Syndromic infants with genetic/chromosomal anomalies and associated CHD are listed in table 19.1. Overall, recognised syndromes accounted for 10.7% of all CHD. There were 10 cases of AVSD in the same period (table 19.2). The birth prevalence of syndromic CHD for this period was 0.96/1000 live birth. Down's syndrome accounted for 75% of all syndromic CHD (figure 19.1).

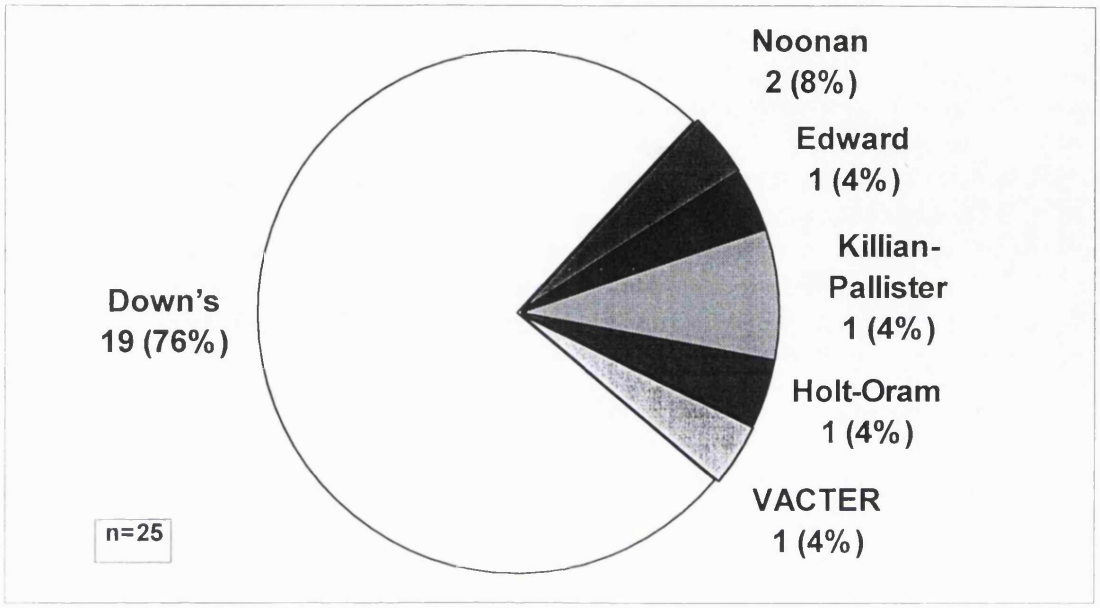
Table 19.1: Recognised syndromes associated with CHD in 1990-1994

Lesion	n	Syndrome	Percentage of syndromic CHD
Complete AVSD	5	Down's	2.2%
Partial AVSD	1	Down's	0.4%
DORV	1	Edward	0.4%
TOF	1	Down's	0.4%
TOF	1	Killian-Pallister	0.4%
PS	2	Noonan	0.9%
ASD	1	Down's	0.4%
VSD	11	Down's	4.8%
VSD	1	Holt-Oram	0.4%
VSD	1	VACTER	0.4%
Totals	25		10.7%

Table 19.2: Syndromic and non-syndromic AVSD in 1990-1994

	Partial AVSD	Complete AVSD	Totals
Down's	1	5	6
Non-Down's	2	2	4
Totals	3	7	10

Figure 19.1: Percentage distribution of syndromic CHD (1990-1994)



19.2.2 Malformations

There is no agreed way of classifying malformations. Due to the small numbers involved, malformations were divided into major and minor groups according to the need for intervention. 0.03% of neonates had major malformations in addition to CHD. All malformations in the absence of recognised syndromes are listed in table 19.3.

Table 19.3: Malformations associated with CHD

Major malformations	n
Cleft lip and palate	2
Spina bifida and hydrocephalus	1
Biliary atresia	1
Tracheo-eosophageal fistula, bilateral hypoplastic auditory meatus and vertebral anomalies	1
Absent radii and hypoplastic thumbs	1
Unilateral microphthalmia, bilateral chorioretinal colobomas, tracheobronchomalacia and dysplastic ears	1
Birth prevalence of CHD with major malformations/1000 live births (n=7)	0.27
Minor malformations	**n**
Undescended testis	3
Hypospadia	1
Unilateral talipes equinovarus	1
Triphalangeal thumbs	1
Syndactyly of toes and brachydactyly with hypoplastic nails of fingers	1
Unilateral pulmonary sequestration	1
Unilateral short and bowed femur	1
Moderate bilateral hydronephrosis	1
Isolated syndactyly of toes	1
Partial midline cleft palate and clinodactyly	1
Birth prevalence of CHD with minor malformations/1000 live births (n=12)	0.46

The proportions of CHD with Down's syndrome and with syndromes overall are shown in table 19.4.

Table 19.4: Proportion of CHD with syndromes

Syndrome	n	% of CHD	95% CI	
Down's	19	8	5	12
All	25	11	7	15

19.3 Discussion

The numbers found in this study tally with figures generally quoted for genetic and chromosomal abnormalities associated with CHD (Kenna et al 1975, Ferencz et al 1989), as well as those quoted for malformations found in association with CHD (Mitchell et al 1971). These figures do not include cases of 22q11 microdeletion as testing for this condition is not yet widely available in Malta.

Syndromic CHD constitutes an important cause of CHD. Termination of pregnancy is illegal in Malta and there is no organised antenatal screening programme. In the absence of such a programme, it is expected that syndromic CHD will continue to be an important cause of CHD for the foreseeable future.

20. Recurrence of CHD

20.1 Introduction

MAPCAD was queried to obtain siblings and parents with CHD for live births with CHD born in 1990-1994.

20.2 Results and discussion

20.2.1 Recurrence in siblings

6% of live births with CHD born in 1990-1994 had affected siblings (table 20.1). Cases of CHD along with their affected siblings were subdivided into inflow, outflow and septal defects (appendix 15). The majority were outflow problems (67%). Only 1 case has undergone genetic testing and was found to have 22q11 microdeletion (PS and ASD). Close concordance can be seen in outlet and septal defects.

Table 20.1: CHD in probands and affected siblings

Proband	Affected sibling/s
Severe PS	Mild PS
Mild PS	Mild PS
Severe PS	Severe ASD
Severe PS, severe ASD	Severe PS, severe ASD
TOF	TGA
Severe PS, severe ASD	*Twin sibling:* Truncus, IAA
	Older sister: Severe PS, severe ASD, mild VSD
Congenitally corrected transposition, VSD, PS, congenital heart block	Mild VSD
Severe VSD	Mild VSD
Mild VSD	Severe PDA
Truncus with IAA	Coarctation
Mild VSD	Severe VSD
IAA	Mild VSD
Left atrial isomerism, DORV, TGA	Aberrant MV chorda-mild MI

20.2.2 Affected parents

2% of live births with CHD in 1990-94 had affected parents (table 20.2). This proportion is lower than previously described and this is almost certainly due to incomplete ascertainment of milder forms of CHD prior to 1990 (Whittemore et al 1994). The association of VSD with PS in recurrence of CHD has been previously described (Dennis and Warren 1981).

Table 20.2: Affected parents of children with CHD (n=5)

Offspring	Father	Mother
Critical PS	VSD	
VSD closed spontaneously		VSD-small
Critical PS		PS-operated
VSD closed spontaneously		PDA-operated
VSD, PS, ASD	PS- operated	

20.3 Discussion

The prevalence of CHD in Malta cannot be reduced by antenatal screening as termination of pregnancy is illegal and there are no organised antenatal screening programs whatsoever.

Genetic testing for 22q11 is currently unavailable in Malta. Screening of children and adults for this condition would allow genetic counselling of positive cases who may then elect to have few or no children. The cost of screening may well outweigh the cost of treatment and complications thereof.

21. Service requirements

21.1 Introduction

This chapter uses birth prevalence data already discussed in chapter 5 to extrapolate likely future service requirements on a 5-yearly basis for a population with a live birth rate of 5300/annum.

21.2 Results

Approximately 230 patients with CHD will be born every 5 years (95% CI: 200-260). These will have varying need of follow-up, from very intensive to occasional clinic visits on a once yearly or even less frequent basis.

Lesions needing intervention are shown in table 20.1, subdivided into severe and complex groups (Abu Harb et al 1994). Lesions were further subdivided according to likelihood of need for more than 1 intervention.

Table 21.1: Likely need for intervention on Maltese live births with CHD on a 5-yearly basis

Very unlikely to require >1 intervention	n	Unlikely to require >1 intervention	n	Likely to require >1 intervention	n
Severe					
VSD	22	PS	15	TOF	21
ASD	11	AVSD	10	TAPVD	3
PDA	5	TGA	6	AS	2
		Coarctation	6		
		Miscellaneous	6		
Totals	38		43		26
Complex					
				DORV	7
				Truncus arteriosus	4
				PA	2
				TA	2
				Totals	15

The perioperative mortality results in chapter 9 were used to calculate the 5-yearly number of survivors after surgical intervention. Assuming a 1% perioperative mortality for severe CHD and a 9% perioperative mortality for complex CHD, the pool of survivors of CHD is expected to increase by 120 cases having undergone intervention every 5 years (95% CI: 99-141 - table 20.2). 4 patients born in this period underwent/will undergo univentricular palliation. Also based on the birth prevalence data of CHD for 1990-94 (chapter 5), another 107 patients who are not expected to require intervention need to be catered for. Serial follow-up and investigation of these patients must be taken into account when estimates for provision of services are calculated.

Table 21.2: Extrapolation of survivors of surgical intervention for next 5 years

Severity of CHD	n	% perioperative mortality	Survivors
Severe	107	1%	106
Complex	15	9%	14
Totals	122		**120**

21.3 Discussion

21.3.1 Factors which are likely to increase service requirements

Progressive improvements in surgical results will continue to reduce the already low perioperative mortality. Furthermore, increasing use of low-risk interventional techniques and development of new interventions for transcatheter treatment of patients who would otherwise require operation will result in even more survivors. These patients have special problems which include:

Follow-up of adolescent and adult survivors

The majority of CHD survivors are followed up at general adult medical outpatients (Sutherland et al 1990). This is also the case in Malta where most adults with CHD are under the care of adult consultants, most of whom do not have an interest in cardiology. Some severe and complex cases continue to be followed at COP. Many older patients feel uncomfortable in this setting.

The problem of continuing care of adult survivors includes not only ongoing medical problems (Thorne and Deanfield 1996) but also insurability difficulties (Hellestedt 1994), issues related to type of contraception affording minimum risk, and pregnancy and family planning issues (Leonard et al 1996) including counselling regarding recurrence of CHD in siblings and offspring (Whittemore 1986, Whittemore et al 1994).

Furthermore, the recurrence risks of CHD in offspring of patients with CHD is higher than the population mean. Older studies excluding parents with known syndromes calculated recurrence risks of CHD in offspring of affected parents of 5-10% (Dennis and Warren 1981, Whittemore et al 1994). This is 5-10 times higher than the average population birth prevalence of 0.8-0.9% (8-9/1000 live births).

Services will also need to cater for survivors with neurological complications of surgery (Fallon et al 1995, Miller et al 1995), although there is some evidence to suggest that neurological abnormalities may be present even before surgery is undertaken (Rogers et al 1995). Psychological and social problems may become apparent later on in life (Otterstad et al 1986).

Support will also be necessary for bereaved families of non-survivors or survivors with physical/mental deficit.

For these reasons, adult CHD units have in existence since 1980 (National Heart Hospital, London).

Investigations
EC has proven to be an invaluable, non-invasive tool for diagnosis and follow-up of CHD. Children are especially suitable due to small thoracic dimensions. The heart is close to the surface of the chest allowing high frequency, high definition probes to be used with excellent image quality. However, the subcostal and precordial EC windows naturally decrease with age, and cardiac operations tend to further reduce these windows. For these reason, the need for TOE in older survivors of CHD is certain to increase (Sreeram et al 1990b). MRI has also been found useful as a non-invasive diagnostic tool in CHD (Higgins et al 1984). An MRI unit will be acquired by the Radiology Department at SLH which will be used for serial follow-up of selected patients.

Surgery
Patients who have only had palliative surgery may now have survived to a surgical era where more definitive repair is feasible. Alternatively, if repair is impossible, further palliation may need to be undertaken in order to improve quality of life in symptomatic patients and increase overall survival. Furthermore, patients who have had definitive repair may also require reoperation such as valve (native/artificial) and conduit replacements, and pacemaker replacements (Rosenthal et al 1984).

Another surgical factor which may increase service requirements is surgery for hitherto unoperated Maltese live births with CHD (e.g. HLHS). This may be partly offset by reduction in total operations due to the continually increasing role of lower-risk interventional cardiology.

Heart transplantation may have to be considered for Maltese patients in whom further surgery is impossible.

Operations may also be necessary for cosmetic reasons such as the improvement of appearances of unsightly scars and realignment of offset sternotomies.

21.3.2 Factors which may decrease service requirements

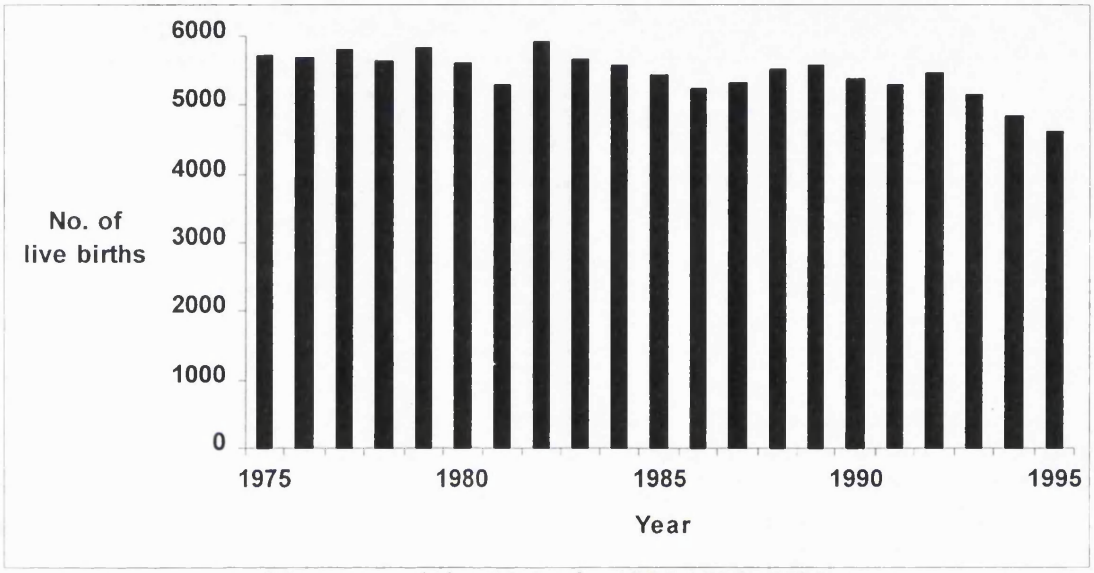
Declining birth rate
A decline in the Maltese birth rate will reduce the total number of live births with CHD. This trend has, in fact, become apparent with a diminution in the total number of live births over 1993-1995 (figure 21.1).

Antenatal screening services
Theoretically, a degree of primary prevention of live births with CHD is possible. Basic antenatal fetal EC screening and more detailed EC screening of high risk deliveries such as those with a parental history of CHD or prior sibling with CHD would identify fetuses with CHD. The parents could then be counselled regarding severity of CHD in the affected fetus and may elect for termination of pregnancy. Similarly, antenatal screening for Down's syndrome e.g. using maternal serum (Haddow et al 1992) would identify affected fetuses and the parents may opt for termination of pregnancy.

However, termination of pregnancy is illegal in Malta, and will remain so for the foreseeable future. Furthermore, even if introduced, it is estimated that both of these factors would have a minimal impact on service provision for CHD with a 2% reduction in patients with CHD, a 3% reduction in operations and a 5% reduction in infant mortality rate (Abu Harb et al 1995).

Screening for 22q11 microdeletion in high-risk individuals such as survivors of conotruncal anomalies would allow counselling and family planning (see chapter 20).

FIGURE **21.1: Total live births in Malta: 1975-1995**



Mean annual live births for 1975-1988=5588

21.3.3 Staff requirements

The Maltese childhood population (≤ 14 years of age) totalled 83,429 at the end of 1996 (DOH 1996). It has been estimated that up to one full-time paediatric cardiologist may be required per 90,000 childhood population (Daniels and Choussat 1994). This does not include follow-up of adult survivors of certain forms of CHD who would be better off under the shared care of a paediatric and adult cardiologist (Sutherland et al 1990).

Logically, services in Malta should emphasise diagnostic CHD facilities and clinical and EC follow-up (Tybulewicz et al 1996). The number of paediatric patients requiring CC in Malta are too few for even a one local cardiologist to train in or even maintain proficiency (chapter 8). The role of CC has been usurped by EC and the purpose of this procedure is increasingly interventional rather than diagnostic (Stark 1994) with fewer CC overall. Our present system whereby visiting consultant paediatric cardiologists perform the necessary CC appears to be the most suitable arrangement of all, not only financially, but also in terms of patient safety.

Similarly, Maltese live births with severe CHD requiring surgery are too few for a local cardiac surgeon to maintain proficiency in any but the simplest procedures.

22. Conclusions

The birth prevalence of CHD in Malta was not found to be increased and there were no familial patterns of inheritance despite the relatively closed gene pool. However, the spectrum of CHD appears to be different to that reported in previous studies with a predominance of lesions which predispose to RVOTO and a paucity of lesions which produce LVOTO.

A clear seasonal variation was found as well as a North-South regional difference despite the small size of the Island. These patterns may yield clues to predisposing factors leading to CHD.

The analysis of past trends has shown that treatment of CHD is effective, and extrapolation of likely future trends will be invaluable for better planning of health service provision for this important group of malformations.

The overall result should be improved quality of care for patients with CHD.

The epidemiological aspects of this study would be enhanced if more data were to collected from parents of children with CHD born in the period 1990-1994 in order to isolate possible causative factors for North-South differences. These would include maternal and paternal age at time of conception of the affected child with CHD, presence of diabetes and level of diabetic control, gestational age, parity and exposure to potential occupational teratogens along with social class. It may be difficult to ascertain these factors at this point, but this is a known limitation in any retrospective study.

23. Future considerations

Malta has proven to be an ideal location to study the epidemiology of CHD and past trends in management of CHD. The literature does not report a study which looks at as many different aspects of diagnosis and treatment of various CHD lesions.

MAPCAD has proven to be an invaluable tool for this research, and should be maintained up to date in order to continue to serve as an epidemiological and clinic database for patients with CHD.

All patients with CHD who have undergone intervention in one form or another are on the database. No attempt was made to actively locate adult survivors. It would be a worthwhile exercise to track down surviving adults and assess long-term outcome in a population setting, evaluating factors such as functional capacity, social status and occupation.

The epidemiological areas of particular interest are the predominance of RVOTO in the Maltese population (chapter 5), seasonal variation (chapter 6), and geographical differences in birth prevalence. Accumulation of data over the coming years should further serve to reinforce these findings.

The geographical differences are being studied in more detail by contacting the parents of children with CHD born in 1990-94 and ascertaining where the grandparents were born. Insularity was greater forty years ago with little population movement out of geographical regions. A predominance of the gene pool from the Southern region two generations ago will reinforce the geographical variation. Parental social class and age is also being ascertained in order to analyse the potential influence on work and lifestyle on live births with CHD.

Serious consideration should be given to perform genetic studies on all patients with CHD to assess the prevalence of 22q11 microdeletion in these patients. Antenatal screening for 22q11/Down's syndrome is pointless as the only option is termination of pregnancy, which is illegal in Malta in any case.

A prospective study to analyse the modern natural history of VSD, ASD and PS has been organised by the author and has been underway for the past 6 months. Newly diagnosed cases are followed clinically and by EC according to a standard protocol which measures gradients and dimensions of chambers and of defects. The primary aim is to correlate defect size with timing of spontaneous closure and initial gradient with spontaneous resolution in PS.

A national malformations database has been set up by the Department of Health Information for the registration of all births with congenital anomalies, and MAPCAD serves as the CHD reporting limb of this database. Studies of other malformations in Malta should reveal equally useful insights into lesions other than CHD.

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Appendix 1: Ethical approval-GOSHC

Great Ormond Street Hospital for Children NHS Trust

and the Institute of Child Health

The child first and always

Great Ormond Street
London WC1N 3JH

Direct Line: 0171-829 88
Fax: 0171-829 8673

Mr Victor Grech
GOSH

December 1994

Our Ref: ME/ly

Dear Victor

Thank you very much for asking me to review your Grant Application - Natural and Unnatural History of Congenital Heart Disease and Maltese Islands 1958-1998 and the Outcome of Treatment.

I have read your grant application with care and do not see any ethical objection to this study being carried out. I think that on the contrary it is likely to add to the overall health of the Maltese community and not to present any ethical problems. I assume however that all the data stored would comply with the data protection act; and the relevant anonymity rules.

Accordingly, I am happy to give Chairman's action approving this protocol.

Yours sincerly

Martin Elliott
Consultant Cardiothoracic Surgeon

c.c
Alison Simcock
Administrator Ethical Committee

Appendix 2: Ethical approval-SLH

L-UNIVERSITÀ TA' MALTA
Msida – Malta
SKOLA MEDIKA

UNIVERSITY OF MALTA
Msida – Malta
MEDICAL SCHOOL

REF. TAGĦNA:
OUR REF:

REF. TIEGĦEK:
YOUR REF:

Our Ref: 9/95

11th April 1997

This is to certify that the protocol on the research project entitled *"THE NATURAL AND UNNATURAL HISTORY OF CONGENITAL HEART DISEASE IN THE MALTESE ISLANDS: 1958-1998, AND OUTCOME OF TREATMENT"* submitted by Dr V Grech has been approved on 25th August 1995 by Professor M N Cauchi then Chairman of the **RESEARCH ETHICS COMMITTEE** of the Faculty of Medicine & Surgery.

PV Agius

Dr P Vassallo Agius
Chairman
Research Ethics Committee

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Appendix 3: Dataset collected related to study

Demography

Surname	Name	Sex	Address	Telephone no.
Consultant	File no.	Other no.	Postcode	

Diagnosis

Cardiac	Non-cardiac	Malformations	Syndrome	Karyotype

Follow-up

Date last seen	or date died	Next due VCC	Latest echo	Next due COP
Clinical comments		Echocardiography comments		Catheter dates
Cardiac catheter comments		Suitability for medical students		Current status
Pending				

Operation/s

Procedure	Date admitted	& discharged	Surgeon	Centre
Urgency	Complications	Outcome		

Miscellaneous

Family history	Date diagnosed	& mode

Appendix 4: Example of a dBASE program DIAGMODE.PRG used to extract mode of diagnosis according to age at diagnosis

```
*** Mode of diagnosis for CHD
*** DIAGMODE.PRG

*** MODIFIED FOR THESIS - BORN >= 1945 AND <=1994

*** 1=echo 2=catheter 3=operation.  4=postmortem 5=clinically only

set status off
set talk off
set safety off
clear
use MAPCAD.DBF

set alternate to F:\xl-data\dboutput\diagmode.txt
set alternate on

? "Acquired from MAPCAD"
?
? "Trends in modes of diagnosis."
?
? "Query updated on:"
?
? DATE()
?
?"=ECHO.=CATHETER=AT OP=AT PM=CLIN. ONLY"

VARYEAR=1945
MODE=1
T=0

set filter to (severity=1.or.severity=2.or.severity=3).and.
isblank(diag_date)=.f..and.year(dob)>=1945.and.year(dob)<=1994
.and..not.(diag_1code="P551".and.severity=1.and.isblank(f_pend_op)=.t.)
.and..not.(diag_1code="P70".and.severity=1.and.isblank(f_pend_op)=.t.)

index on ltrim(str(year(diag_date)))+ltrim(str(diag_mode)) to temp
set index to temp
goto top
```

```
do while VARYEAR<2000.and.eof()=.f.

if year(diag_date)<VARYEAR
skip
loop
endif

? substr(ltrim(str(VARYEAR)),3,2)

do while MODE<6
count to T while year(diag_date)=VARYEAR.and.diag_mode=MODE
??"="+ltrim(str(T))

MODE=MODE+1
enddo

MODE=1
VARYEAR=VARYEAR+1
enddo

do while VARYEAR<2000
?ltrim(right(str(VARYEAR),2))+"=0=0=0=0=0"
VARYEAR=VARYEAR+1
enddo

set filter to year(dob)>=1945.and.(severity=1.or.severity=2.or.severity=3)
count to t0
?
? "Total CHD="+ltrim(str(t0))
?
? "MAPCAD total="+ltrim(str(reccount()))
?
set alternate off
close all
erase temp.ndx
set status on
set safety on
```

Appendix 5: Text output from program (DIAGMODE.TXT) in appendix 4

Acquired from MAPCAD

Trends in modes of diagnosis.

Query updated on:

11/09/96

YEAR OF DIAGNOSIS	ECHO.	CATHETER	AT OP	AT PM	CLIN. ONLY
45	0	0	0	0	0
46	0	0	0	0	0
47	0	0	0	0	0
48	0	0	0	0	0
49	0	0	0	0	0
50	0	0	0	0	0
51	0	0	0	0	0
52	0	0	0	0	0
53	0	0	0	0	0
54	0	2	0	0	0
55	0	0	0	0	0
56	0	2	0	0	0
57	0	0	1	0	0
58	0	3	2	0	0
59	0	1	0	0	0
60	0	2	1	0	0
61	0	2	0	0	0
62	0	3	0	1	0
63	0	9	0	0	0
64	0	3	0	0	0
65	0	3	0	0	0
66	0	6	2	0	0
67	0	12	2	0	0
68	0	10	5	1	0
69	0	9	4	0	0
70	0	12	2	0	0
71	0	9	2	0	0
72	0	11	4	0	0
73	0	17	2	0	0
74	0	22	1	1	0
75	0	11	1	0	0
76	0	39	4	3	0
77	0	22	1	1	0
78	0	14	0	0	0
79	1	21	1	2	0
80	0	22	0	1	0
81	0	11	0	4	0
82	3	12	2	3	0
83	5	10	1	7	0
84	4	11	0	5	0
85	22	7	0	4	0
86	40	4	1	3	0
87	42	5	0	3	0
88	38	4	1	0	0
89	52	2	0	0	0

90	72	1	0	1	0
91	63	0	0	1	0
92	64	0	0	0	0
93	47	1	0	1	0
94	61	0	0	1	0
95	14	1	0	0	0
96	5	0	0	0	0
97	0	0	0	0	0
98	0	0	0	0	0
99	0	0	0	0	0

Total CHD=982

MAPCAD total=1209

Appendix 6: Method used for calculation of confidence intervals for birth prevalence of CHD lesions

A rate is a proportion. CI for rates are commonly calculated using CI for single proportions. The equations generally used are simplified equations based on a normal approximation, rather than the true binomial distribution (equations 1 and 2).

Equation 1

$$SE = \sqrt{p \times (1-p) / n}$$

Equation 2

$$CI = p \pm (z \times SE)$$

where:

SE = standard error
CI = confidence interval
p = proportion affected
n = total number (denominator)
z = z value of distribution (e.g. z for 95% CI = 1.96)

The normal approximation becomes progressively more inaccurate when the proportion approaches 0 or 1 i.e. towards the upper and lower tails of the distribution. When $0.3 \leq p \leq 0.7$, exact CI using the binomial distribution can be calculated using equations 3 and 4 (Fleiss 1981).

Equation 3

$$\text{Upper CI} = \frac{(2np + z^2 + 1) + z\sqrt{z^2 + (2 - 1/n) + 4p(nq - 1)}}{2(n + z^2)}$$

Equation 4

$$\text{Lower CI} = \frac{(2np + z^2 - 1) - z\sqrt{z^2 - (2 + 1/n) + 4p(nq + 1)}}{2(n + z^2)}$$

where:

q = 1-p
(other symbols as above)

Appendix 7: Birth prevalence and 95% CI for selected severe CHD lesions (AVSD, coarctation, TGA, TOF, truncus, HLHS, DIV/UVH, DORV, TA and PA)

	Birth prevalence	95% CI	
Carlgren 1959	1.59	1.28	1.95
Gardiner 1951	0.33	0.24	0.44
Mustacci 1963	0.48	0.32	0.74
Feldt 1971	1.70	1.29	2.23
Bound 1971	1.96	1.63	2.37
Mitchell 1971	1.95	1.61	2.37
Hoffman 1978	1.69	1.17	2.40
Dickinson 1981	1.56	1.37	1.77
Laursen 1980	1.60	1.52	1.69
Mayberry 1990	1.30	0.76	2.22
Fixler 1990	1.44	1.32	1.57
Manetti 1993	2.44	2.02	2.94
Samanek 1989	1.83	1.57	2.13
Ferencz 1987	1.62	1.49	1.76
Jackson 1996	1.70	1.53	1.89
Grech 1997	2.30	1.77	2.98

Appendix 8: Comparison of rates of CHD in 2 recent studies with present study

	Present Study	95% CI			Samanek 1989	95% CI			Jackson 1996	95% CI		
Years studied	1990-94				1980				1979-88			
Livebirths	26117				91823				203880			
CHD livebirths	230				589				1543			
Per 1000 live births	8.84	7.76	10.08		6.41	5.91	6.96		7.57	7.20	7.96	
VSD	3.94	3.24	4.80		2.01	1.74	2.33	*	2.74	2.52	2.98	*
PS	1.65	1.21	2.24		0.46	0.33	0.62	*	0.70	0.59	0.82	*
TOF	0.80	0.51	1.25		0.23	0.15	0.36	*	0.32	0.25	0.41	+
ASD	0.42	0.22	0.78		0.73	0.57	0.93		0.37	0.30	0.47	
AVSD	0.38	0.19	0.73		0.26	0.17	0.40		0.31	0.24	0.40	
DORV	0.27	0.07	0.47		0.10	0.03	0.16	#	-	-	-	
Coarctation	0.23	0.05	0.41		0.37	0.26	0.52		0.35	0.28	0.45	
TGA	0.23	0.05	0.41		0.35	0.24	0.50		0.30	0.23	0.39	
PDA	0.19	0.07	0.47		0.30	0.21	0.45		0.68	0.57	0.80	*
Truncus	0.15	0.05	0.42		0.08	0.03	0.16		0.06	0.04	0.11	
TAPVD	0.11	0.03	0.37		0.08	0.01	0.12		0.16	0.11	0.22	
AS	0.08	0.01	0.31		0.49	0.36	0.66	~	0.38	0.30	0.47	#
TA	0.08	0.01	0.31		0.04	0.02	0.14		-	-	-	
PA	0.08	0.01	0.31		0.05	0.09	0.26		0.17	0.12	0.24	
HLHS	0.00	-	-		0.26	0.17	0.40		0.19	0.14	0.26	

* $p<0.0001$ + $p=0.0003$ ~ $p= 0.005$ # $p=0.02$

Appendix 9: Total monthly live births in Malta for 1990-1994 (COS 1990-94)

	1990	1991	1992	1993	1994	Totals
Jan	405	498	491	408	437	2239
Feb	417	437	395	376	377	2002
Mar	423	433	431	432	405	2124
Apr	433	436	416	412	382	2079
May	455	428	458	436	375	2152
Jun	457	443	395	398	400	2093
Jul	490	465	468	462	453	2338
Aug	490	464	443	444	411	2252
Sep	496	464	443	452	419	2274
Oct	433	437	464	471	377	2182
Nov	398	431	497	426	390	2142
Dec	471	366	573	430	400	2240
Totals	5368	5302	5474	5147	4826	26117

Appendix 10: Analysis of quarterly distribution of Maltese livebirths with severe CHD for 1990-1994

Quarter	θ	Severe CHD	All live births	Corrected CHD	√n	sin(θ)	√n sin(θ)	cos(θ)	√n cos(θ)
1	45	16	6365	16.4	4.05	0.71	2.86	0.71	2.86
2	135	24	6324	24.8	4.98	0.71	3.52	-0.71	-3.52
3	225	38	6864	36.1	6.01	-0.71	-4.25	-0.71	-4.25
4	315	39	6564	38.8	6.23	-0.71	-4.40	0.71	4.40
Totals		n=117	n=26117		W=21.27		S=-2.27		C=-0.50

Mean Quarterly deliveries=6529.2

x=-0.19	$d=V(S^2+C^2)/W=0.11$	**p=0.003**
y=-0.04	a=4d=0.44	**θ=192°**
d=0.19	2/n=0.017	

χ^2 (2 degrees of freedom)= 11.1

Appendix 11: Minimum, maximum and mean ages in months at diagnosis of CHD

Year	1945-54	1955-64	1965-74	1975-84	1985-94
Mild CHD					
Mean	245.2	140.7	92.2	40.4	6.0
Minimum	45.8	0.5	1.1	0.01	0.01
Maximum	465.5	429.7	302.5	215.8	97.5
n=418	n=9	n=23	n=24	n=70	n=218
Severe CHD					
Mean	245.3	146.3	94.2	49.3	6.7
Minimum	45.8	0.5	1.0	0.01	0.01
Maximum	465.5	429.7	302.5	215.8	97.5
n=609	n=81	n=92	n=83	n=141	n=212

Appendix 12: Catheterised and uncatheterised patients prior to 2nd, 3rd and 4th operations for severe CHD

5 year period	Catheterised	Uncatheterised	Ratio catheterised to uncatheterised
1960-64	2	6	**3.0**
1965-69	2	2	**1.0**
1970-74	5	9	**1.8**
1975-79	10	9	**0.9**
1980-84	7	6	**0.9**
1985-89	7	6	**0.9**
1990-94	9	8	**0.9**

Appendix 13: Catheterised and uncatheterised patients prior to 1st, 2nd, 3rd and 4th operations for complex CHD

5 year period	Catheterised	Uncatheterised	Ratio catheterised to uncatheterised
1960-64	2	1	**0.5**
1965-69	3	0	**0.0**
1970-74	2	0	**0.0**
1975-79	4	1	**0.3**
1980-84	5	1	**0.2**
1985-89	9	11	**1.2**
1990-94	20	13	**0.7**

Appendix 14: Quarterly live births with TOF for 1990-91

Quarter	n
1st Quarter	1
2nd Quarter	4
3rd Quarter	7
4th Quarter	4

Appendix 15: Lesions associated with recurrence of CHD probands and affected siblings

Outflow tract		Septal defect		Inflow tract		Total
PS	9	VSD	7	MV abnormality	1	
Truncus	2	ASD	1			
Coarctation/IAA	2					
TOF	1					
TGA	1					
PDA	1					
Isomerism sequence	1					
Congenitally corrected TGA	1					
Totals	18		8		1	27
Percentage	67		30		3	

Publications arising from this study

Grech V. Trends in Preoperative cardiac catheterisation in CHD. Journal of the Maltese College of Family Doctors. In press.

Savona-Ventura C, Grech V. Congenital malformations in a central Mediterranean island. International Journal of Risk and Safety in Medicine. In press.

Grech V, Savona-Ventura C. Declining mortality from congenital heart disease in Malta. Maltese Medical Journal. In press.

Grech V. Ventricular septal defect in Malta. Cardiology in the Young. In press.

Grech V. An excess of Tetralogy of Fallot in Malta. Journal of Epidemiology and Community Health. In press.

Grech V. History, diagnosis, surgery and epidemiology of pulmonary stenosis in Malta. Cardiology in the Young. In press.

Grech V. Spectrum of congenital heart disease in Malta: an excess of lesions causing right ventricular outflow tract obstruction in a population based study. European Heart Journal. In press.

Grech V, Danvers R. Application of colour-Doppler echocardiography machines to non-congenital heart problems in tertiary referral centres. Echocardiography Journal (on line)

Abstracts

Grech V, Elliott MJ, Wren C. Automation of data analysis in paediatric heart disease. 3rd Maltese Medical School Conference:30th November 1995

Grech V, Elliott MJ, Wren C. Diagnostic Trends in CHD in Malta. 7th Annual Meeting of the British Paediatric Cardiac Association: 22nd November 1996