ASPECTS OF THE PREVALENCE, AETIOLOGY AND PREVENTION OF ANENCEPHALUS AND SPINA BIFIDA IN GLASGOW, 1972-78.

AN EPIDEMIOLOGICAL STUDY

BY

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TO THE MOTHERS AND CHILDREN

OF GLASGOW

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STATEMENT OF ORIGINALITY

I hereby declare that

(a) this thesis was my own composition; and

(b) that the thesis contains an account of studies designed, executed and analysed by myself, with partial recourse to assistance of a specialised nature (e.g. statistical, computing and secretarial) where and when required.

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ABSTRACT

This study was prompted by reports of a long-term decline in the prevalence of neural tube defects, the confusion surrounding their aetiology and the recent introduction of maternal serum alpha-fetoprotein (A.F.P.) screening in the West of Scotland. Its objectives were to establish the prevalence of anencephalus and spina bifida in Glasgow between 1972 and 1978, to explore the possible aetiological role of maternal age, parity, social class and locality of residence, and to evaluate the impact of the programme of serum A.F.P. screening on the prevalence of the defects in Glasgow. Data were obtained from the previously validated Glasgow Register of Congenital Malformations and from various sources of routinely collected information.

Between 1972 and 1978, there were 92,325 births in Glasgow. Anencephalus occurred in 168 of these, representing a prevalence rate at birth of 1.82 per 1000 births; spina bifida affected 242 infants, representing a prevalence rate of 2.62 per 1000 births. The prevalence of anencephalus, but not of spina bifida, had fallen significantly since an earlier Glasgow survey in 1964-68. In a world context, however, Glasgow remained a high prevalence area.

Both advanced maternal age and high parity (particularly the latter) were associated with an increased risk of anencephalus and spina bifida, as was lower social class. Since the earlier Glasgow study, the age and parity associated risks had increased strikingly, while the social class trend (particularly of spina bifida) had diminished slightly. A multiple linear regression analysis indicated that a significant proportion (34%) of the variance in the prevalence of anencephalus within Glasgow could be explained by high parity in the maternal population while none of the studied maternal factors could explain the distribution of spina bifida. A hypothetical aetiological model is proposed whereby biological (including genetic and reproductive) factors and socio-environmental influences (other than poverty) might interact. The model further postulates that the former factors might be more important in the aetiology of anencephalus and the latter factors more important in the aetiology of spina bifida, particularly in high prevalence areas.

Serum A.F.P. screening appeared to have effected a significant reduction in the prevalence of anencephalus but not of spina bifida over the study period. There was some evidence that those women most at risk of delivering an affected infant were least likely to benefit from the screening programme. It is suggested that these epidemiological data should make a useful contribution to the public and professional debate of the scientific and ethical issues raised by the A.F.P. screening programme.

I. INTRODUCTION

1.1. HISTORICAL NOTE

There is evidence that congenital malformations, including those affecting the central nervous system, have afflicted the human race since its origins. According to SIGERIST (1951), Pales described both a bifid sacrum and a probable congenital dislocation of the hip in neolithic remains discovered in France. SAINT-HILAIRE (1826) demonstrated a mummified anencephalic fetus which had been buried in the catacombs of Hermapolis on the Nile. In ancient Mesopotamia, the birth of a child with a congenital defect was regarded as a portentous and usually sinister omen. Babylonian scholars, intent upon the "science" of divination (the study of omens), inscribed details of malformed infants on clay tablets. A hundred of these, covered with cuneiform script, were excavated near the River Tigris in the nineteenth century. BALLANTYNE (1894) asserted that most of the cases recorded on the tablets could be identified as recognised congenital deformities.

Belief in divination was prevalent in many parts of the ancient world. The Romans sacrificed children with severe defects (particularly hermaphrodites) in times of crisis or danger. Infanticide was widely practised in ancient societies for either eugenic or supernatural reasons. The Spartans, for instance, placed unwanted infants on the inhospitable slopes of Mount Taygetus where the high mortality rate "proved" the victims' inferiority. Many of these barbarous practices were inspired by a profound fear of monstrosities and their significance. This attitude was reinforced and legitimised, to some extent, by primitive theories not only of divination but of "hybridity" and "maternal impression". The hybridity theory claimed that a union between members of different species might be fertile and produce monstrous offspring,

such as the Cretan minotaur and other mythological creatures. The idea that maternal impressions, visual or otherwise, might influence the fetus, spans the centuries. In ancient Greece, pregnant women were exhorted to view magnificent statues and paintings, while Merrick, the celebrated Victorian "Elephant Man", apparently attributed his deformities to his mother's fright at having been knocked down by an elephant at a circus shortly before his birth (MONTAGUE 1970). As KENEN (1980) has pointed out, while pregnant women are no longer told to avoid viewing particular objects, they are advised to eschew alcohol, tobacco, certain drugs and other modern environmental hazards.

It was not until the advent of printing in the fifteenth century that detailed descriptions of congenital malformations were recorded in Europe with any frequency. Subsequently, anatomists, surgeons and pathologists began to document their experiences of such conditions. By the middle of the nineteenth century, classical teratology (the study of monstrosities) had reached its zenith. Throughout the twentieth century, the appeal of the subject broadened steadily to include geneticists, biochemists, sociologists, philosophers and epidemiologists. This rapidly proliferating number of disciplines associated with the study of congenital defects reflected a shift in social attitudes away from fear or morbid curiosity towards a more sophisticated appreciation of the biological, social, medical and ethical ramifications of the problem, although residues of past myths and superstitions undoubtedly persisted. Moreover, as the pattern of disease changed with the decline in the frequency and impact of the epidemic infections, the perception of the nature of the challenge posed by congenital malformations in general, and neural tube defects in particular, was dramatically transformed.

1.2. ANENCEPHALUS AND SPINA BIFIDA IN MODERN TIMES

The contribution of congenital malformations to childhood mortality and morbidity has acquired progressively more significance over the past few decades, particularly in Western industrialised societies where, according to HOLT (1974), "survival in childhood is taken for granted, family size is restricted and parents are concerned about the quality of their children." While infant mortality generally has declined steeply since the First World War, infant mortality from congenital abnormalities has remained fairly constant, thereby enhancing their relative importance as a cause of death in early childhood (OFFICE OF HEALTH ECONOMICS 1978). This trend may be observed even within a fairly short time span. For example, congenital malformations were reported as being responsible for 23 per cent of infant deaths in Scotland in 1972. By 1978, this proportion had risen to 29 per cent although the total number of infant deaths had fallen substantially. Throughout this period, however, the proportion of infant deaths attributed to anencephalus and spina bifida (A.S.B.) remained virtually static at around six per cent. Estimates of morbidity from congenital defects are rare because of the methodological difficulties. A research group from the UNIVERSITY OF YORK (1976) pooled data from the York register of disabled children and the National Child Development Study (1958 Cohort) and derived a national prevalence rate of 6.7 per 1,000 children under 16. If accurate, this figure represents 70,000 to 80,000 children in the United Kingdom with very severe congenital disabilities of which about 20 per cent are likely to be due to spina bifida.

The prevalence of a congenital defect in the population depends both on the number of children affected at birth and on their survival. Anencephalus always results in either stillbirth or neonatal death.

In the case of spina bifida, the natural history is more complex because of the changing role of surgical intervention. The early emergency closure of spinal defects was advocated enthusiastically in the 1960's and survival rates consequently increased steadily throughout that decade. Following the reservations expressed by LORBER (1971) about this activist policy, which was responsible for the survival of a large number of severely handicapped children, a more selective basis for treatment was adopted and the mortality rate began to rise again in the 1970's (WEATHERALL and WHITE 1976).

Research interest in congenital disorders remained at a fairly low level around the world before the Second World War. Attitudes changed, however, when the prospects of identifying specific environmental teratogens were improved by the demonstration of the probable causal role of rubella (GREGG 1941) and later thalidomide (McBRIDE 1961) in the development of some human malformations. The recognition of the teratogenic effects of those two agents led to an intensification of the search for other aetiological factors. Maternal infection (COFFEY and JESSOP 1959), diet (NELSON 1957; RENWICK 1972) and drugs (RICHARDS 1969; LAURENCE, CARTER and DAVID 1968) have all been investigated in relation to neural tube defects but none has been shown to be of central importance. The general anxiety about the unwitting exposure of the pregnant population to environmental teratogens led to the establishment of national and local surveillance systems designed to detect and investigate deviations from the expected birth prevalence of defects. In Britain, a national register has been operated by the Office of Population Censuses and Surveys since 1964 (WEATHERALL 1976) and local registers have been created in Birmingham (McKEOWN and RECORD 1960), Liverpool (SMITHELLS 1962), South Wales (RICHARDS and LOWE 1971) and

Glasgow (STONE 1979). These have proved invaluable sources of data on the epidemiology of congenital disorders although their role as public health tools appears to have been limited.

Despite the disappointing progress achieved in the unravelling of aetiology, the past few years have witnessed a remarkable breakthrough in the prevention of neural tube defects. BROCK and SUTCLIFFE (1972) described a method of diagnosing anencephaly and open spina bifida in utero by the measurement of alpha-fetoprotein (A.F.P.) in the amniotic fluid. Amniocentesis is now offered to women with a family history of neural tube defect and is therefore potentially capable of detecting ten per cent of all children with open neural tube defects (LANCET 1974). In order to detect the remaining 90 per cent, a screening test for the prenatal determination of A.F.P. in the maternal serum has been developed (BROCK, BOLTON and SCRIMGEOUR 1974). At present, maternal serum A.F.P. screening is still undergoing evaluation. Despite the call by the CLINICAL GENETICS SOCIETY (1978) for its implementation on a national scale, a Working Group set up by the Department of Health and Social Security recommended that screening should be encouraged "in favourable circumstances" only (WORKING GROUP ON SCREENING FOR NEURAL TUBE DEFECTS 1979). Several centres are involved in local screening programmes, however. These include Edinburgh, Oxford, London and Glasgow, and their progress is being observed with interest.

1.3. ANENCEPHALUS AND SPINA BIFIDA IN THE WEST OF SCOTLAND

There has been an intense local interest in the subject of neural tube defects in the West of Scotland since EDWARDS (1958) drew attention to the high prevalence there in comparison with the rest of Scotland. Edwards exploited the availability in Scotland of detailed stillbirth and infant death registration data to study the geographical pattern of distribution of A.S.B. for the period 1950-56. He found the highest rates of anencephalus in the burghs of Port Glasgow and Greenock (3.85 per thousand births) and of spina bifida in the counties of Dumfries, Kirkcudbright and Wigtown (3.10 per thousand births). These findings were confirmed by a later study of FEDRICK (1976b).

The prevalence of A.S.B. in Glasgow between 1964 and 1968 was estimated by WILSON (1970) using a retrospectively compiled register which drew its data from three sources: local stillbirth and death registrations, the local "At Risk" and "Handicapped Children" registers, and the inpatient records of the city's two paediatric surgical units. The prevalence of anencephalus was found to be 2.83 per thousand births and that of spina bifida 2.80 per thousand births.

In an exhaustive review of the literature, ELWOOD, J.M. and ELWOOD, J.H. (1980) discussed the large variation in the prevalence of anencephalus and spina bifida both within and between countries. International comparisons have repeatedly suggested that North West Europe is most at risk, particularly the Brittany and Normandy coasts of France and the British Isles (PENROSE 1957). And within the British Isles there appears to be a gradient of increasing prevalence from the relatively low risk South-East of England to the relatively high risk

"Celtic fringe" of Wales, Scotland and Ireland (STOCKS 1970). The reason for this distinctive pattern is obscure but is likely to be related both to ethnic and environmental factors.

The position of Glasgow and the West of Scotland with respect to the risk to its population of anencephalus and spina bifida may be summarised in the following terms : it is a high risk locality within a high risk region of the world's highest risk geographical area, the British Isles. Against this sombre background, it is perhaps not surprising that the most ambitious community-wide programme for the antenatal screening and prevention of neural tube defects has been operating in the West of Scotland since 1975 (FERGUSON-SMITH et al. 1978).

1.4. ORIGINS OF THE PRESENT STUDY

Despite the enormous expenditure of effort over the past few decades, the continued occurrence of anencephalus and spina bifida presents an undiminished challenge to research workers. The widely acknowledged importance of the defects, in terms of their contribution to childhood mortality and morbidity, their impact on family life and their drain on the public purse, acts as a spur to the continuing search for answers to the many outstanding questions. Three particular questions stimulated the present study, namely :

1. What is happening to the prevalence of anencephalus and spina bifida?
2. What is the aetiology of the defects?
3. What has been the impact of the programme of ante-natal screening on the prevalence of anencephalus and spina bifida?

Each of these questions will now be considered in more detail.

Question 1 : What is Happening to the Prevalence of Anencephalus and Spina Bifida?

MACMAHON and YEN (1971) presented evidence of a long-term epidemic of both anencephalus and spina bifida in Boston, Massachusetts and Providence, Rhode Island. They studied births in two large hospitals over the period 1885 to 1965 and found an upward trend beginning about 1920, peaking in 1930-34 (at 6.0 per 1,000 births for both defects) and declining until about 1955. A declining prevalence from 1930 had been reported in an earlier paper by NAGGAN (1969) who analysed data from four Boston hospitals over a shorter time period (1930-65). Other North American and British studies have pointed to a double peak, first in 1930-40 then in the early 1960's, leading ELWOOD, J.M. and ELWOOD, J.H.

(1980) to speculate about the possibility of a world-wide pandemic.

Short-term trends show less consistent patterns however, with great variation between one area and another. Nevertheless, the prevalence of anencephalus appears to have been declining, in several British cities (including Glasgow) in recent years. The explanation is not clear, but BRADSHAW, WEALE and WEATHERALL (1980) have suggested that the decline in notifications of neural tube defects to the central register operated by the Office of Population Censuses and Surveys may be attributed both to demographic factors (especially a changing pattern of maternal age, parity and social class) and the effects of antenatal diagnosis.

Secular trends are important for two reasons. They may indicate the occurrence of epidemics which lend themselves, par excellence, to aetiological investigation. And they provide health planners with valuable baseline data on which to assess both the need for services and their efficacy. In Glasgow, the introduction and development of an antenatal screening programme render the examination of the trend in the prevalence of anencephalus and spina bifida especially relevant.

Question 2 : What is the Aetiology of Anencephalus and Spina Bifida?

LECK (1974) has highlighted a paradox about research in this area: while a great deal is known about the way in which the prevalence of anencephalus and spina bifida varies, very little is known about the causes of the variations. The most specific statement which can be made about the aetiology of the defects is that environmental factors are probably interacting with a genetically susceptible population. The

weight of evidence seems, however, to favour environmental influences, since the prevalence rate is so sensitive to place, even in high-risk ethnic groups. Dietary and infective causes have long been suspected, but each specific hypothesis in turn has had to be discarded. One of the most consistent and impressive findings is the steep social class gradient : social classes IV. and V. (Registrar General's classification) have a risk up to fourfold that of social classes I. and II. This trend has been found in British, Canadian and American studies, and appears to be independent of maternal age, parity and geographical region. Since no specifically social-class related aetiological agent has been implicated, this repeatedly observed phenomenon has proved tantalisingly unhelpful in formulating a convincing causal hypothesis. Maternal age and parity, which are inter-related, appear to influence the risk of the defects, although conflicting results have been published. Other factors of possible aetiological significance are ethnicity, a history of neural tube defect, previous abortion, place of residence, season of conception and drugs. The picture is indeed complex and confusing. Clarification of some of the issues is urgently needed.

Question 3 : What has been the Impact of the Programme of Antenatal Screening on the Prevalence of Anencephalus and Spina Bifida?

If the objective of antenatal serum A.F.P. screening is to prevent the birth of children with open neural tube defects in a defined population, it is necessary to evaluate its effectiveness epidemiologically. In other words, it is not sufficient to demonstrate a reduction in prevalence among those screened; evidence of a significant decline in the prevalence in the population as a whole must be sought. CHAMBERLAIN (1978) has drawn attention to the practical constraints on the

achievement of this potential benefit for the community, and has estimated that screening is likely to avert only 63 per cent of anencephalic births and 45 per cent of spina bifida births in England and Wales. This denominator-oriented perspective is markedly pessimistic when contrasted with the more clinically-oriented approach of those who operate the screening programmes, often with great enthusiasm and dedication. A practical (as opposed to theoretical) attempt to monitor the possible impact of screening on the population prevalence is being undertaken by the central register based at the Office of Population Censuses and Surveys. The limitations of this system, which covers England and Wales only and is dependent on voluntary notifications, render more intensive local studies essential.

Glasgow is the ideal "laboratory" in which to seek answers to the three questions posed above. Its population is exposed to a high risk of neural tube defect, it operates a community-based register of congenital malformations (which has been found to be valid for neural tube defects, as will be discussed later), and it is served by a recently initiated serum A.F.P. screening programme.

1.5. DEFINITIONS

EPIDEMIOLOGY has been defined as the study of the distribution and determinants of disease frequency in man (MACMAHON and PUGH 1970).

LILIENFELD (1976) has expanded on the definition in a way which illuminates the nature of the discipline :

> "The epidemiologist is interested in the occurrence of disease by time, place and persons. He tries to determine whether there has been an increase or decrease of the disease over the years; whether one geographical area has a higher frequency of the disease than another; and whether the characteristics of persons with a particular disease or condition distinguish them from those without it."

A distinction may be drawn between three types of epidemiological study (HOGARTH 1976) :

descriptive epidemiology, concerned with observing the distribution of disease in populations;

analytical epidemiology, concerned with investigating, by retrospective and prospective studies, hypotheses formulated to explain these observations; and

experimental epidemiology, concerned with experiments which attempt to measure the effect of controlled trials of the manipulation of suspected harmful influences or of preventive measures in populations.

The present study has involved the use of the first two of the above epidemiological approaches.

Other terms appearing in the text include :

CONGENITAL MALFORMATION : an abnormality of structure attributable to faulty development.

ANENCEPHALUS : a congenital malformation in which there is a virtual absence of the forebrain and the skull vault.

SPINA BIFIDA : a congenital malformation in which there is a defect in the vertebral arches through which herniation of either the meninges or the spinal cord or both may or may not occur.

A more detailed account of the nature of the lesions will be found in II.

INCIDENCE RATE OF A CONGENITAL MALFORMATION : the proportion of embryos developing the malformation during a specified period of time. (In practice, this figure is not usually possible to calculate).

PREVALENCE RATE OF A CONGENITAL MALFORMATION : the proportion of births (live and still, delivered from 28 weeks gestation) with the malformation. Some studies in the literature refer to this as an "incidence rate". The term "prevalence" of a congenital malformation is short-hand for "prevalence rate at birth", usually defined as the number of instances of the disorder per 1,000 total births. The difference between the true incidence of a defect and its prevalence is proportional to the (usually unknown) number of fetuses with the defect which are aborted.

VALIDITY OF DATA : the extent to which the results of a method agree with an independent external criterion. (This is sometimes known as "concurrent validity").

ITEM VALIDITY : a measure of the accuracy of the recording of various items of information about a defect.

CASE VALIDITY : a measure of the success with which diagnosed cases of a defect are ascertained.

ASCERTAINMENT OF A CONGENITAL MALFORMATION : the method employed to identify or count all affected births occurring in a defined population during a given time period. One of the commonest methods of ascertainment is by means of a register.

REGISTER : a written record or official list regularly kept. It is usually designed to collect information on one specific topic, in contrast with master patient files and record linkage systems, which provide means of collecting, storing and retrieving information on many topics not predetermined or limited in scope.

REGISTRY : a place where a register is kept.

EVALUATION : the systematic and scientific process of determining the extent to which an action or set of actions were successful in the achievement of predetermined objectives.

SCREENING : the presumptive identification of unrecognised disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.

PARITY : the total number of deliveries (live and still) prior to the present confinement.

SOCIAL CLASS (based on the widely used Classification of the Registrar General) :

SOCIAL CLASS I : "Higher" professional and administrative occupations.

SOCIAL CLASS II : Employers in industry and retail trades; the "lesser" professions.

SOCIAL CLASS III : Skilled occupations.

SOCIAL CLASS IV : Semi-skilled occupations.

SOCIAL CLASS V : Unskilled occupations.

Where a particular occupation had not been classified, reference was made to the Classification of Occupations of the OFFICE OF POPULATION CENSUSES AND SURVEYS (1970).

II. THE NATURE OF ANENCEPHALUS AND SPINA BIFIDA

2.1. EMBRYOLOGY

The lesions of anencephalus and spina bifida are believed to originate from the non-closure of the neural tube which is formed by the dorsal folding of the neural plate. (The neural plate itself is merely a thickening of the outer germ layer, the ectoderm, of the embryonic central nervous system). Normally, the closure or "neurulation" of the neural tube starts in the cervical region and spreads in cranial and caudal directions leaving temporary canals or neuropores connecting the central neural canal to the amniotic cavity. In the human embryo, these neuropores seal off about four weeks after fertilisation.

The mechanism of neurulation is complex and incompletely understood. The mesoderm and the neural tube are believed to interact in a dynamic and mutually important way. It is the mesodernal substratum (the prechordal plate and the notochord) which really controls the development of the central nervous system, while the latter in turn exerts a crucial influence on the formation of the mesenchymal structures, including the vertebral bodies and arches. Although conflicting hypotheses have been proposed, there is general agreement among embryologists that the key to the pathogenesis of neural tube defects lies in a disturbance of the neural-mesodernal interaction. The cause of this disturbance is unknown (KALLEN 1968; WARKANY 1971).

2.2. ANATOMY

Anencephalus is an abnormality involving structures derived from the cephalic end of the neural tube (WARKANY 1971). Although there are a number of anatomical variations, there is usually complete absence of the forebrain and skull which are replaced by a mass of haemorrhagic fibrovascular tissue containing some neural elements. The brain stem is present, but the midbrain and cerebellum may be absent. There are usually normal eyes and optic nerves which end blindly at the base of the skull. The bones at the base of the skull, particularly the sphenoid and petrous temporal bones, are malformed, and the cranial vault bones (the parietal, frontal, squamous temporal and occipital bones) are scarcely identifiable. The facial bones are deformed because of their articulation with the abnormal skull base.

Anencephalus may be subdivided into three anatomical types : incomplete, in which the defect does not extend to the foramen magnum; complete, in which the defect extends through the foramen magnum; and craniorachischisis, in which complete anencephalus is accompanied by defective closure of the spine. It is usually distinguished from other conditions which lead to herniation of brain tissue through a defect in the skull. These include cranial meningocoele (the herniation of meninges only) and encephalocoele (the herniation of meninges and brain tissue).

The commonest abnormality associated with anencephalus is probably spina bifida, which is present in upwards of one in twenty anencephalic infants (ELWOOD and NEVIN 1973). Other associated malformations include exomphalos, congenital heart disease, urinary tract anomalies and oral clefts (DAVID and NIXON 1976).

Spina bifida is the caudal equivalent of anencephalus. A dorsal defect in the vertebral arches is always present. If the defect is not visible, it is usually described as spina bifida occulta. There are two variants of spina bifida occulta : the uncomplicated type, in which only one vertebra is involved and there are no associated disorders, and the complicated type, in which more than one vertebra are affected and the spinal canal is widened. In the newborn infant, the only external evidence of an underlying osseous defect may be the presence of hypertrichosis, telangiectases, abnormal pigmentation, lipomas or dimples.

If there is an external protrusion, the defect is described as spina bifida cystica which includes meningocoele (a saccular protusion involving meninges only) and myelocoele (involving neural tissue also). (The term myelocoele includes defects sometimes described as myelomeningocoele or meningomyelocoele). Spina bifida cystica lesions may be open (that is, having no skin cover) or closed (having skin cover). The vast majority of defects are open (sometimes called spina bifida "aperta" or rachischisis. Spina bifida defects are frequently associated with an Arnold-Chiari malformation, hydrochephalus and talipes.

2.3. CLASSIFICATION OF ANENCEPHALUS AND SPINA BIFIDA FOR EPIDEMIOLOGICAL PURPOSES

The classification of anencephalus and spina bifida is somewhat arbitrary being based on the presumed aetiological relationship between the lesions. The rubrics of the International Classification of Diseases (Ninth Revision) are useful guides (WORLD HEALTH ORGANIZATION 1977) and have been employed in this study.

Anencephalus (or anencephaly) is considered to be separate from exencephaly and iniencephaly, but a combination of anencephalus and spina bifida is classified under the former heading.

Spina bifida includes all of the "cystica" defects, whether open or closed, but does not include spina bifida occulta. Encephalocoele is excluded, as is hydrocephalus unless it is clearly secondary to spina bifida.

Because anencephalus and spina bifida are believed to be closely related aetiologically, the term "neural tube defects" may be used to denote both. Indeed, it is common for the two defects to be aggregated for statistical or epidemiological purposes as "anencephalus and spina bifida" ("A.S.B."), exploiting the convention whereby the coexistence of the two defects in one individual is counted once (as "anencephalus").

More precise anatomical, pathological or clinical classifications are useful in other contexts. They are superfluous to the requirements of most epidemiological analyses, however, and are therefore not employed in this study.

2.4. CLINICAL ASPECTS OF ANENCEPHALUS AND SPINA BIFIDA

2.4.1. Diagnosis

The clinical history and physical examination cannot in themselves confirm a diagnosis of anencephalus or spina bifida *in utero* but they can arouse suspicion that a defect may be present. In this context, it is useful to consider the characteristics of the "high-risk mother" (ELWOOD, J.M. and ELWOOD, J.H. 1980). The most important feature is a previous reproductive or family history of neural tube defect, which confers a risk of between two and five per cent of bearing an affected child. Other risk factors include a prior history of spontaneous abortion, stillbirth or infant death (regardless of cause), area of residence (particularly the north and west of the British Isles), Celtic, Sikh and possibly Arab ethnic origin and intense poverty.

Various special laboratory techniques have been developed in an attempt to assist the obstetrician in making a diagnosis of neural tube defect. Measurement of maternal urinary oestriol excretion, radiographic examination and fetoscopy all held early promise which was not fulfilled. They have been supplanted by two techniques, ultrasonography and amniocentesis, which have dramatically improved the accuracy of antenatal diagnosis. Direct visualisation of the fetus ultrasonically has led to the diagnosis of anencephalus in the first trimester (MACVICAR 1976), while amniotic alphafetoprotein examination prior to 20 weeks gestation is capable of detecting a very high proportion of cases of anencephalus and spina bifida (BROCK and SUTCLIFFE 1972).

2.4.2. Complications of Pregnancy and Delivery

Hydramnios is a frequent accompaniment of pregnancy associated with anencephalus or spina bifida (STEVENSON 1960). Threatened abortion and antepartum haemorrhage also appear to affect more anencephalic than normal pregnancies (SMITHELLS, CHINN and FRANKLIN 1964). Premature labour, probably secondary to hydramnios, is more common in anencephalic pregnancies than in livebirths taken as a whole, as is postmaturity (ELWOOD, J.M. and ELWOOD, J.H. 1980). Face and breech deliveries are more likely in anencephalic than control births (GUHA-RAY 1975); it is assumed that this is true also of spina bifida deliveries. Retained placenta and post-partum haemorrhage appear to be more likely in deliveries of anencephalics. Most anencephalic fetuses are stillborn while the remainder succumb within a few hours or days after birth. Most spina bifida fetuses survive the perinatal period but are often afflicted by considerable handicap, the full extent of which may not be revealed for some months or years.

2.4.3. Clinical Management of Anencephalus and Spina Bifida

A sensitive approach to the varying responses of parents to the delivery of a malformed child is essential. In the case of anencephalus, bereavement sooner or later has to be faced with all its attendant problems. Spina bifida, however, presents the clinician with more complex difficulties of a medical, surgical and ethical nature (RICHARDS and McINTOSH 1973).

With the exception of crude surgery, methods of treating spina bifida were unavailable until the development of a mechanical

shunt for the control of advancing hydrocephalus (NULSEN and SPITZ 1951). Thereafter, early closure of open lesions became widespread resulting in improved survival rates and, in some cases at least, an improved quality of life. Unfortunately, as RICHARDS and McINTOSH (1973) and others have pointed out, improved survival was associated with an increase in the proportion of severely handicapped children amongst the survivors. Following the advice of LORBER (1971), surgeons have reverted to a more selective policy. Selection criteria include the degree of hydrocephalus, the extent of physical deformity and the site of the lesion. Not unexpectedly, the mortality rate appears to have risen as a result of this more conservative approach, hopefully in conjunction with a decline in the proportion of severely disabled survivors (WEATHERALL and WHITE 1976).

Following surgery, a coordinated approach to the continuing assessment and care of these children is required. The medical, social and educational services are all likely to become involved since the majority (more than 80 per cent) of surviving children have some degree of handicap, whether physical, mental or both (WILSON 1970). And because of the relatively high risk of recurrence, parents should be offered the services of a genetic counselling clinic before embarking on further pregnancies.

III. AIM AND OBJECTIVES

3.1. AIM AND OVERALL DESIGN OF THE STUDY

The aim of the study was to investigate the epidemiology of anencephalus and spina bifida in Glasgow with special reference to their prevalence, aetiology and prevention. The reasons for the identification of these three areas have been discussed (1.4).

More specifically, three objectives were formulated :

(1) to establish the prevalence of anencephalus and spina bifida (A.S.B.) in Glasgow over the period 1972-78;

(2) to explore the possible aetiological role of a number of variables (maternal age, parity, social class and locality of residence), both individually and in terms of their interaction; and

(3) to evaluate the impact of the programme of antenatal screening for neural tube defects on the prevalence of A.S.B. in Glasgow.

In order to meet these objectives, three sub-studies were designed: a Descriptive Study, an Aetiology Study and a Prevention Study.

3.2. OBJECTIVES OF THE DESCRIPTIVE, AETIOLOGY AND PREVENTION STUDIES

3.2.1. Objectives of the Descriptive Study

The main objective of the Descriptive Study was to establish the prevalence of anencephalus and spina bifida in Glasgow in the period 1972-78.

Related to the above were several subsidiary objectives designed to elucidate the descriptive epidemiology of anencephalus and spina bifida in terms of "time", "place" and "person".

The objective of the "time" study was to investigate possible changes in the prevalence of the lesions :

(a) since the earlier Glasgow studies of the 1960's;

(b) within the time period 1972-78; and

(c) according to season of birth.

The objective of the "place" study was to compare the Glasgow prevalence of anencephalus and spina bifida with other geographical locations, both in the United Kingdom and elsewhere, and to determine the distribution of affected births within Glasgow.

The objective of the "person" study was to compare the distributions of certain personal characteristics (of either the mother or fetus) in affected births with those of all births. These personal characteristics were sex, whether singleton or multiple birth, whether live or still born, birth weight, gestation and the presence of other defects.

3.2.2. Objective of the Aetiology Study

The objective of the Aetiology Study was to explore the possible aetiological role of a number of variables both individually and in terms of their interaction.

The variables were maternal age, parity, social class and locality of residence. The reasons for their selection were empirical, theoretical and pragmatic.

The empirical grounds have been discussed (I.1.4.) : previous research had demonstrated associations between these factors and the occurrence of neural tube defects, although the nature, strength and aetiological importance of the relationships were not clearly established.

The theoretical basis of the study was the following hypothesis, which represented an attempt to disentangle the interaction between the variables from individually important effects. The hypothesis may be expressed in two parts :

(1) that the prevalence of anencephalus and spina bifida in Glasgow is directly proportional to maternal age and parity and inversely proportional to social class;

(2) that the geographical distribution of the maternal place of residence of affected births within Glasgow displays a pattern of variation between localities which can be attributed neither to chance alone nor to the distribution within the total birth population of confounding variables (maternal age, parity and social class) but which is evidence of the possible existence of an unevenly distributed local environmental teratogen.

The pragmatic reason for the choice of variables was the availability or potential availability of the necessary data from various sources : the Register of Congenital Malformations, hospital case-records, and miscellaneous published and unpublished routine statistical sources.

3.2.3. Objective of the Prevention Study

The objective of the Prevention Study was to evaluate the impact of the programme of antenatal screening for neural tube defects on the prevalence of anencephalus and spina bifida in Glasgow over the study period 1972-78. The evaluation consisted of :

(a) a comparison of the actual birth prevalence of the defects with the prevalence that would have been expected had the screening programme not been operating;

(b) a comparison of the characteristics (maternal age, parity, social class and place of residence) of those women who had terminations with those who delivered fetuses with anencephalus and spina bifida; and

(c) a comparison of the survival characteristics of anencephalic and spina bifida fetuses in the period prior to the introduction of screening (1972-74) with the period when the screening programme was operating (1975-78).

From the results, it was hoped to extract any important policy implications for health authorities promoting or contemplating the initiation of antenatal screening programmes for the prevention of neural tube defects.

IV. MATERIALS 1. THE POPULATION AT RISK

Glasgow is a large industrial city with a declining population, an unstable economic base and a multitude of social and environmental problems (MANSLEY 1972). Geographically compact, it is the centre of the most densely populated urban area in Scotland, the Clydeside conurbation (FIGURES 1 and 2).

A description of the demographic features of the population at risk is doubly hampered - first by the administrative reforms of 1974 which redrew both local government and health service boundaries, and second by the changing nature of the population itself.

On April 1st, 1974, with the reorganisation of the National Health Service, the population under observation was enlarged (by 35 per cent) to accommodate those areas, formerly outside the boundaries of the City of Glasgow, which were included within the area of the newly created Greater Glasgow Health Board and its five constituent Districts. From the point of view of the Register of Congenital Malformations, this presented a number of problems. There was no way of assessing whether or not the risk of malformations in the additional population was likely to be comparable with that of the original; there was doubt as to whether the ascertainment of defects would prove as efficient with the larger number of births; channels of communication had to be established with new health service personnel unfamiliar with the notification process; and there was concern that a shifting population base might jeopardise potential epidemiological analyses of the data. Despite these anxieties, the redefinition of the observed population seemed to offer certain advantages. First, the predicted continuing decline of both

the population and birth rate in Glasgow would have resulted in progressively fewer notifications to the Register thereby reducing the scope for worthwhile statistical analysis. And second, it was obvious that the integration of the Register with the administrative changes in the health service would greatly facilitate the uninterrupted collection of both numerator and denominator data.

The unstable nature of the population itself is most clearly demonstrated when the effects of the administrative changes are removed. TABLE 1 shows the estimated magnitude of the population decline within the area of the Greater Glasgow Health Board from 1972 to 1978. There appeared to have been a steady reduction in both the total population and the annual number of births, associated with an annual outward migration of approximately 20,000 people (approximately two per cent of the total population). These estimates were based, in part at least, on projections of population, migration and fertility derived from the last census in 1971. By examining inter-censal changes, it was possible to obtain a more accurate impression of demographic and social trends. MILLAR (1975) demonstrated the selective effect of migration on the age-structure of the population of Glasgow which had resulted in an increase in the population of the "dependent" age-groups (i.e. children and the elderly). By contrast, the socio-economic characteristics of the Glasgow population had remained relatively stable since the Second World War. Compared with Scotland as a whole and England and Wales, however, the socio-economic structure of Glasgow possessed an above average proportion of foremen, supervisors and manual workers, and a low proportion of professional, managerial and employer groups (TABLE 2). Indeed, HOLTERMANN (1975) found that Glasgow consistently displayed the most severe "urban deprivation" of any city

in Great Britain as measured by a wide variety of census-based socio-economic indicators.

Finally, TABLE 3 incorporates the denominator change. It demonstrates the way in which the total number of births were artificially maintained by the boundary extension. Also notable are the declining rates of perinatal and infant mortality and the relatively poorer record of Glasgow in these respects, particularly in the earlier years.

V. MATERIALS 2. THE GLASGOW REGISTER OF CONGENITAL MALFORMATIONS

5.1. ORIGINS AND OBJECTIVES OF THE REGISTER

The Glasgow Register of Congenital Malformations commenced data collection on January 1st, 1972, under the auspices of the Social Paediatric and Obstetric Research Unit (established jointly by the University of Glasgow Department of Child Health and the Corporation of Glasgow Health Department).

The Register had three declared objectives (SOCIAL PAEDIATRIC AND OBSTETRIC RESEARCH UNIT 1972) :

(1) the detection of epidemics;

(2) the calculation of prevalence rates and the epidemiological investigation of malformations; and

(3) the study of cohorts of survivors - to identify their diagnostic, therapeutic, social, educational and eventually employment needs.

From its inception, the scope of the Register was ambitious. Multiple sources of ascertainment were employed and few defects were explicitly excluded from registration. Its geographical remit was defined by the boundaries of the former City of Glasgow. Following the reorganisation of both the National Health Service and local government in 1974, responsibility for the Register was assumed by the Greater Glasgow Health Board. The City of Glasgow, along with its Corporation Health Department, had disappeared as an administrative entity. The catchment area of the Register was consequently expanded to include the additional population included within the boundaries of the new Greater Glasgow Health Board area.

5.2. THE REGISTRATION PROCESS

5.2.1. Methods and Sources of Ascertainment

To achieve maximum completeness of ascertainment, multiple sources were employed. Over the years, the number and nature of these sources changed, either because one or more of them had ceased to exist or because other more rewarding sources became available.

Ascertainment was both "active" and "passive". "Active" methods necessitated the scrutiny of data held centrally or in clinical departments. "Passive" methods were designed to ensure the communication of details of malformations from the notifying agency directly to the Register. In practice, however, data were obtained using a combination of "active" and "passive" methods for each source. For example, the tedious task of examining the death register was greatly eased by a sympathetic clerkess who, though not officially on the staff of the Register, "spotted" relevant diagnoses. Conversely, if a dubious or ambiguous notification were received "passively", a member of the Registry staff would undertake to cross-check the diagnosis by inspecting personally the source of the data.

Five main sources of ascertainment were used, along with a group of a miscellaneous nature :

1. The Birth Notification Postcard

   In response to a special request from the Social Paediatric and Obstetric Research Unit, details of any obvious congenital defects were recorded by a member of the Labour Ward staff (usually a midwife) on the statutory birth notification postcard. For administrative reasons, the format of the card was altered in 1976 and congenital defects were no longer recorded.

2. The Obstetric and Social Factors Form

As part of the attempted Glasgow Child Health Record Linkage Scheme (subsequently abandoned), a health visitor completed the form for every child one month after birth. Because of the extra burden of work it placed on health visitors, the form was withdrawn in 1977.

3. The Stillbirth Register

Each week, the Greater Glasgow Health Board received a computer printout from the Office of the Registrar General for Scotland (in Edinburgh) of all stillbirths born to Glasgow residents registered in the previous seven days. If known, the "underlying" and "other" causes of stillbirth were listed in that order. When a congenital defect appeared as a cause, the child was notified to the Register.

4. The Death Register

Precisely the same procedure operated as for the Stillbirth Register, except that the name and date of birth were cross-checked on the Birth Register (a computer printout of all births to Glasgow residents sent by the Registrar General for Scotland to the Greater Glasgow Health Board) to ensure that only children born to Glasgow residents were included in the Register of Congenital Malformations.

5. The Handicapped Children's Register. Forms HS23 and SMR7

The Handicapped Children's Register was maintained centrally by the Scottish Home and Health Department in cooperation with health boards. Registration, which was voluntary, took place via forms HS23 (1972-74) and SMR7(from mid-1974). All children aged 0 to 16 years were eligible. Ascertainment was obtained from multiple sources - family doctors, midwives, health visitors, clinical medical officers and school medical officers. Most major congenital defects were likely to be judged "handicapping" by the notifying professional. Since the Handicapped Children's Register was administered by the same staff as the Register of Congenital Malformations, the task of ascertaining defects from this source was relatively straightforward, except for the cross-checking of addresses with the Birth Register (as described above).

6. Other Sources

(a) The Computerised Neonatal Record (Form SMR11)

This form was introduced in 1975. Its purpose was to act as the basic document for a life medical record (WALKER 1977). One of three copies was retained by the maternity units which permitted Registry staff to examine batches of the forms periodically. The main shortcoming of this source was its incomplete coverage : by 1977, only two of the four major maternity units in Glasgow were completing the SMR11 routinely.

6. (b) The Health Visitor Child Health Record

This was an indirect source of data. Following the demise of the Obstetric and Social Factors Form in 1977, health visitors were supplied with copies of the Congenital Malformations Registration Form onto which they were encouraged to transcribe details of children with congenital defects from their Child Health Records. This record was initiated at the statutory home visit to every child ten days after birth.

(c) The Hospital Dismissal Letter

In most of the Glasgow maternity hospitals, when a child with a congenital abnormality was discharged, a copy of the letter from the paediatrician to the family doctor was sent to the Register. Occasionally, if the information contained in the letter was incomplete or ambiguous, the hospital case-record itself was examined.

Until 1977, the five major sources of ascertainment listed above accounted for the great majority of notifications. From the time of the withdrawal of the original Birth Notification Postcard and the Obstetric and Social Factors Form, "other sources" have become progressively important to the Register.

5.2.2. Criteria for Registration of Congenital Malformations

All notified anatomical, biochemical and genetic congenital anomalies identified by a doctor, midwife or health visitor in a child born (alive or stillborn) to a Glasgow resident from January 1st 1972, were registered. Abortions (i.e. fetal deaths under 28 weeks gestation)

were not registered with the exception of those performed therapeutically as part of the programme of secondary prevention of Down's Syndrome and open neural tube defects. Defects arising in both singleton and multiple births were recorded.

The maternal address, where in doubt, was verified by cross-checking the name and date of birth of the child with the Birth Register of the Registrar General for Scotland. A child was automatically excluded from the Congenital Malformations Register if the maternal address at birth was located outside the boundaries of the area under observation (i.e. the City of Glasgow, January 1972 - March 1974, the Greater Glasgow Health Board Area, April 1974 - December 1978).

5.2.3. The Registration Form

This underwent one major revision at the time of the administrative boundary changes. The original version did not record maternal age and parity; however, these items of information were often either unavailable or not recorded even after the revised form was introduced.

One form was completed for each notification. Thus, many malformations were registered by means of several Registration Forms, each arising from a separate source. This permitted a comparison of data on a single child from multiple sources and any observed discrepancies were investigated further.

The individual items on the form were self-explanatory with two exceptions. The "B. Form No." was the number of the Health Visitor

Child Health Record ("B" = "Birth"). The "Health Board No." was a unique 10-digit identifying code assigned to every child born to a Glasgow resident. (Its first six digits were derived from the date of birth of the child).

Forms were normally completed either by the doctor in administrative charge of the Register or by a health visitor. A copy of the form is reproduced in Appendix 1.

5.2.4. Follow-up of Population After Birth

Registers which confine their period of observation to the first month or first year of life will inevitably miss cases diagnosed in later years. No formal time-limit on the follow-up of the Glasgow Register was implemented. Effectively, therefore, the follow-up period in this study (which was concerned with the period 1972-78) ranged from two to eight years at the time of writing.

5.2.5. Administration

The Register was located at the Area Headquarters of the Greater Glasgow Health Board. In overall administrative charge was a medical officer, supported by a clerkess. The Registration Forms were completed, checked and filed chronologically (by date of birth) in A4 size box files, one for each year. Updating, amendments and analysis were all performed manually.

By chance, the Children's Handicap Register was maintained by the same personnel from the same office. Since the Handicapped Register was used as a source of ascertainment for the Congenital Malformations Register (and, more rarely, vice-versa), the arrangement was mutually beneficial to both.

5.3. OPERATION, USES AND VALIDITY OF THE REGISTER

A comprehensive evaluation of the Register was carried out by the author prior to embarking on the present study. The review encompassed the years 1972 to 1977 inclusive and consisted of four interlinked studies designed to investigate the operation, uses, validity and research potential of the Register (STONE 1979).

The findings of the evaluation may be summarised as follows :

(1) the Register had fulfilled only one of its several objectives, the calculation of prevalence rates;

(2) the validity of registered data was high in respect of the accuracy and completeness of the individual items on the Registration Form (with the exception of maternal data, which were often incomplete) but very variable in respect of the extent of ascertainment of specific defects. For example, "surgical" defects (such as hypospadius and oral clefts) and defects posing diagnostic difficulties (such as congenital heart disease) were less completely ascertained than the grosser, more obvious defects not amenable to surgical "cure";

(3) the use of registered data alone to study the prevalence and natural history of a defect or group of defects could be highly misleading. For example, while the prevalence of registered congenital heart disease in 1972 in Glasgow was 5.4 per 1,000 total births, a revised rate of 10.8 per 1,000 total births emerged when unregistered cases identified from other sources were included in the analysis; and the prognosis (in terms of mortality and morbidity) of congenital heart disease was substantially "improved" when registered data (which were

biased in the direction of greater severity) were augmented by unregistered cases.

(A more detailed description of the evaluation may be found in APPENDIX 2).

On the basis of these findings, the Register was judged to be valid both in terms of the detailed information contained therein (with the exception of maternal data) and in terms of its capacity to identify neural tube defects.

VI. METHODS 1. DATA COLLECTION AND PROCESSING

6.1. NUMERATOR DATA : ANENCEPHALUS AND SPINA BIFIDA BIRTHS AND TERMINATIONS

The Glasgow Register of Congenital Malformations was the focal point of the data handling procedures employed in the study. The Register collected information on both affected births and therapeutic terminations (which were filed separately). The flow of data on births and terminations, however, was substantially different in each case, converging only at two points: the Register and the analysis. FIGURES 3 and 4 illustrate the many steps involved in the transmission of data along the pathways from source to statistical manipulation.

Following the birth of a child with a neural tube defect (FIGURE 3), an initial diagnosis was made, either firmly or tentatively. Thereafter, the immediate priority was a clinical one. Since the Register played no role in the management of the child or family, the notification of the defect to the Register was often belated. A major limiting factor was the protracted clerical process involved in identifying defects from sources (such as form SMR11 and the Handicapped Children's Register) which had to be actively scrutinised by Registry staff.

Because certain data were incomplete, ambiguous or otherwise unsatisfactory, verification was sometimes required. For example, a diagnosis of "spina bifida" required amplification to distinguish "occulta" from "cystica".

The main difficulties associated with the completion of a registration form related to diagnostic classification. Combinations of defects were listed in order of severity, with the principal malformation heading the list. Often, however, two or three malformations seemed equally severe and an arbitrary ordering had to be made. (If anencephalus was present, however, it was always regarded as the principal malformation).

The registration forms were filed, along with relevant material such as copy letters, in date of birth order. This presented few problems. Occasionally, forms became soiled, torn, crushed or filed in the wrong order. To protect against the irretrievable loss of data, a separate card index file, containing basic identifying information, was kept. A vigilant attitude to confidentiality was maintained.

Apart from diagnostic details, which were subject to amendment as new information became available, updating was concerned mainly with one event : death. This was indicated by means of an adhesive red star affixed to the form where appropriate. The death of a child was ascertained from the Death Register. The date, place and causes of death were recorded.

All registration forms bearing details of cases of anencephalus and spina bifida were extracted from the Register and examined. Missing data (usually maternal age, parity and social class) were sought from hospital case records with the assistance of Medical Records Officers. (For this purpose, the permission of both the Obstetric and Paediatric Divisions of Glasgow was obtained).

Data from the registration forms were transferred, using trained clerical workers, to the coding forms (APPENDIX 3). Diagnostic coding, which was closely supervised, was based on the Ninth Revision of the International Classification of Diseases (WORLD HEALTH ORGANIZATION 1977). The coded data were then punched onto 80-column cards, entered on a computer file and checked by members of the Computer Applications Unit of the Greater Glasgow Health Board. A series of computer printouts was generated for analysis, some of which required the aggregation of birth and termination data.

The flow of data on aborted fetuses with neural tube defects was quite separate (FIGURE 4). Pregnancies were terminated in the wake of diagnostically elevated amniotic-alphafetoprotein (A.F.P.) estimations, most of which were performed, in turn, following an elevated serum A.F.P. result. All aborted specimens were examined pathologically and the case details transmitted to Department of Medical Genetics of Yorkhill Hospital, Glasgow, the serum A.F.P. Screening Centre for the West of Scotland. Access to the so-called "Termination Book" of the Department of Medical Genetics was granted to Registry staff who entered the case details into a "Termination File" of the Glasgow Register of Congenital Malformations. For the purpose of the present study, these data were extracted from the Register and transferred to a series of index cards. A search for missing data (usually maternal age, parity and social class) was carried out, again with the assistance of hospital Medical Records Officers, prior to analysis. Because of the relatively small numbers, termination data were analysed manually.

6.2. DENOMINATOR DATA : TOTAL BIRTHS

Estimates of total births, including their geographical distribution, their maternal age, parity and social class characteristics, were obtained both from published sources, including the Annual Reports of the Registrar General for Scotland, 1972-78, and the Statistical Reports of the Greater Glasgow Health Board (GREATER GLASGOW HEALTH BOARD 1980) and unpublished sources (data held by the Information Services Unit of the Greater Glasgow Health Board). Amongst the latter were ad hoc tabulations of data provided by the Registrar General for Scotland to the Board, and ad hoc tabulations of SMR2 (Maternity Discharge Form) data.

VII. METHODS 2. THE FRAMEWORK FOR THE ANALYSIS OF THE DESCRIPTIVE, AETIOLOGY AND PREVENTION STUDIES

The data required for all three studies were either recorded prospectively by the Glasgow Register of Congenital Malformations or were available retrospectively from hospital case-records. The methods of data collection and processing have been described (V. and VI.).

The general principle underlying all of the statistical analyses was to present the results in the form which related numerators to denominators. Where a control population was required, such as in testing aetiological hypotheses, the total birth population was employed.

7.1. THE ANALYSIS OF THE DESCRIPTIVE DATA

To obtain estimates of prevalence, numerators and demoninators were transformed into annual rates per 1,000 total (live and still) births. The "time" analysis required the calculation of prevalence rates for :

(a) Glasgow, 1972-78, the period being treated as a single unit for comparison with an earlier period;

(b) Glasgow 1972-78, the annual rates being calculated and examined for evidence of a secular trend; and

(c) Glasgow, 1972-78, the period being disaggregated into quarter of birth and examined for evidence of a seasonal trend.

The "place" analysis required the calculation of prevalence rates for :

(a) Glasgow, 1972-78, the period being treated as a single unit for comparison with other geographical locations; and

(b) the five Health Districts of the Greater Glasgow Health Board in a search for evidence of an uneven geographical distribution within the city.

The "person" analysis required either the calculation of prevalence rates in terms of certain personal characteristics or the comparison of the distribution of those personal characteristics in the numerator and denominator populations. The personal characteristics were : the sex of the fetus, whether the fetus was liveborn or stillborn, the weight of the fetus, the gestational age at delivery and the presence of other congenital defects.

In the analysis, the defects were treated both separately (as anencephalus and spina bifida) and together (as anencephalus or spina bifida : "A.S.B."). Account was taken of the antenatal screening programme by including terminated pregnancies (which were assumed to have been likely to deliver at 37 weeks gestation had they proceeded to term) in the analyses where appropriate.

7.2. THE ANALYSIS OF THE AETIOLOGICAL DATA

Prevalence rates were calculated in terms of the following variables : maternal age at delivery, maternal parity (previous livebirths and stillbirths at delivery), maternal social class (derived from the Registrar General's classification I. to V.) and place of maternal residence at birth defined in terms of Health Districts and twelve groupings of Glasgow post-code sectors. The latter were selected on the basis of geographical contiguity and, as far as possible, social homogeneity (APPENDIX 4). The data were examined for evidence of trends within these variables. The geographical distribution of affected births was also examined in conjunction with the possible confounding effects of the other three variables by means of a multiple regression analysis. In addition, the interactions of maternal age and parity and of social class and place of residence were observed. All of these analyses were designed to test the hypotheses presented earlier (3.2.2.). Termination data were included in all of the aetiological analyses.

7.3. THE ANALYSIS OF THE PREVENTION STUDY

The prevalence rates of anencephalus and spina bifida over the study period (1972-78) were analysed in terms of :

(a) the birth prevalence of the defects; and

(b) the "expected" prevalence (births plus terminations).

This permitted an evaluation of the impact of the screening programme on the prevalence of the defects during the study period.

The distribution of maternal characteristics (age, parity, social class and place of residence) among women whose affected pregnancies had been terminated were compared with the distribution of the same characteristics among those delivering affected infants and any significant difference noted.

Finally, evidence was sought of a shift in the distribution of the survival characteristics of anencephalic and spina bifida fetuses following the introduction of screening in 1975.

VIII. RESULTS 1. THE DESCRIPTIVE STUDY

8.1. THE PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA IN GLASGOW, 1972-78.

In the study period (1972-78), there were 92,325 total births to Glasgow residents. The Glasgow Register of Congenital Malformations ascertained the following numbers (and prevalence rates) of anencephalic and spina bifida births (fetuses born at 28 weeks or more gestation) in those years :

Anencephalus : 168 births (1.82 per 1,000 total births)

Spina bifida : 242 births (2.62 per 1,000 total births)

Anencephalus and spina bifida ("A.S.B.") :

410 births (4.44 per 1,000 total births).

8.2. THE PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA IN TERMS OF TIME, PLACE AND PERSON

8.2.1. "Time"

The time trends in prevalence were examined at three levels : secular, annual and seasonal.

Evidence of a secular trend was sought by comparing the prevalence found in the present study with that reported in an earlier Glasgow study by WILSON (1970) who also drew upon multiple sources of ascertainment. As indicated in TABLE 4, there was a statistically significant decline ($P < 0.001$) in the prevalence of anencephalus but not of spina bifida.

The annual changes in prevalence within the study period itself are shown in TABLE 5. There was a marked decline in the prevalence of anencephalus, particularly between 1975 and 1978, but a less clear decline in the prevalence of spina bifida.

These data were analysed statistically by means of a linear regression analysis. This enabled a straight line to be fitted mathematically to a set of data expressed in terms of a scattergram of pairs of observed values (x , y) plotted on the abscissa and ordinate respectively.

The equation of a straight line is

$$y = a + bx$$

where 'a' is the intercept and 'b' is the slope of the line.

Regression lines were fitted to the anencephalus and prevalence data as shown in FIGURE 5. Two points should be noted : first, there was less year to year fluctuation in the prevalence of anencephalus than in the prevalence of spina bifida; second, the downward slope with time of the anencephalus regression line was statistically significant ($P < 0.001$) while the slope of the spina bifida regression line was not.

The seasonal variation in anencephalic and spina bifida births is shown in TABLE 6. There appeared to have been an excess of anencephalic births in the late summer (July - September) and an excess of spina bifida births in the late winter (January - March), but in neither case did the deviation from the seasonal distribution of total births reach a statistically significant level.

The analysis was extended to include the 72 fetuses which had been terminated as a result of the ante-natal screening programme for the detection of neural tube defects. It was assumed that each terminated fetus would have delivered in the month of its "expected date of delivery" as recorded in the antenatal case-sheet. The seasonal pattern remained similar to that of affected births, and again did not deviate significantly from that of total births.

In the absence of sufficient data on the date of the last menstrual period, it was not possible to test for a seasonal trend in the conception rate.

8.2.2. "Place"

The relative position of Glasgow in the "league table" of worldwide series is shown in TABLE 7. The United Kingdom has consistently been reported to experience a higher prevalence than the continent of Europe or North America. Africa (with the exception of Alexandria) and Asia have lower rates still. Within the United Kingdom itself, Belfast has the highest prevalence while London has the lowest. Glasgow occupies an intermediate position.

The distribution of the maternal addresses of anencephalus and spina bifida deliveries around the five Health Districts of the Greater Glasgow Health Board was not significantly different from the distribution of total births (TABLE 8). When terminated fetuses (following antenatal screening) were included in the analysis, however, a statistically significant ($P < 0.05$) pattern in the distribution of anencephalus emerged, with the Northern District displaying the highest prevalence (3.2 per 1,000 total births), closely followed by the South Western and Eastern Districts (3.1 and 3.0 per 1,000 total births respectively); the South Eastern District had a much lower prevalence of anencephalus (1.3 per 1,000 total births). The pattern of distribution of spina bifida "pregnancies" was rather different, the highest prevalence being observed in the Eastern District and the lowest in the South Western District, but the differences were not statistically significant (TABLE 9).

8.2.3. "Person"

The following personal characteristics of anencephalic and spina bifida fetuses and their mothers were examined :

the sex distribution of affected infants; whether the births were singleton or multiple, live or still; the birth weight distribution; the distribution of gestational age at delivery; and the presence or absence of other congenital malformations in the affected fetuses.

There was a highly statistically significant excess of females among anencephalic births ($P < 0.001$) and a significant excess of females among spina bifida births ($P < 0.005$) (TABLE 10). The female : male ratios (2.1 : 1 for anencephalus and 1.2 : 1 for spina bifida) remained fairly static over the seven years of the study period.

Of the 410 anencephalic and spina bifida fetuses, only three (0.7%) were delivered with a twin (TABLE 11). This represented a slightly lower frequency of twins than in Glasgow births as a whole for 1975-78 (the only period for which control data were available), but the numbers were too small to render a statistical inference meaningful.

The pattern of survival of anencephalic fetuses was very different from that of either spina bifida or total births (TABLE 12). Almost 90 per cent of the anencephalics were stillborn, in contrast with the 17 per cent of spina bifida births and the one per cent of all births which were stillborn. Ten per cent of both anencephalic and spina bifida births resulted in death within the first week of life, compared with only one per cent of all births. Only three (two %) of the anencephalic fetuses survived beyond the first week compared with almost three-quarters (73%) of spina bifida and 98 per cent of all births.

As expected, there were striking differences between anencephalic births, spina bifida births and total births in the birth

weight distribution (TABLE 13). More than two-thirds (69%) of the anencephalic fetuses weighed less than 1500 grams, while only 16 per cent of spina bifida fetuses and one per cent of all fetuses were in the very low birth weight category. Conversely, a small minority (8%) of anencephalic fetuses were of "normal" birthweight (2,500 grams or more) in contrast with the large majority of both spina bifida and all fetuses (73% and 93% respectively) in this weight range.

The distribution of gestational age reflected, to some extent, the birth weight findings (TABLE 14). Two-thirds (65%) of anencephalic births delivered before 37 weeks; the proportions of spina bifida and total deliveries were both small (7% and 5% respectively) at this premature stage. About one-fifth of anencephalic births delivered between 37 and 41 weeks, while the majority of both spina bifida and total deliveries (76% and 93% respectively) delivered in this "normal" range. Deliveries beyond 42 weeks, a very small fraction (2%) of all births, were more frequent (approximately 17%) among the anencephalic and spina bifida births.

Twenty-four (14%) of the anencephalic fetuses and 48 (20%) of the spina bifida fetuses were known to have had other congenital malformations in addition to the neural tube defect. The frequency of associated malformations was not significantly different between anencephalus and spina bifida (TABLE 15). Only 20 (12%) of the anencephalic fetuses were reported to have had an associated spina bifida defect. The most frequently reported defects associated with spina bifida were deformities of the limb (26 defects). Other defects, including congenital heart disease and urinary tract anomalies, were much rarer (TABLE 16).

IX. RESULTS 2. THE AETIOLOGY STUDY

Because post-code sector denominator data on maternal age and parity were derived from one source (form SMR2) and social class from another (the Registrar General's Birth Register), it was not possible to cross-tabulate either maternal age or parity with social class. Account was taken of the possible confounding effects of all three variables on the geographical distribution of the affected births in the multiple linear regression analysis.

9.1. THE INFLUENCE OF MATERNAL AGE, PARITY, SOCIAL CLASS AND LOCALITY OF RESIDENCE

The age-specific and parity-specific distribution of anencephalus and spina bifida prevalence rates were "J-shaped" (FIGURES 6 and 7). The very high prevalence rates in the older age-groups and the higher parity groups were based, however, on relatively small denominators (TABLES 17 and 18). The association of anencephalus and spina bifida with maternal age and parity were both highly significant ($P < 0.001$).

Because maternal age and parity are highly correlated, the interaction between the two was analysed by means of crosstabulations (TABLES 19 and 20). The distributions by age and parity were strongly associated for both anencephalus and spina bifida ($P < 0.001$). By plotting the prevalence rates by age within parity groups (FIGURES 8 and 9) and the prevalence rates by parity within age groups (FIGURES 10 and 11), the parity effect was found to be stronger and more consistent than the age effect.

A distinct gradient of prevalence with maternal social class was evident, more marked for spina bifida ($P < 0.05$) than anencephalus ($P > 0.10$) (TABLE 21).

The distribution of the prevalence of anencephalus and spina bifida within Glasgow (subdivided into 12 post-code sector groupings) is shown in TABLE 22. Anencephalus and spina bifida were dissimilar in this respect, and in neither case did the geographical distribution deviate significantly from chance expectations until the defects were aggregated as "A.S.B." ($P < 0.05$).

To study the interaction between maternal social class and Health District of residence, a crosstabulation of data according to these two variables was prepared (TABLES 23 and 24). No statistically significant association was found. A similar analysis of social class distribution within post-code sector groupings similarly failed to reveal a statistically significant association, but the numbers in each cell were small (TABLE 25).

9.2. THE MULTIPLE LINEAR REGRESSION ANALYSIS

The possible confounding effects of maternal age, parity and social class on the geographical pattern of distribution of the defects were tested by an analysis of multiple linear regression.

The multiple regression equation may be expressed as :

$$Y = a + bX_1 + cX_2 + dX_3 + eX_4$$

where Y = the prevalence rate,

a = the intercept,

X_1 = the 12 post-code sector groupings,

X_2 = maternal age,

X_3 = maternal parity,

X_4 = the "denominator error", and

b, c, d and e = the regression coefficients.

TABLE 26 shows the component variables and data which were included in the analysis. The "cut off" points of maternal age, parity and social class were selected on the basis of the distributions of prevalence found when each variable was analysed independently. The "denominator error" was the difference in the number of total births derived from the two sources of denominator data, the maternity discharge form (SMR2) and the Registrar General's Birth Register.

The analysis yielded the following results. The only significant influence on the geographical distribution of anencephalus was parity (five or more), as indicated by the equation :

$$Y = 0.689 + 0.607\ X_3$$

[S.D. of coefficient = 0.236
t ratio = 2.58 (10 d.f.) $P < 0.05$]

Thus, parity (five or over) explained 34 per cent of the variance of anencephalus prevalence.

In the case of spina bifida, none of the variables contributed significantly to the geographical distribution.

The findings of the multiple regression analysis may be summarised as follows. Only maternal parity (five or more) contributed significantly to the geographical variance of anencephalus, while none of the variables contributed significantly to the geographical variance of spina bifida. In both cases, the numbers were too small to rule out the possible role of chance in determining the geographical pattern even after adjustment, in the case of anencephalus, for high parity.

X. RESULTS 3. THE PREVENTION STUDY

10.1. THE IMPACT OF ANTENATAL SCREENING ON THE PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA

TABLE 27 shows the birth prevalence, termination rate and "pregnancy prevalence" (births and terminations) of anencephalus between 1972 and 1978. The considerable impact of the 59 terminations on the prevalence rate was reflected by a statistically significant difference ($P < 0.05$) between the distribution of anencephalic births and "pregnancies" over the study period. Moreover, the decline in the prevalence over time all but disappeared when the terminations were included. A linear regression analysis of the "pregnancy" data yielded the following equation :

$$Y = 4.94 - 0.033\ X$$

(Standard deviation of the regression coefficient = 0.087,

t ratio = - 0.38, $P > 0.10$, NS).

In other words, all of the decline in the prevalence of anencephalus was due to the increasing number of terminations following alpha-fetoprotein screening.

The much smaller number of terminations of spina bifida resulted in the birth prevalence and "pregnancy" prevalence remaining similar (TABLE 28). Neither the difference between the birth and pregnancy distribution nor the regression of the "pregnancy prevalence" on time reached statistical significance. The impact of antenatal screening on the prevalence of spina bifida was therefore minimal.

10.2. THE MATERNAL CHARACTERISTICS OF TERMINATED AND UNTERMINATED FETUSES

Births of affected infants and terminations following antenatal screening were compared with respect to maternal age, parity, social class and Health District of residence. No statistically significant differences were observed in the distribution of maternal age (TABLE 29), social class (TABLE 30) or Health District of residence (TABLE 31). The difference in the parity distributions was, however, statistically significant ($P < 0.05$) suggesting that the high-risk high parity group was under-represented among terminations (TABLE 32).

10.3. THE SURVIVAL OF ANENCEPHALIC AND SPINA BIFIDA FETUSES, 1972 - 74 AND 1975 - 78.

There was no evidence of a statistically significant change in the survival patterns of anencephalic or spina bifida fetuses following the commencement of antenatal screening for neural tube defects in 1974-75 (TABLES 33 and 34).

XI. DISCUSSION 1. THE DESCRIPTIVE STUDY

11.1. LITERATURE REVIEW

The descriptive epidemiology of anencephalus and spina bifida is most conveniently considered under three headings : time, place and person.

11.1.1. "Time" Studies

Changes in the prevalence of the defects with time are of two basic types : long-term (or secular) changes, and short-term (or seasonal) ones.

Since the description by NAGGAN (1969) of the decline in the prevalence of anencephalus and spina bifida in Boston, Massachusetts, over the period 1930-65, there have been several reports consistent with a long-term epidemic pattern. MACMAHON and YEN (1971) extended Naggan's observations to cover the years 1875 to 1965 in Providence, Rhode Island and Boston. They demonstrated a rising prevalence until 1930-34 when a peak rate (for both defects combined) of 5.95 per 1,000 births was reached followed by a steady decline until the early 1950's. A peak rate of 4.5 per 1,000 in 1931-34 also occurred in Rochester, New York (BIGGAR, MORTIMER and HAUGHIE 1976). JANERICH (1973) found a decline in prevalence in New York State from 1945 similar to that of Boston and Providence. ELWOOD, J.M. and ELWOOD, J.H. (1980) studied mortality rates in the Canadian provinces and concluded that the trends in Ontario closely paralleled those of Boston, Providence and New York State. In the other provinces, a later peak occurred in the 1950's followed by a downward trend (except in British Columbia). In their study of 14

Canadian cities, ELWOOD, J.M. and ELWOOD, J.H. (1980) confirmed that a decline in mortality rates had taken place between 1950 and 1970. The greatest fall (68 %) affected female first births with similar decreases observed in later female births (42 %), later male births (38 %) and male first births (28 %).

Fewer British data on secular trends are available but ELWOOD(1973) reported a steady rise in the prevalence rate in Dublin since 1900 with two peaks in 1938-41 and 1960-61. LECK and ROGERS (1967) drew attention to the similarity of the trends in Dublin, Scotland and Birmingham, where peaks occurred twice (1940-43 and 1956-61) in all three locations over a thirty-year period (1936-65). Overall, there appears to have been an increasing prevalence since 1900 in the British Isles, peaking in the early 1940's and late 1950's, and subsequently declining in recent years.

Reports from other parts of the world show an inconsistent secular pattern, with some countries, such as Israel (NAGGAN 1971) and Holland (ROGERS and WILKIN 1978) experiencing broadly similar secular trends to those of the British Isles and North America, and others not, such as Hungary (CZEIZEL and REVESZ 1970) and Chile (CRUZ-COKE 1972).

The secular trends reported in the literature may be summarised as follows : there appears to have been an increase in prevalence in the British Isles and North America since 1900 until approximately the 1930's and 1940's subsequent to which the prevalence tended to decline, with the exception of a second peak (or series of peaks) in the 1950's and 1960's. Anencephalus and spina bifida did not appear to diverge greatly in prevalence trends. Female first born may have been particularly

affected by the secular changes. Data from other countries are sparse and do not appear consistent with the North America and British reports.

Explanations of the secular trend are highly speculative. An infectious agent, such as Influenza A virus (COFFEY and JESSOP 1959), has been suggested but the lack of correlation between three Birmingham influenza epidemics and an increased prevalence of central nervous system abnormalities (LECK 1963) is strong counter-evidence. MACMAHON and YEN (1971) drew attention to the superficial correspondence in time of the Boston peak rates of anencephalus and spina bifida with the financial crash of 1929 and the passage of the Prohibition Amendment to the United States Constitution in 1920. Both BAIRD (1974) and JANERICH (1974) suggested a generational effect whereby mothers born and brought up during periods of severe economic adversity became more vulnerable to conceiving an affected child. The hypothesis propounded by RENWICK (1972) that the causal agent resided in blighted potatoes was an attractive one, but has not survived the doubts cast by repeated contrary findings and by potato avoidance trials (ELWOOD, J.M. and ELWOOD, J.H. 1980; NEVIN and MERRETT 1975).

As well as displaying long-term, secular trends, the prevalence of anencephalus and spina bifida appears to vary according to a characteristic seasonal pattern. In an early study, McKEOWN and RECORD (1951) found a winter excess of affected births in Birmingham and Scotland. Similar findings have been reported from Glasgow (WILSON 1971), Belfast (ELWOOD 1970), London (CARTER and EVANS 1973) and Sweden (SANDAHL 1977), but in South Wales (LAURENCE, CARTER and DAVID 1967) and Aberdeen (ELWOOD and MACKENZIE 1971), a summer excess of anencephalic

births was described. An Australian study reported a statistically significant spring excess of spina bifida births (PARKER 1978), and several North American studies failed to detect any significant seasonal trend. ELWOOD, J.M. and ELWOOD, J.H. (1980), however did find a winter excess of anencephalic births in Canada in the years 1954-62 but not between 1963 and 1972. The winter excess in the earlier period was virtually confined to first births. A diminishing seasonal trend over time has also been reported in Birmingham (LECK and RECORD 1966), Scotland (FEDRICK 1976b) and England and Wales (ROGERS and WEATHERALL 1976).

The seasonal pattern of anencephalus and spina bifida births has, along with the secular pattern, defied satisfactory explanation. Diet, climate and infection have been investigated with conflicting and hence inconclusive results. One of the major obstacles is methodological: most statistical tests for seasonality have insufficient power to detect a significant trend unless the amplitude of the trend is large (WALTER and ELWOOD 1975). Since most studies have applied standard χ^2 tests to relatively small sample sizes displaying small seasonal fluctuations, inconsistent results are almost inevitable. In addition, the extrapolation of birth dates to conception dates may be misleading, and analyses based on the date of the last menstrual period are probably more likely to yield worthwhile results (ROGERS and WEATHERALL 1976). The apparent lability of seasonality over time and in different locations may therefore be partly artefactual.

11.1.2. "Place" Studies

Geographical variation is one of the most consistent features of the descriptive epidemiology of anencephalus and spina bifida. The prevalence varies between continents, countries, regions, cities, towns

and villages.

TABLE 7 (in Chapter VIII) lists several studies in various parts of the world which have reported the prevalence of both defects. They are ranked according to the combined ("A.S.B.") prevalence rates. As noted previously, the United Kingdom appears to have experienced the highest prevalence in the world, with a gradient of increasing prevalence from the South-East of England to the North-West of the country. A similar gradient has been described in Europe, where PENROSE (1957) observed areas of higher prevalence in Brittany, Normandy, Holland and Denmark. Within North America, the prevalence increases from West to East (HEWITT 1963; KURTZKE, GOLDBERG and KURLAND, 1973). In South America, the Far East and Africa, the prevalence is relatively low, while in the Middle East higher rates have been observed occasionally; in particular, the World Health Organization's international study revealed a high rate (3.8 per 1,000 births for anencephalus and 1.7 per 1,000 births for spina bifida) in Alexandria's Shatby hospital (STEVENSON et al. 1966). In high prevalence areas, the ratio of spina bifida prevalence to that of anencephalus is usually around one, but tends to be much lower in low prevalence areas, possibly because of the greater difficulties in ascertaining spina bifida.

Geographical variations have also been found on analysing the distribution of prevalence within relatively small populations and areas. In Scotland, for example, FEDRICK (1976b) confirmed the earlier finding of EDWARDS (1958) of a higher rate in the lowlands than in the highlands. LAURENCE, CARTER and DAVID (1967) described a rising west-to-east gradient of prevalence in South Wales, and WILSON (1971) drew attention to area differences in the prevalence rate within Glasgow. Clustering

in space and time has been reported in England (PLEYDELL 1960; AYLETT 1974), but studies in Glasgow (FEDRICK and WILSON 1971), Cardiff (ROBERTS, LAURENCE and LLOYD 1975) and the United States (TRICHOPOULOS et al. 1971) have failed to identify significant clustering.

The possible reason for the striking geographical patterns are speculative and fall into three main categories : methodological, genetic and environmental. The most important methodological determinant of varying prevalence estimates is incomplete ascertainment. As LECK and RECORD (1963) pointed out, the ascertainment of congenital defects appears to be negatively correlated with the size of population under observation. NAGGAN (1976) has stressed the importance of "active" ascertainment procedures by highly-motivated research workers as opposed to "passive" case-finding by means of questionnaire surveys or routine data collection. The former method generally achieves a more complete level of ascertainment than the latter, even when the defect ought to be easily identifiable from routine sources. Conversely, prevalence may be overestimated if the numerator is drawn from a larger population than the denominator: this may have occurred in the case of the Alexandria study (STEVENSON et al. 1966). The geographical data are highly suggestive of a genetic role in susceptibility to the defects. The British pattern, for example, would seem to indicate that individuals of Celtic origin are at high risk. Migrant studies, however, have undermined this hypothesis. In Canada, the maternal county of origin (whether Ireland, Scotland, Wales or England) appears to have made little impact on the prevalence rate in their offspring (ELWOOD, J.M. and ELWOOD, J.H. 1980). Studies in Boston (NAGGAN and MACMAHON 1967) and Israel (NAGGAN 1971) have also demonstrated the modification of the

risk to immigrants in a new environment. Specific environmental aetiological factors, however, have yet to be identified despite the evidence pointing in their direction. A dietary cause has been suspected for many years, possibly related to potato consumption (RENWICK 1972), vitamin deficiency (SMITHELLS, SHEPPARD amd SCHORAH 1975) or poverty (BAIRD 1974). In a multiple regression analysis of data on 36 Canadian cities, ELWOOD, J.M. and ELWOOD, J.H. (1980) were able to explain 44 per cent of the total variation in terms of two factors : the magnesium concentration in drinking water and income. The aetiological significance of these findings is not clear.

11.1.3. "Person" Studies

The personal characteristics relevant to the present study are sex, whether singleton or multiple births, whether live or still birth, birth weight, gestation and the presence of associated malformations. (Maternal age, parity, social class and place of residence are discussed elsewhere).

At birth, females are more often affected by anencephalus and spina bifida than males. In their review of 40 study areas, ELWOOD, J.M. and ELWOOD, J.H. (1980) confirmed the observations of SEARLE (1959) and NAGGAN (1971) of an inverse relationship between the male proportion (ranging from 0.23 to 0.46) of anencephalus and the prevalence at birth. The sex ratio was less marked in 21 spina bifida series, and no relationship with prevalence was found. Curiously, the relationship between sex ratio, prevalence and geography in anencephalus was confined to the British and European studies. The male proportion appears also to be correlated with gestational age

and birth weight, and is therefore usually higher in infant deaths than in stillbirths. There appears to have been an increase in the male proportion of anencephalus over time in Britain (ROGERS and MORRIS 1973) and Canada (ELWOOD, J.M. and ELWOOD, J.H. 1980) as the prevalence rates have declined.

Explanations for the characteristic sex ratio are numerous but inconclusive. A differential abortion rate is an obvious possible cause and the few studies of early abortuses lend some support for this view (CREASEY and ALBERMAN 1976; BELL and GOSDEN 1978). Other hypotheses include a sex-specific vulnerability to gonadotrophin deficiency, as proposed by JANERICH (1975) and sex-linked genetic models, such as that of KNOX (1970), who envisaged an interaction between unlike-sex dizygous twins whereby an environmental trigger would result in the female "attacking" and subsequently absorbing the male. This model predicted an association between the dizygous twinning rate and the prevalence of neural tube defects, a phenomenon for which there is little or no evidence (ELWOOD 1976; JAMES 1979). Most twin studies are difficult to evaluate because, as YEN and MACMAHON (1968) have observed, zygosity is seldom determined, the numbers are inevitably small, and adjustment for age and parity is rare. CARTER (1974) has stated that while twin studies are unlikely to clarify the role of genetic factors, the existing evidence (including a lack of twin pairs concordant for neural tube defects and a lower twin-rate in the index cases of large series than in the general population) tends to undermine a genetic hypothesis.

The vast majority (80-98 per cent) of anencephalic infants are stillborn although the proportion appears to vary from one area to

another (ELWOOD and MACKENZIE 1971). Between 75 and 85 per cent of spina bifida infants are liveborn. In Canada, an increasing proportion of anencephalic deaths have been registered as infant deaths rather than stillbirths in recent years (ELWOOD, J.M. and ELWOOD, J.H. 1980). A similar phenomenon has been observed in England and Wales (BRADSHAW, WEALE and WEATHERALL 1980).

Data on the birth weight distribution of anencephalus and spina bifida births are few. CZEIZEL and REVESZ (1970) reported that more than 80 per cent of anencephalus and 20 per cent of spina bifida infants weighed less than 2,500 grams (compared with 11 per cent of all Hungarian births). Gestation, which is closely related to birth weight and is partly a reflection of the presence or otherwise of hydramnios, has attracted more attention. MILIC and ADAMSON (1969) described a series of 66 anencephalic pregnancies with a significantly shorter mean gestation than a large control group. Moreover, the anencephalic pregnancies exhibited a bimodel pattern with 44 significantly shortened and 22 significantly prolonged. A similar pattern was reported by ELWOOD, J.M. and ELWOOD, J.H. (1980). Neither of these two studies included data on spina bifida births.

Anencephalus and spina bifida frequently occur together, although precise figures may be misleading because of the tendency to omit mention of spina bifida when anencephalus is recorded. A study in Wales found that nine per cent of anencephalic and 15 per cent of spina bifida fetuses had defects outside the nervous system (ROBERTS and POWELL 1975). A necropsy series of 294 anencephalics found a much higher proportion (41 per cent) with associated defects of other systems. The most commonly associated defects were urogenital, cardio-vascular and gastro-intestinal anomalies (DAVID and NIXON 1976).

11.2. COMMENT ON THE FINDINGS OF THE DESCRIPTIVE STUDY

The prevalence rates of anencephalus and spina bifida (1.82 per 1,000 births and 2.62 per 1,000 births respectively over the period 1972 to 1978) confirm the previous finding of WILSON (1970) that Glasgow is a relatively high prevalence area. Since that earlier study of the years 1964 to 1968, there was a marked and statistically significant decline in the prevalence of anencephalus. Spina bifida declined minimally in prevalence. This trend may also be observed in the prevalence of the defects within the seven years of the study period itself. As described elsewhere (in 10.1.) this was almost entirely due to the operation of the programme of antenatal screening for neural tube defects which commenced in May 1975. A consequence of the sharp fall in the anencephalus prevalence rate was the associated fall in the ratio of anencephalus to spina bifida from 1.01 (the usual figure in western countries) to 0.69. In oriental and other low-prevalence communities, the ratio of anencephalus to spina bifida is usually much higher, possibly because the ascertainment of anencephalus is easier and hence more complete.

The seasonal variation in affected births did not deviate significantly from all births, but the apparent winter excess of spina bifida births is consistent with most published British analyses, including that of WILSON (1971) in Glasgow. The excess of anencephalic births in the summer months has occasionally been reported elsewhere, but the change from a winter excess (observed in the earlier Glasgow series) to a summer excess (observed in the present study, though not achieving statistical significance) was unexpected. The seasonal trend, however, is one of the features of the epidemiology of these defects which is inexplicably labile in time and place.

By world standards, Glasgow must be considered a high prevalence area, yet within the United Kingdom it occupies an intermediate position. As the antenatal screening programme becomes more firmly established locally, Glasgow may experience a decline in the prevalence of anencephalus substantial enough to bring it into line with the relatively low rates of the South and East of the country. The speed with which this process might occur is impossible to predict since it is dependent on so many factors related to the validity, acceptability and efficiency of screening.

The distribution of affected births (or pregnancies) around the five Health Districts does not conform to any obvious pattern of social or environmental characteristics. In general, the most economically deprived conditions are to be found in the Eastern District, in which an excess (though not a statistically significant one) of mothers of spina bifida infants resided at the time of birth; the distribution of mothers of anencephalics deviated significantly from the total birth population, but the Northern District had the highest prevalence rate in this case. The fact that anencephalus and spina bifida mothers were distributed differently around the city might suggest a different aetiology for each defect. On the other hand, WILSON (1971) found an excess of both defects in the Eastern part of the city in 1964-68. It is therefore difficult to draw any firm conclusion from the District data.

The high proportion of females affected, particularly by anencephalus, is consistent with most reported series, as is the lower twinning rate than that of the control population.

The high proportion of anencephalic fetuses which were stillborn accords with experience elsewhere; the proportion of spina bifida fetuses which were stillborn is slightly lower than that reported in most studies. In comparison with the earlier Glasgow series, the figures suggest a modest trend towards an "improved" survival rate for both defects. Possible reasons for this include more vigorous perinatal care, a diminishing reluctance to acknowledge the presence of life in a grossly deformed fetus and the selecting out of the more extensive (and lethal) lesions by antenatal screening. This last hypothesis is explored further in the Prevention Study (13.2).

The predominance of very low birth weight anencephalic fetuses (69 per cent weighing less than 1500 grams) is scarcely surprising in view of the absence of a substantial quantity of cerebral and skull tissue, as well as the well known association of anencephalus with hydramnios. The distribution of birth weight in spina bifida fetuses was closer to normal. The distribution of gestational age paralleled the birth weight findings. Data on both birth weight and gestation are relatively rare in the literature, particularly in the case of spina bifida, and these data help to remedy this deficiency.

Estimates of the frequency of associated congenital defects outside of the central nervous system vary depending on the thoroughness with which the fetuses are examined. The present study is fairly typical of non-necropsy series which report between ten per cent and 20 per cent of affected infants having associated defects. Necropsy series usually report higher proportions, but they are often based on samples which are not representative of neural tube defects as a whole.

Taken as a whole, the Descriptive Study achieved both its main objective, to establish the prevalence of anencephalus and spina bifida in Glasgow over the study period, and its subsidiary objectives. Despite numerous problems of interpretation, the data offer some useful insights into several important epidemiological characteristics, trends and hypotheses.

11.3. CRITIQUE OF THE METHODOLOGY OF THE DESCRIPTIVE STUDY

The evaluation of any research findings must be tempered by an appreciation of the extent and seriousness of methodological weaknesses which might generate misleading data and hence ill-founded conclusions. This section attempts to assess the methodology of the Descriptive study with a view to highlighting particular problems and limitations associated with the collection, analysis and interpretation of the data.

11.3.1. General Methodological Constraints

These arose out of two factors : the basic source of data for the study and the objectives of the study.

The source of data was, essentially, the Glasgow Register of Congenital Malformations. Although neural tube defect data had been collected prospectively it was necessary to establish retrospectively which aspects of the data to include in the study and which to exclude. Consequently, flexibility in the choice of data was minimal. Similarly, the choice of variables for analysis was limited by the use of total birth data (from the Registrar General and other routine sources) as the "control" population.

The objectives of the study were formulated in such a way as to require an extremely broadly-based analysis of the selected variables without a rigorously defined framework within which to test specific hypotheses. Consequently, the power of most of the analyses to test aetiological hypotheses was limited despite the relevance of many of the data to aetiology.

11.3.2. Specific Methodological Constraints

1. Validity of the Data

The validity of the data on neural tube defects recorded by the Glasgow Register of Congenital Malformations was investigated by both HAGARD (1977) and STONE (1979) and found to be high. Hagard, however, examined data derived mainly from the West of Scotland antenatal screening programme which at that time only screened about half of the pregnant population. Stone used several methods of validation, but most of these involved either "defects of the central nervous system" as a whole, or spina bifida alone. The generally high level of validity reported by these studies, however, was confirmed by repeated attempts of the Registry staff to ascertain "missed" cases from hospital records, post-mortem reports and the local register of stillbirths and infant deaths. These searches yielded virtually no new information.

The denominator data were assumed to be valid. One potential source of error was the denominator change which took place in 1974 following the reorganisation of the National Health Service. It is possible that estimates of total births might have contained inaccuracies shortly after the reorganisation but these were likely to have been small. An additional source of difficulty was the slightly different composition of the population at risk consequent upon the enlargement of the City of Glasgow boundary to become the Greater Glasgow Health Board boundary. Since the impact of this change on the estimated prevalence rates of most other defects recorded by the Registrar was indiscernible, the effect on the neural tube defect prevalence rate was believed to be negligible also.

A more detailed account of the validation study conducted by STONE (1979) may be found in APPENDIX 2.

2. Statistical Confidence in the Prevalence Estimates

In order to interpret the importance of annual fluctuations in prevalence rates, or of different prevalence rates in different variable categories, account must be taken of the numerical size of the observed phenomena and of the role chance may play in the variations. The smaller the numbers, the more difficult it becomes to interpret changing rates. Even when the numbers appear substantial, the confidence limits (the range within which the "true" value has a given probability of lying) may be surprisingly wide (TABLE 35). On the other hand, increasing the size of the observed population may be counterproductive in terms of completeness of ascertainment (LECK and RECORD 1963). This is one of the few situations where statistical and epidemiological requirements appear to conflict. In the present study, it was felt that a reasonable compromise had been achieved.

3. "Time" Analyses

The period 1972-78 was probably too short a time within which to detect a significant secular trend, unless some dramatic short-term effect (such as antenatal screening) had occurred. More helpful in this respect was the existence of data from a previous study performed ten years earlier. The brevity of the time-scale and the consequent small numbers also excluded the possibility of undertaking more sophisticated analyses of the interaction between several relevant variables over time, such as maternal age, parity and birth cohort.

The seasonal analysis was deficient in three respects. First, season of birth is less important than season of conception; the latter requires the availability of information on the "last menstrual period" which was not available. Second, the use of three-monthly quarters is an unsatisfactory substitute for a monthly analysis, but the latter requires a reasonable number of cases in each month. And third, standard χ^2 testing is an extremely crude method of testing for a seasonal trend in comparison with the methods which have been developed in recent years (WALTER and ELWOOD 1975).

4. "Place" Analyses

Geographical analyses are difficult to interpret when data have been collected in different locations by different workers at different times. Differences in methods and completeness of ascertainment, definitions, classification and analysis may produce spurious differences or obliterate real ones. And Health Districts were created in 1974 as administrative entities which were neither internally homogeneous nor identifiable as distinct communities. Differences between them are difficult to correlate with known geographical features. These geographical comparisons, whether at international, regional or local level, must be regarded with circumspection.

5. "Person" Analyses

The very small number of multiple births in the series raises doubts about the validity of this finding although other studies have reported low twin rates in index cases. Of particular interest, from a genetic perspective, is the zygosity of affected

twins but this information was not available.

The tendency for some grossly defective living fetuses to be described as "stillborn" has been noted, although quantification of this practice is clearly difficult.

The birth weight data may or may not be accurate. A more fundamental criticism of the data is the difficulty in identifying any substantial theoretical or practical purpose to which such information might be put.

Finally, the frequency and nature of associated defects can only be established with certainty by subjecting every affected live and stillborn infant to a thorough examination and recording all of the findings carefully. Even the most painstaking clinical or pathological assessment will fail to reveal every associated abnormality, however. The rewards, scientifically or clinically, would scarcely be worth the effort even if such a study were mounted.

XII. DISCUSSION 2. THE AETIOLOGY STUDY

12.1. LITERATURE REVIEW

12.1.1. Maternal Age and Parity

Since they are highly correlated with each other, maternal age and parity are considered together.

Studies of the effect of these variables on the prevalence of anencephalus and spina bifida may be divided into three groups. The first and largest group has reported a U-shaped distribution of risk with maternal age and parity; in other words, the highest prevalence rates were found in the young, low-parity mothers and in the old, high-parity mothers with those in the intermediate ranges experiencing the lowest rates. Most of the British and some of the North American data conform to this pattern, and include those of RECORD and McKEOWN (1949) from Birmingham, EDWARDS (1958), RECORD (1961), FEDRICK (1976b) from Scotland, CARTER and EVANS (1973) from London, CARTER, DAVID and LAURENCE (1968) from Wales, FEDRICK (1970) from England and Wales, HOROWITZ and MACDONALD (1969) from Quebec, INGALLS, PUGH and MACMAHON (1954) from Rhode Island, and ELWOOD, J.M. and ELWOOD, J.H. (1980) from Canada. Several authors have concluded that the parity effect is the stronger of the two, including RECORD and McKEOWN (1949), INGALLS, PUGH and MACMAHON (1954) NAGGAN and MACMAHON (1967) and ELWOOD, J.M. and ELWOOD, J.H. (1980). From data on 491 singleton anencephalic and 16,994 control births generated by the 1958 Perinatal Mortality Study of England and Wales, FEDRICK (1970) observed a bimodal pattern whereby young low-parity mothers and old high-parity mothers were at higher risk. ELWOOD J.M. and ELWOOD, J.H. (1980), using data drawn from 14 Canadian

cities, were able to examine the components of "parity" (namely previous livebirths and previous stillbirths) separately and found that a history of previous livebirths lowered the risk while previous stillbirths increased it.

The second group of studies have reported either a linear increase in risk with age and parity, or an increased risk associated with only one of the two variables. In this category are the findings of COLLMAN and STOLLER (1962) in Australia, NAGGAN and MACMAHON (1967) in Boston, Massachusetts, NAGGAN (1971) in Israel, WILSON (1971) in Glasgow, and GRANROTH, HAAPAKOSKI and HAKAMA (1978) in Finland.

The third group of studies appears to challenge the findings of the first two groups. FEDRICK (1976a), FRÉZAL et al.(1964) and ANDERSON, BAIRD and THOMSON (1958) all described an excess prevalence in younger, low-parity mothers only.

In order to assess and interpret these conflicting results, it is important to attempt to exclude possible sources of error as a result of the use of varying definitions of "parity". The observation of ELWOOD, J.M. and ELWOOD, J.H. (1980) of the divergent effects of previous livebirths and stillbirths on prevalence is relevant. Since most studies fail to define parity, the assumption that previous stillbirths are always included may not be justified.

Another pitfall of these data is to draw erroneous aetiological inferences from the age and parity relationships with prevalence revealed by cross-sectional studies. JANERICH (1974)

reanalysed cross-sectional New York State data, which had shown a U-shaped age-prevalence relationship, in terms of cohort-specific or longitudinal rates and demonstrated a declining risk with maternal age. The apparently increasing risk with maternal age suggested by the cross-sectional analysis was an artefact produced by the progressively higher age-specific risk experienced by each succeeding elder cohort. This phenomenon would only hold for areas of declining prevalence, however. The influence of parity, too, may be distorted by relying on cross-sectional data. BAKKETEIG and HOFFMAN (1979) analysed Norwegian birth data longitudinally and demonstrated that the U-shaped relationship of perinatal mortality to parity was an artefact of the cross-sectional approach. Perinatal mortality actually fell with parity within cohorts of mothers based on sibship size. The artefact was caused by the progressively increasing risk (independent of parity) of successive sibship-size cohorts. JAMES (1969) suggested that the risk of anencephalus declined with increasing parity within sibship cohorts, and in British Columbia ELWOOD, J.M. and McBRIDE (1979) found similar results for anencephalus and spina bifida combined. These results are consistent with the observations of ELWOOD, J.M. and ELWOOD, J.H. (1980) who found that a history of previous livebirths exerted a "protective" effect compared with a history of previous stillbirths, and with the known tendency to become pregnant again after an adverse outcome of earlier pregnancies (RECORD, R.G. and ARMSTRONG 1975).

The relationships between maternal age, parity and the prevalence of anencephalus and spina bifida are therefore extremely complex. Maternal date of birth and sibship cohort analyses have

illustrated the limitations of cross-sectional data. Aetiological models which might explain some of the observations are of two main types, "biological" and "social". The "biological" models seek to integrate the epidemiological association of neural tube defects and parity with events presumed to take place at the cellular level *in utero*. KNOX (1974) extended his original fetus-fetus interaction hypothesis to include the possibility that residual trophoblastic material from a previous pregnancy might interact with the affected pregnancy. A similar line of thought was pursued by CARTER, DAVID and LAURENCE (1968) and CLARKE *et al.* (1975) who presented evidence that there were always more miscarriages and stillbirths before the affected children than immediately after. This is consistent with the earlier data of RECORD and McKEOWN (1950) who also observed an inter-pregnancy interval (prior to the affected child) which was shorter than expected. Support for the trophoblastic "rest" hypothesis also comes from a case-control study of GARDINER *et al.* (1978), who found a statistically significant excess of mid-line defects in children born to mothers whose previous pregnancy had ended in a spontaneous abortion compared with births to mothers who had had a normal previous baby. Data on sex ratio and twinning rates (discussed, for example, by ELWOOD, J.M. 1976, and ROGERS 1976) are relevant to the testing of these hypotheses since the deficiency of twins concordant for neural tube defects and the apparently preferential miscarriage rate of affected male fetuses also require explanation. Genetic models are worthy of consideration, since it is unclear whether the increased risk of neural tube defect is directly related to events arising out of previous pregnancies or whether this merely reflects a predisposition to both. Single gene, cytoplasmic and multifactorial inheritance have all been

advocated, but only the last is capable of contributing to an understanding of the maternal age and parity related risks of the defects.

The "social" models of aetiology imply that underlying social or environmental factors are operating on particular cohorts of women (who may, nevertheless, be genetically vulnerable) and that the maternal age and parity effects are secondary. In some support of this view are the analyses of JANERICH (1975) of New York State data, the Aberdeen studies of BAIRD (1974) and ANDERSON, BAIRD and THOMSON (1958), who suggested that mothers born in the years of the economic depression of the 1930's were at particular risk, as reflected by the high rates (and short stature) of these women. ELWOOD, J.M. and ELWOOD, J.H. (1980) also found high prevalence rates in 1925 and 1930 maternal birth cohorts in Canada. MACMAHON and YEN (1971) put forward a similar hypothesis as did EMANUEL and SEVER (1973). RENWICK (1972) accounted for the age and parity related risks in terms of the "potato-peeling implications" of large families with voracious appetites, although later work has not supported this interpretation. ELWOOD, J.M. and ELWOOD, J.H. (1980) pointed to the increased risk associated with primiparity as evidence against the cell rest hypothesis. They offered an alternative proposition that the higher rates observed in high total parity cohorts was a manifestation of an association between an adverse obstetric history and social, nutritional or other as yet unidentified factors. Indirect evidence in support of this view was the finding of a high proportion of low birth-weight infants in high sibship size cohorts in the study of BAKKETEIG and HOFFMAN (1979), combined with the known association of low birth weight with poverty (BERGNER and SUSSER 1970).

BAIRD (1974) found a correlation between the occurrence of central nervous system defects and low birth-weight among the offspring of mothers born in the economically depressed years of 1928-34. And much other evidence exists to implicate socio-economic adversity in the aetiology of neural tube defects. Some of this will now be discussed.

12.1.2. Maternal Socio-economic Status

The term "maternal social class" represents a rather ill-defined concept used as an approximate measure of the mother's socio-economic status. It is a composite index of occupation, social status and economic capacity and is insensitive to the varying balance of these characteristics in different individuals within the same social class and to changes in an individual's occupation over time. The usual five-fold classification of the English Registrar General appears crude and arbitrary; for example, "non-working" women are classified according to the occupation of their husbands or fathers. Yet despite its obvious shortcomings, the system has been found to be extremely useful in the study of many diseases.

A social class trend in the prevalence of anencephalus and spina bifida has been reported in most series in Britain, with social classes IV. and V. experiencing a risk between two to four times that of social classes I. and II. (EDWARDS 1958; FEDRICK 1970; WILSON 1971; RICHARDS, ROBERTS and LLOYD 1972; ELWOOD and NEVIN 1973; CARTER and EVANS 1973). Exceptions are the early Birmingham study of RECORD and McKEOWN (1949) and the later one of LECK (1972) in the same city. Although they used different systems of social classification to that of the Registrar General, NAGGAN and MACMAHON (1967) found a similar

trend in Boston as did HOROWITZ and MACDONALD (1969) in Montreal; in Boston, however, the trend was confined to non-Jewish subjects. NAGGAN (1971) also failed to observe a social class trend in Israel, but he emphasised the inadequacy of the system of classification he was obliged to use. No social class gradient was found in the Hungarian study of CZEIZEL and REVESZ (1970).

A social class trend in prevalence could reflect the confounding effect of other maternal factors such as maternal age, parity, ethnicity and place of residence. Several studies, including those of RICHARDS, ROBERTS and LLOYD (1972) and FEDRICK (1970) controlled for these without substantially affecting the social class gradient. The most favoured interpretation of the phenomenon is an environmental one, usually expressed in rather non-specific terms. Poor nutrition may be the important aetiological influence as proposed by BAIRD (1974); alternatively, an increased exposure to an environmental toxin at the place of work or in the home cannot be ruled out, and suspicion has been cast upon the paper and printing trades (FEDRICK 1976a), the rubber industry (AYLETT, ROBERTS and LLOYD 1974) and polyvinylchloride (PVC) manufacture (INFANTE 1976), although a case-control study could identify no increased risk of neural tube defect associated with exposure to PVC polymerisation (EDMONDS et. al. 1978). Infection, particularly with influenza, could affect social class V. more severely because of the likely association with overcrowding, but LECK (1963) found no evidence of an increase in the prevalence of neural tube defects after epidemics. He suggested that the association with the virus reported by COFFEY and JESSOP (1959) might indicate a lowered resistance to infection among women more liable to have affected

offspring, regardless of whether they actually acquire infections or receive treatment (LECK 1974).

In summary, the social class gradient in the risk of delivering an infant with anencephalus and spina bifida, which has been reported in most studies, awaits explanation. Any acceptable aetiological model must take account of the relative consistency of the observation.

12.1.3. Maternal Locality of Residence

This factor, which may be of fundamental aetiological importance, is discussed elsewhere (11.1.2. and 12.2.2.)

12.2. COMMENT ON THE FINDINGS OF THE AETIOLOGY STUDY

12.2.1. Maternal Age, Parity and Social Class

The "J-shaped" relationship displayed by both maternal age and parity with prevalence is consistent with the results of the first and largest group of studies discussed above. The strikingly higher risk found in the older, high-parity mothers has not been previously reported, however. The dominant effect of parity over age is also consistent with most other studies. The social class trend is similar to that observed elsewhere, although one might have expected a steeper gradient given the notorious extremes of socio-economic status to be found in Glasgow.

When these results are compared with those published by WILSON (1971), who studied neural tube defects in Glasgow for the birth years 1964-68, some intriguing differences may be observed. First, the association of anencephalus with maternal age was weakly "U-shaped" in 1964-68 while the association of spina bifida with maternal age was weakly negative; in contrast, in 1975-78, the pattern of association with maternal age was similar for both defects (FIGURES 12a and 12b). Second, the later study indicated a grossly increased risk in older, high-parity mothers compared with the earlier data (FIGURES 13a and 13b). Third, the social class trend for both defects was more marked in the earlier study (FIGURES 14a and 14b). Between the two study periods, substantial demographic changes had taken place, with an increase in the proportion of young (under 20 years) mothers, a decline in the proportion of older mothers (TABLE 36), an increase in the proportion of primiparous mothers and a sharp decline

in the higher parity mothers (four or more previous deliveries (TABLE 37). There was, in addition, an increase in the proportion of births in social classes I. and II. and a decline in the proportion of births in social classes IV. and V. (TABLE 38). The net effect of these changes on the prevalence of anencephalus and spina bifida appears to have been negligible (if the terminations resulting from screening are included in the prevalence estimates) in that the increased risk in the older, high-parity groups was offset by the smaller proportions of women in these categories. The reasons for the dramatic upward swing in the risk for these groups are not immediately apparent. The more important effect was exerted by parity, but why should high parity have carried a greater risk in 1975-78 than in 1964-68? Socio-economic factors may have been responsible, but the diminution of the social class gradient suggests that the answer lies elsewhere.

In pursuing this problem further, it is necessary to reflect upon the nature of parity. "Parity" in this study, was defined as the total number of previous deliveries, whether live or still. Thus, "multiparous women" may be regarded as consisting of two component groups : one having had a "good" obstetric history of several previous successful pregnancies, the other having had a "bad" obstetric history of previous pregnancies ending in miscarriage or stillbirth. (There is, of course, a third group of women whose obstetric experience is a mixture of "good" and "bad"). It is reasonable to assume that the growth of reliable contraception caused a greater diminution in the size of the first group of women than in the size of the second because of the greater probability of undertaking another pregnancy

after a stillbirth than after a livebirth (JAMES 1968). Thus, the high-parity group in 1975-78 may have contained a much higher proportion of women with a "bad" obstetric history than the high-parity group of 1964-68. But would this qualitative change in the high-parity group explain the increase in the risk of anencephalus and spina bifida?

The Canadian 14-city study of ELWOOD, J.M. and ELWOOD, J.H. (1980) suggests that it would. By separating the "previous livebirths" from "previous stillbirths" components of parity, they demonstrated that the risk of neural tube defect declined with previous livebirths and increased with previous stillbirths. The characteristic "U-shaped" relationship of parity and risk resulted from the amalgamation of these two distinct components. If the high-parity group of women in the 1975-78 study contained an unprecedentedly high proportion of the "previous stillbirth" component, and the ELWOOD, J.M. and ELWOOD, J.H. (1980) observation held for Glasgow, a greatly increased risk in the high parity group would have been expected.

The work of ELWOOD, J.M. and ELWOOD, J.H. (1980), JAMES (1969), RECORD and McKEOWN (1950) and others all points in a similar direction : mothers of affected infants have more pregnancies, shorter inter-pregnancy intervals, and more previous stillbirths and miscarriages than mothers of unaffected infants. Aetiological models which might explain this cluster of adverse obstetric factors are usually "biological" or "social" in nature, as previously discussed. The Glasgow data suggest that the secular increase in the risk of

high-parity women was not mediated through adverse socio-economic circumstances since the social class gradient became less steep over the same time period. The remaining hypotheses which might explain the findings include the following :

(1) that neural tube defects are caused by an internal "biological" (not excluding genetic) process in which a combination of high fertility and poor obstetric history plays either a primary or secondary role; and

(2) that the obstetric features merely reflect the influence of some external environmental factor, other than poverty, acting directly on the developing fetus.

In attempting to narrow the aetiological possibilities further, the role of one aspect of the local environment, namely locality of residence, will now be considered.

12.2.2. Maternal Locality of Residence

The Health District distribution of maternal residence (discussed in 11.2) shed little light on the potential role of intra-urban teratogens. Since the Health Districts were internally heterogeneous administrative entities, it was felt that the sub-division of the city into 12 post-code sector groupings might prove more useful. In fact, the distribution of anencephalus and spina bifida prevalence around these 12 units did not deviate significantly from a random distribution, except when the two defects were combined. This suggests that small numbers may have limited the statistical power of the analysis; unfortunately, the aggregated ("A.S.B.") data

were not particularly helpful because of the divergent pattern of distribution of each defect.

Rather than abandon the geographical approach, one relatively modest hypothesis was felt to be worth testing: that the intra-urban distribution of the defects might be due to (indeterminate) environmental factors rather than simply to the distribution of known risk factors in the maternal population. The multiple linear regression analysis enabled an evaluation of the effect of maternal age (over 40 years), parity (five or more) and social class (V.) on the pattern of the geographical distribution of the two defects. High parity was the only factor to influence significantly the distribution of anencephalus, while none of the factors made a significant impact on the distribution of spina bifida. One might tentatively conclude that anencephalus and spina bifida are distributed in such a way as to indicate different aetiologies, with anencephalus apparently reflecting maternal risk factors rather than the effect of specific environmental teratogens, and spina bifida reflecting either the influence of an unknown environmental agent or, possibly, chance.

The results of the geographical analysis, therefore, further complicate the aetiological options emerging from the study of maternal age and parity. Anencephalus and spina bifida may not share a common aetiology, at least as far as environmental agents are concerned. Evidence from family, ethnic and other studies is strongly suggestive of a genetic element playing a role in the occurrence of both defects, particularly in low prevalence areas (CARTER 1974). In higher prevalence areas, an additional "biological"

or "social" aetiological process may be superimposed, the former predominating in anencephalus and the latter in spina bifida. A poor obstetric history (a feature common to both defects) may represent a secondary effect of more important underlying influences, or it may indicate a more direct role of reproductive factors in the aetiology. Low socio-economic status, per se, is probably not central to the aetiological process (especially of anencephalus) but may represent a secondary association (more marked in the past) with the obstetric risk factors.

This formulation of the possible aetiology of anencephalus and spina bifida may appear convoluted and diffuse. Unfortunately, a more didactic exposition is difficult to justify in the light of the inherent limitations of the available data. An attempt will be made later (in 14.1.2) to crystallise this discussion of aetiology into a more precise hypothetical form.

12.3. CRITIQUE OF THE METHODOLOGY OF THE AETIOLOGY STUDY

12.3.1. General Methodological Constraints

Some of the methodological constraints described in relation to the Descriptive Study apply with equal force to the Aetiology Study. In particular, the restricted range of variables available for study in the control population rendered the objectives necessarily narrow in scope; and the small numbers available for analysis, especially in the "geographical" part of the study, reduced the power of the statistical tests applied.

12.3.2. Specific Methodological Constraints

1. The inclusion of termination data in the analyses was logical, but may have introduced a small degree of bias since some terminated fetuses may not have reached term if these pregnancies had been allowed to continue. Ideally, an aetiological study should attempt to observe events as close to conception as possible, but if the sample of cases contains a mixture of observations recorded at varying times throughout pregnancy (such as at 20 weeks and at term), interpretation becomes more problematical.

2. The maternal age, parity and social class data were confined to the years 1975-78 because of the restricted availability of control data, while the "locality of residence" and multiple regression analyses were based on the birth years 1975-77 only, for similar reasons.

3. The relationship observed between maternal age and parity and prevalence were cross-sectional and could not therefore take account of the confounding effects of secular or completed sib-ship trends.

4. Because maternal age and parity could not be correlated directly with social class (because the data were drawn from two separate sources of data), the inter-relationships between all of the variables could not be investigated fully.

5. Because parity data were impossible to disaggregate, the differential effects of previous livebirths and previous stillbirths could not be examined.

6. The interpretation of the data required the integration of findings from other studies with those of the present analysis. This indicated the absence of a single, coherent hypothetical model against which the results could be tested. Given the relatively unsophisticated level of current knowledge about the aetiology of neural tube defects, this was probably inevitable.

XIII. DISCUSSION 3. THE PREVENTION STUDY

13.1. LITERATURE REVIEW

13.1.1. The Concept of Prevention in Relation to Neural Tube Defects

Preventive medicine may operate at one or more of three levels : primary, secondary and tertiary (LEAVELL, H.R. and CLARKE, E.G. 1965).

Primary prevention relies on measures designed to promote health or protect individuals from harmful influences. It utilises knowledge of the earliest (prepathogenesis) stage of the natural history of disease.

Secondary prevention attempts to advance the clinical horizon to the point where intervention can effectively alter the course of the disease. It depends on an understanding of a later (pathogenesis) stage of the natural history.

Tertiary prevention is concerned with the rehabilitation of individuals in whom irreversible defects and disabilities have occurred.

The choice of an appropriate form of prevention for a particular disorder is determined by several criteria, which may not be stated explicitly (STONE 1980a). A prerequisite of choice is the availability of alternative options, however, and these are few in respect of neural tube defects.

The primary (or "true") prevention of any congenital defect

is the most desirable objective. Genetic counselling may be offered to parents who have had an affected offspring since they appear to be exposed to a recurrence risk of between three and five per cent (ELWOOD, J.M. and ELWOOD, J.H. 1980), about ten times the initial risk. At best, however, genetic counselling could only prevent a small minority (assumed to be about ten per cent) of all affected births since the remainder arise, unsuspected, ab initio. The only other form of primary prevention which appears remotely promising is the use of periconceptional vitamin supplementation. In an intervention study of women who had previously given birth to one or more infants with a neural tube defect, SMITHELLS et al. (1980) reported that one (0.6 per cent) of 178 infants of fully supplemented mothers had a neural tube defect compared with 13 (five per cent) of 260 infants of unsupplemented mothers. Unfortunately, the study was not a randomised controlled trial, despite the authors' attempts to convince their local ethical committees of the need for one. Moreover, there was an excess of control (unsupplemented) mothers who resided in geographical areas (such as Northern Ireland) known to experience a high risk of neural tube defects (STONE 1980b). Further definitive evidence of the preventive value of vitamin supplementation is awaited.

Thus the only immediate prospect for the large-scale prevention of neural tube defects lies in secondary prevention by means of maternal serum and amniotic-fluid alphafetoprotein screening.

13.1.2. Antenatal Screening for Neural Tube Defects

Alphafetoprotein (A.F.P.) is a normal fetal protein

(molecular weight 64,000) synthesised mainly in the liver. It passes into the amniotic fluid and reaches a peak at the end of the first trimester thereafter declining rapidly (SEPPALA and RUOSLAHTI 1972). Abnormally high levels of A.F.P. in the amniotic fluid of 37 pregnancies leading to anencephalus or spina bifida were reported by BROCK and SUTCLIFFE (1972), a finding which was repeatedly confirmed (ALLAN et al. 1973; LORBER, STEWART and WARD 1973; NEVIN, NESBITT and THOMSON 1973; SELLER et al. 1973). The levels were highest in association with anencephalus and extensive open spina bifida lesions but were often normal when the defects were covered by skin or other tissues. The discovery that maternal serum A.F.P. could be linked with neural tube defects (BROCK, BOLTON and MONAGHAN 1973) opened up the possibility of screening all pregnant women. In 1974, the United Kingdom Collaborative Study Group was set up to evaluate the efficiency of maternal serum A.F.P. measurement in the antenatal detection of neural tube defects. By pooling data obtained retrospectively from 19 centres, they found that almost all cases of anencephalus were associated with maternal serum A.F.P. levels above the 97th centile of the distribution of "normal" pregnancies, while most of the open spina bifida cases were similarly associated with high A.F.P. levels. The authors concluded that, while the results suggested that screening would probably be worthwhile, many unanswered questions remained, including those relating to the logistics of performing the test at the appropriate gestational age and the risk of amniocentesis (UNITED KINGDOM COLLABORATIVE STUDY 1977).

It is now possible to evaluate the practical implications of screening as a result of the prospective studies which have reported

their findings. These have been undertaken in Sweden (KJESSLER et al. 1977), London (BENNETT et al. 1975; CLARKE et al. 1977), Belfast (BOND et al. 1977), Edinburgh (BROCK et al. 1978), Glasgow (FERGUSON-SMITH et al. 1978) and elsewhere. The Glasgow study generated the largest amount of information on the operation of a screening programme in a relatively high-risk area. Over 17,000 women in the West of Scotland were screened between May 1975 and June 1977. The programme consisted, in essence, of three stages:

(1) all pregnant women (except those in affected families who were offered immediate amniocentesis) were offered the serum test;

(2) positive tests, when confirmed on a repeat serum sample, were followed by amniocentesis;

(3) if the amniotic A.F.P. was also elevated, termination of the pregnancy was offered.

The results are shown in TABLE 39.

These data demonstrate a number of important points about serum A.F.P. screening. First, the selection of a cut-off point in the normal distribution is crucial to the validity of the test. In Phase I, the 99th centile was clearly too high since many affected cases were missed, although the high specificity ensured that few unnecessary amniocenteses were performed; when the cut-off point was lowered to the 97th centile in Phase II, the sensitivity increased, resulting in fewer missed cases, but the price was a high proportion of unnecessary amniocentesis which, according to a MEDICAL RESEARCH COUNCIL WORKING PARTY (1978) approximately doubles the normal risk of

fetal loss. Second, it is extremely difficult to screen all deliveries at the recommended gestation (16 to 20 weeks), although the Glasgow workers had almost doubled the proportion by Phase II. Third, anencephalus is more easily detected than spina bifida by serum A.F.P. screening; this, it is assumed, reflects a correlation between the size of the lesion and the leakage of A.F.P. into both the amniotic fluid and the maternal bloodstream. Fourth, on the same principle, closed spina bifida lesions are extremely difficult to detect by screening. Fifth, a high detection rate may not be followed by a high therapeutic abortion rate. Despite these reservations, however, the authors concluded that their findings strongly supported the case for the introduction of a voluntary national screening programme.

Both this conclusion and the form of presentation of the results have been challenged by ELWOOD, J.M. and ELWOOD, J.H. (1980). They argued that the exclusion of closed spina bifida from the detection rate (or sensitivity) estimates was misleading. Furthermore, they questioned the benefits of screening for anencephalus, which always results in stillbirth or early death. After recalculating the sensitivities to take account of retrospective reinterpretation of a number of elevated serum A.F.P. results, they estimated the detection rate of spina bifida to be 30 per cent and 28 per cent in Phases I and II respectively.

In assessing the evidence for and against screening, many factors other than the validity of the test itself must be taken into account. One of these is cost, and an economic analysis based on the West of Scotland programme was described by HAGARD, CARTER and MILNE (1976),

who concluded that, on economic grounds, screening may be worthwhile only in high prevalence areas. GLASS and COVE (1978) estimated that the public sector costs of a group of spina bifida children would exceed the costs of a screening programme (assuming a test sensitivity of 45 per cent) within four years. Other relevant issues include the risks of amniocentesis, the availability of staff and equipment (particularly for ultrasonography), the uptake of screening by the pregnant population, quality control of the assay methods, organisational aspects of antenatal services, ethical problems and the epidemiological effects. A Working Group, under the Chairmanship of Sir Douglas Black, reviewed all of these matters, giving general support to the principle of large-scale screening programmes (WORKING GROUP ON SCREENING FOR NEURAL TUBE DEFECTS 1979). They did not, however, recommend the introduction of a national programme.

Apart from the financial implications of screening, reservations have been expressed in two main areas : ethical and epidemiological.

13.1.3. Ethical Aspects of Antenatal Screening for Neural Tube Defects

The ethical implications of antenatal screening for neural tube defects are twofold : first, the general ethical obligations surrounding screening of any type; and second, the specific ethical dilemmas posed by A.F.P. screening.

Screening is fundamentally different from conventional medical practice in that the doctor undertakes to identify the individual

requiring his assistance rather than awaiting the patient's request for advice. This distinction obliges the potential screener to ensure that the proposed test meets certain requirements; in particular, the outcome of screening must not be presumed to be beneficial, it must be demonstrable as such. By contrast, if the initiative is taken by the patient, the doctor (or health authority) undertakes to help the patient with no prior commitment to success. As a result, screening has probably been subjected to more critical scrutiny than any other area of medical practice (HOLLAND 1974). The potential benefits must be weighed against the potential hazards. The former include reduced mortality and morbidity, financial savings, and peace of mind for the "healthy"; the latter include the inconvenience, discomfort or anxiety associated with the test, the unnecessary and possibly dangerous intervention inflicted on false positives, and the misplaced reassurance offered to the false negatives (STONE and HOLLAND 1978).

Antenatal screening for neural tube defects has stimulated a great deal of controversy in both the medical and lay press. HARRIS (1974) has aired some of the major issues as have ELWOOD, J.M. and ELWOOD, J.H. (1980) and KENNEDY (1980). These may be summarised as :

(1) the moral objection, relative or absolute, to abortion;

(2) the importance of allowing prospective parents the right to "opt in" to a serum screening programme after full counselling;

(3) the perception of the "benefit" of aborting anencephalic fetuses, none of whom would survive for any substantial period after birth;

(4) the danger of devaluing the importance of aetiological research;

(5) the danger of neglecting the clinical and social needs of spina bifida children who survive despite the operation of a screening programme; and

(6) the need for the ethical aspects of screening for neural tube defects to be discussed beyond the narrow confines of the medical profession.

13.1.4. The Epidemiological Evaluation of Antenatal Screening for Neural Tube Defects

The method of evaluating any programme depends upon a clear statement of that programme's objectives. With respect to screening for neural tube defects, it is difficult to find such a statement in the literature. By implication, however, one of the objectives is epidemiological: to reduce the prevalence of the defects in the population.

There have been few attempts to assess the impact of screening on the prevalence of anencephalus and spina bifida, although this was regarded as an important part of monitoring by the Black Committee (WORKING GROUP ON SCREENING FOR NEURAL TUBE DEFECTS 1979). CHAMBERLAIN (1978) attempted to extrapolate the results of published studies to a single year (1975) for England and Wales. On the basis of an annual prevalence of 1.5 anencephalic births per 1,000 total births and 2.2 spina bifida births per 1,000 total births, and taking into account four constraining factors (failure to reach the whole

population, the relatively low sensitivity of the test, the failure of some amniocenteses, and the refusal of some parents to participate), she estimated that screening was likely to avert only 523 (63 per cent) anencephalic births out of a potential total of 824, and 555 (45 per cent) births out of a potential total of 1,230. (These estimates excluded births to previously affected families, who would have been offered amniocentesis immediately). The only epidemiological evaluation based on actual as opposed to hypothetical observations has been that of BRADSHAW, WEALE and WEATHERALL (1980). Using the system of notification operated in England and Wales since 1964 by the Office of Population Censuses and Surveys, they reported a decline of approximately 24 per cent in the prevalence of anencephalus and spina bifida over the period 1972 to 1977. They attributed the trend to a combination of demographic factors (the contraction in the proportion of mothers at highest risk) and the expansion of antenatal screening since 1975. They also observed, in 1976-77, an increase in the survival rate of children born alive with neural tube defects and speculated that the combination of antenatal screening and termination was reducing the number of births of the more severely malformed children.

Studies of this kind are essential to the evaluation of the impact of antenatal screening at a population level. Their paucity can only hinder an informed discussion of the case for and against the continued extension of screening beyond its present boundaries.

13.2. COMMENT ON THE FINDINGS OF THE PREVENTION STUDY

The epidemiological impact of the programme of antenatal screening for neural tube defects is clear: the prevalence of anencephalus was reduced significantly while the prevalence of spina bifida was not. The difference in effectiveness was due almost entirely to the relatively low sensitivity of the serum A.F.P. assay, although the other constraining factors pointed out by CHAMBERLAIN (1978) played a part.

In the view of ELWOOD, J.M. and ELWOOD, J.H. (1980), the evaluation of serum A.F.P. screening should be concerned primarily with spina bifida since anencephalus is always fatal and is never a burden on society. If this premise is accepted, the results of screening for spina bifida are certainly disappointing whether the objective of screening is expressed in clinical or epidemiological terms.

The comparison of the maternal characteristics of affected births and terminations offers some insights into the efficiency of screening. Because the chances of undergoing a termination do not seem to vary significantly according to Health District of residence, specific institutions (whose attached antenatal clinics broadly serve the population of their Districts) cannot be accused of non-cooperation in any systematic sense. Mothers at the extreme ends of the age spectrum (under 20 years and over 40 years) appear to be under-represented among terminations compared with affected births, as do mothers in social class V. The differences do not reach statistical significance, however. Women in the high parity group (five and over) are significantly under-represented among terminations. Overall, the pattern could be interpreted as indicating that those mothers at

highest risk of neural tube defect are least likely to receive the benefits of screening.

The hypothesis that screening selects out the most severely affected infants, many of whom would die before or after birth, is not supported by the results since no statistically significant trends in survival were demonstrated. The general direction of the slight trend which is perceptible, however, is such as to raise the possibility that the hypothesis would receive support from observations over a longer time span.

The advocates and opponents of A.F.P. screening have adopted the two classical postures which screening controversies seem to generate: the "evangelists" and "snails". The "evangelists", led by the CLINICAL GENETICS SOCIETY (1978), have urged the immediate establishment of a national A.F.P. screening programme, while the "snails", who consist mainly of a curious alliance of epidemiologists and conscientious objectors, argue that both scientific and ethical issues remain to be resolved. The Black Committee (WORKING GROUP ON SCREENING FOR NEURAL TUBE DEFECTS 1979) achieved a compromise between these two poles of opinion, recommending "local (but not national) action" in favourable circumstances.

The results of the Prevention Study provide ammunition for both sides in the debate. The impressive reduction in anencephalus prevalence could be cited as firm evidence of the potential effectiveness of screening, limited temporarily by technical problems on the verge of solution, while the minimal reduction in spina bifida prevalence could

be used to challenge the whole concept of screening as a cost-effective health promoting exercise. There is little room for argument, however, about the need to improve the performance of screening with respect to spina bifida.

What measures could be taken to remedy this failure? There are several, in accordance with the need to overcome the "constraints" on screening enumerated by CHAMBERLAIN (1978).

First, it is essential to reach a larger proportion of the population at risk. The second phase of the Glasgow study succeeded in screening only 51 per cent of pregnancies at the recommended gestation. One of the major difficulties lies in improving antenatal attendance rates within the period of 16 to 20 weeks gestation. GLASS and COVE (1978) provided evidence that social class V. women (a high-risk group) are more likely to present late than social class I. women. Attendance is determined by booking procedures as well as by maternal motivation, and purely administrative action may improve attendance rates.

Second, the sensitivity of the serum A.F.P. test must be improved. This can be achieved by lowering the "cut off" point, but only at the price of increasing the false positive rate and hence the amniocentesis rate. The most skilled use of ultrasound in identifying false positives may help avoid unnecessary amniocenteses.

Third, the amniocentesis failure rate, already low, could be lowered still further. Dry taps can be avoided by skilled simultaneous ultrasonography, and the false positive and negative

rates may be reduced by the development of ancillary tests, such as amniotic-fluid acetylcholinesterase (SMITH et al. 1979).

Finally, the proportion of women "opting in" and staying in the screening procedure could be increased by ensuring that all pregnant women attending before 20 weeks gestation are offered the test, that its implications are fully explained and any anxieties relating to it are aired. Moral objections must be respected and women must be reassured that they are free to "opt out" at any stage in the process. This "moral dimension" is probably the most crucial (and neglected) determinant of social and individual attitudes to the test.

13.3. CRITIQUE OF THE METHODOLOGY OF THE PREVENTION STUDY

13.3.1. General Methodological Constraints

1. The study was designed to evaluate the programme of antenatal screening for neural tube defects in epidemiological terms. The most satisfactory method of evaluating an intervention of any kind is usually a randomised controlled trial which was not possible in this case. The longitudinal analysis of prevalence trends was not ideal, but the careful recording and analysis of termination data should have minimised the possible distorting effects of influences other than screening.

2. The term "prevention" embraces the notion of intervention at various stages in the natural history of a disease. Intervention in the middle trimester of pregnancy may not be regarded by some as "prevention" in the conventional sense. "True" (or primary) prevention is, of course, not yet possible.

3. The evaluation could not take direct account of the ethical issues involved in screening. One of the ethical obligations of the screener is to be able to offer demonstrable benefit, however. Assuming one aspect of "demonstrable benefit" is a reduction in prevalence, the indirect ethical implications of the study are substantial.

13.3.2. Specific Methodological Constraints

1. The evaluation centred on a comparison of the "birth" prevalence (affected livebirths plus affected stillbirths) with the "pregnancy" prevalence (affected births plus affected products of termination).

Essentially, the "pregnancy" prevalence was regarded as the "expected" prevalence in the absence of screening.

The major flaw in this approach was that it assumed that all of the terminated fetuses would have reached 28 weeks at least. (In fact, for the calculation of the "expected" number of affected births in a given year, terminated fetuses were allocated a birth year according to their "expected date of delivery"). The effect of this inherent error would have been to increase the "expected" prevalence slightly, thereby tending to exaggerate the observed effect of screening. The extent of the "inflation" in the "expected" prevalence was probably no more than five per cent; this was the rate of fetal loss in affected pregnancies estimated by CREASY and ALBERMAN (1976) for the period 20 to 27 weeks.

2. The purpose of the comparison of the maternal characteristics of the "birth" group and the "termination" group was to seek to identify differences in these characteristics between women (with affected pregnancies) who were screened and those who were not. This implies that women who received terminations were broadly representative of women (with affected pregnancies) who were screened. There was no means of testing this assumption.

3. The survival characteristics of affected fetus were observed longitudinally for evidence of a change between the period prior to the commencement of screening (1972-74) and the period after the commencement of screening (1975-78). A significant secular trend would have been difficult to detect over such a short time-scale, particularly as screening began on a fairly small scale in 1975 (reaching only 27 per cent of pregnancies in its first year).

XIV. CONCLUSIONS

14.1. THE DESCRIPTIVE EPIDEMIOLOGY, AETIOLOGY AND PREVENTION OF ANENCEPHALUS AND SPINA BIFIDA

The objectives of the study were to establish the prevalence of anencephalus and spina bifida in Glasgow over the period 1972 to 1978, to elucidate aspects of their descriptive epidemiology and aetiology, and to evaluate the epidemiological impact of screening. These objectives were broadly fulfilled, although the nature, scope and numerical dimensions of the data imposed some important limitations on both the methodological and analytical techniques employed.

14.1.1. The Descriptive Study yielded information on both the prevalence of anencephalus and spina bifida over the study period and the variation of the prevalence in accordance with selected descriptive variables relating to the classical epidemiological triad of "time", "place" and "person".

The results may be regarded as falling into two categories: first, results which tended to support the findings of previous published studies, and second, results which appeared to bring new insights to the understanding of the epidemiology of the defects.

Results which tended to support previous findings included the following :

(1) The prevalence estimates of anencephalus and spina bifida indicated that Glasgow remained a relatively high-risk area ranking in a position intermediate to the relatively higher

risk areasof the North West of the United Kingdom (particularly Belfast) and the relatively lower risk areas of the South East (particularly London);

(2) There was an excess of spina bifida births in the late winter months (January to March), although not to a statistically significant extent;

(3) There was a statistically significant excess of females in affected births, more marked in anencephalus than spina bifida;

(4) The twinning rate was slightly lower in affected births than in the total birth population, although the numbers were too small for worthwhile statistical significance testing;

(5) The vast majority (88 per cent) of anencephalic fetuses were stillborn, while the vast majority (83 per cent) of spina bifida fetuses were liveborn;

(6) Premature and low birth weight deliveries were extremely common in anencephalic births, probably due to the known association of the defect with hydramnios;

(7) Less than one in five of affected fetuses were known to have associated malformations, although this was almost certainly an underestimate.

Results which were notable for being inconsistent with previous findings or which appeared potentially capable of bringing new insights to the understanding of the epidemiology of defects included the following :

(1) There was a statistically significant fall in the birth prevalence of anencephalus from the period (1964-68) studied by WILSON (1971) to the study period (1972-78); this reflected the decline of anencephalus prevalence which occurred within the later period and which was due almost entirely to the introduction of maternal serum A.F.P. screening in 1975;

(2) Related to the above was the artefactually low anencephalus to spina bifida ratio (0.69) in the later period compared to the earlier period when the ratio was close to unity;

(3) Neither the birth prevalence of spina bifida nor the "pregnancy" prevalence of anencephalus declined over time, belying the long-term downward trend in the prevalence of both defects described by others (including MACMAHON and YEN 1971, and BRADSHAW, WEAL and WEATHERALL 1980);

(4) There was a greater year-to-year fluctuation in the spina bifida prevalence rate than in the anencephalus prevalence, although the 95 per cent confidence limits of the estimates were wide enough to encompass the variation, which might therefore have been "random";

(5) There was an excess (which was not statistically significant) of anencephalic births in the late summer months (July to September), compared with the winter excess (also not significant) of spina bifida births. Summer excesses of affected births have occasionally been described in the United Kingdom, but they represent a small minority of reports. Similarly, the differing seasonal pattern of the two defects has been infrequently reported;

(6) While there were no statistically significant differences in the distribution of the defects around the five Health Districts, there was a divergent pattern between the two defects, with spina bifida conforming more readily to the distribution which might be expected if the suspected association of neural tube defects with socio-economic deprivation held true;

(7) The survival of affected fetuses (in terms of stillbirths, livebirths and first-week deaths) appeared to have improved in comparison with the earlier period studied by WILSON (1971) although the difference was not statistically significant;

(8) The distribution of birth weight and gestation indicated that spina bifida fetuses were much closer to "normal" births than anencephalic births in these respects. The potential utility of these particular findings, however, is limited.

Although many of the data are difficult to interpret, their implications may be expressed in relation to prevalence, aetiology and prevention as follows :

(1) The absence of evidence of a secular decline in the prevalence of anencephalus and spina bifida raises the possibility that the widely reported long-term decline in the prevalence may have come to an end, at least in Glasgow;

(2) The divergence in the variation in the prevalence of the two defects with respect to time (year-to-year and seasonal variation) and place (distribution around the Health Districts) suggests that separate aetiological processes may be involved

in anencephalus and spina bifida. The evidence from the Descriptive Study is weak, but is strengthened by the findings of the Aetiology Study;

(3) The programme of antenatal screening for neural tube defects has made a considerable impact on the prevalence of anencephalus but not on the prevalence of spina bifida. In addition, the direction of the change in fetal survival in the perinatal period lends some support to the hypothesis that screening selects out the most lethal lesions (BRADSHAW, WEAL and WEATHERALL, 1980). Both of these issues have been addressed by the Prevention Study in more detail.

The above interpretation may appear to overstep the remit of the Descriptive Study. Descriptive data are, however, of limited interest unless an attempt is made to generate or test aetiological or other hypotheses. A degree of cross-fertilisation of ideas between the three studies was therefore considered justified.

14.1.2. The Aetiology Study examined the influence of maternal age, parity, social class and locality of residence on the prevalence of anencephalus and spina bifida. Again, it is useful to separate the findings into two groups: the first, tending to confirm knowledge acquired in previous studies, and the second offering the prospect of new insights into the aetiology of the defects.

Results which lend support to previous findings include the following :

(1) The "J-shaped" relationship between prevalence and maternal age and parity may be regarded as variants of the more frequently observed "U-shaped" patterns;

(2) There was a high correlation between maternal age and parity, with the latter exerting a stronger effect than the former;

(3) A social class trend, in the direction of a higher prevalence with declining social class, was evident;

(4) The pattern of geographical distribution of affected births within Glasgow did not deviate significantly from that of the total population, confirming the absence of any demonstrable effect of potential teratogens in the intra-urban environment.

Results which appear either at variance with previous findings or capable of injecting new insights into the aetiology of the defects include the following :

(1) The very high risk associated with advanced maternal age (40 years and over) and high parity (five or more previous deliveries) has not been found previously, either in Glasgow or elsewhere;

(2) The increase in the maternal age and parity associated risk since the earlier Glasgow study coincided with a decrease in the gradient of the social class trend. This dissociation of the age and parity effects from the social class effects has not been previously reported;

(3) The social class trend was more marked for spina bifida than for anencephalus; similarly, the decrease in the social class gradient over time was more evident in spina bifida;

(4) The lack of a statistically significant geographical pattern within Glasgow for each individual defect contrasted with a statistically significant pattern of distribution when both defects were combined, suggesting that the negative results found for each defect may have reflected small numbers rather than a real absence of a geographical pattern;

(5) The multiple linear regression analysis indicated that a significant proportion (34 per cent) in the variation of the prevalence of anencephalus could be explained on the basis of the distribution of high parity mothers in the total population, while none of the maternal factors contributed significantly to the variation in spina bifida prevalence.

These findings, taken in conjunction with the results of the Descriptive Study and the conclusions reached by most other workers, support the view that the aetiology of anencephalus and spina bifida is based on a complex interaction of genetic and environmental factors. CARTER (1974) has suggested that genetic factors predominate in low prevalence areas and time periods while environmental influences increase in importance as the prevalence rises. He has proposed that the aetiology is multifactorial, depending on a genetic predisposition to develop the defects which is polygenic, with a threshold beyond which individuals are at risk of either defect if environmental factors also predispose. According to this model, the risk to relatives is greater than the risk to the general population because only a small

proportion of the latter is beyond the threshold of risk; and the rarer the defects, the greater is the risk to relatives in comparison with the risks to non-relatives.

There is much evidence to support Carter's hypothesis. The excess of affected females, the ethnic pattern of risk, the familial clustering of cases and the higher degree of concordance in monozygotic than in dizygotic twins all point to a strong genetic component, and the tendency of some of these phenomena to vary in inverse proportion to prevalence supports the notion of a threshold beyond which environmental influences become more important. Carter's model, however, does not explain the divergent behaviour of anencephalus and spina bifida with respect to several features, including the sex ratio, the relationship between the sex ratio and prevalence and the ethnic variation in prevalence. (On the other hand, the weak preference of sibs for the same lesion as the index case in family studies, along with evidence from teratological, embryological and epidemiological observations, is indicative of a common aetiology). Carter's model is, nevertheless, a useful starting point for the elaboration of a more complex hypothesis which can accommodate the possibility of a divergent aetiology along both genetic and (as has been discussed elsewhere) environmental pathways for each of the two defects.

FIGURE 15 is an attempt to construct such a hypothetical model which extends the existing consensus view of aetiology, as epitomised by Carter's formulation, and which also takes account of the possibly divergent sequence of events in the prepathogenesis of anencephalus and spina bifida, as suggested by the results of the present

and other studies. The model is unsatisfactory in various respects; its imprecision, its failure to explain all of the epidemiological characteristics of the defects, its attempt to oversimplify a very complicated and ill-understood series of relationships, its acceptance at face-value of supportive evidence which may be founded on dubious assumptions. All deductive scientific reasoning is vulnerable to these criticisms, however, and epidemiological deduction is peculiarly prone to hazards. The essential point about such models is that their validity lies not in the accuracy with which they represent "reality" but in their ability to predict observed epidemiological variations and to generate testable hypotheses.

14.1.3. The Prevention Study attempted to evaluate the epidemiological impact of antenatal screening for neural tube defects on the prevalence of anencephalus and spina bifida. No other study appears to have examined the epidemiological impact of screening in a high-risk area. It ought therefore to be capable of making a substantial contribution to the evidence which must be considered in weighing the benefits of screening against the costs. The results may be summarised as follows :

(1) Serum A.F.P. screening significantly reduced the prevalence of anencephalus in Glasgow from 1975-78, but made virtually no impression on prevalence of spina bifida;

(2) There was some evidence that those women most at risk of delivering an affected fetus were least likely to receive a termination consequent upon screening, although it was not clear whether this reflected a failure to reach the population at risk or a failure of compliance by some

screened women;

(3) There was some suggestion that screening had been detecting preferentially those fetuses which were least likely to survive, although the changes in fetal survival did not reach statistical significance.

In epidemiological terms, then, antenatal screening successfully prevented the birth of a significant number of anencephalic infants but did not prevent the birth of a significant number of spina bifida infants. The main constraint on the effectiveness of screening appeared to be the low sensitivity of the test for spina bifida. Since the justification for screening rests primarily on its potential for reducing the individual and social "costs" (in terms of health, happiness and finance) of spina bifida, these findings must seriously undermine the view that the benefits of screening have been demonstrated. The effectiveness of screening may improve as a result of using a combination of a lower "cut-off" point and more accurate diagnostic ultrasonography. Greater efforts to reach the population at risk, the development of more reliable techniques of amniocentesis and amniotic fluid assay, and more careful counselling of parents before they enter the screening process, should collectively yield dividends in terms of enhanced effectiveness and efficiency. Greater attention might be paid to the "moral dimension" of the issue which has become the subject of heated professional and public debate. Above all, both "evangelists" and "snails" have a responsibility to argue their respective cases on as solid a factual foundation as possible. Detection rates, false positives and false negatives, complications of amniocentesis, and a reduction in the burden of illness, handicap

and chronic distress suffered by individuals and families, are the "clinical" components of the scientific argument; the "community" components revolve around the likely benefits to be reaped from reducing the prevalence of neural tube defects and the consequently lower resource implications. Epidemiological data, being population based, are particularly useful in bringing a community perspective to the debate. The findings of the Prevention Study should help to rectify the current paucity of epidemiological analyses of the effectiveness of serum A.F.P. screening.

14.2. DIRECTIONS FOR FUTURE RESEARCH

The conclusions drawn from the results of three studies raise a number of issues to which future research work might be addressed.

The results of the Descriptive Study pose the following questions :

(1) What is happening to the long-term secular trend of anencephalus and spina bifida prevalence? Has the decline in prevalence flattened out? Are there any signs of a renewed "epidemic"?

(2) What is the significance of the labile seasonal trend?

(3) Is the female excess due to a differential fetal loss? If so, why?

(4) Is the twin rate in affected births lower than that in the population as a whole? Are affected twins monozygous or dizygous, concordant or discordant?

(5) Is there a difference in the descriptive epidemiology of the two defects?

(6) To what extent is the descriptive epidemiology of anencephalus and spina bifida being distorted by the expanding programme of antenatal screening for neural tube defects?

The findings of the Aetiology Study suggest that the following questions require to be considered :

(1) Is the secular increase in the risk associated with advanced maternal age and high parity unique to Glasgow? What is its cause?

(2) Is the secular decrease in the social class trend of prevalence, simultaneous with the upward trend in the age and parity related risk, unique to Glasgow?

(3) Is there a real intra-urban geographical effect on prevalence? If so, what is the explanation?

(4) Do anencephalus and spina bifida have separate or partially separate aetiologies?

(5) What is the mode of genetic transmission of susceptibility to anencephalus and spina bifida? Does this vary from low prevalence to high prevalence areas?

(6) What is the role of "biological" factors (hormonal, cellular or genetic) in aetiology? Do these operate in both low prevalence and high prevalence areas?

(7) What is the role of "social-environmental" factors (nutritional, infectious, toxic or others) in aetiology? Do these operate in both low prevalence and high prevalence areas?

(8) What is the role of reproductive factors in aetiology? Does a poor obstetric history represent an outcome or a cause of neural tube defects?

The findings of the Preventive Study indicate that the following issues should be clarified :

(1) Is there any evidence of a significant decline in the prevalence of spina bifida as a result of the serum A.F.P. screening programme?

(2) How can the sensitivity of the serum test be improved without a consequent and unacceptable increase in the amniocentesis rate?

(3) How can a larger proportion of the population at risk (particularly the population at highest risk) be reached? What factors obstruct the achievement of total population screening?

(4) Does screening tend to select out the fetuses with the most extensive lesions and which would be most likely to be incompatible with life or survival beyond the neonatal period?

14.3. POLICY IMPLICATIONS

The findings of the study have implications for three major areas of national (United Kingdom) policy : research, prevention and care. These will be stated briefly.

The research policy implications arise from one inescapable fact : despite decades of epidemiological, laboratory and clinical research, the cause of neural tube defects remains unknown. But should a major research effort continue in this direction? Most informed opinion would probably favour an affirmative response, but two factors may have tended to induce a sense of complacency amongst some dispensers of research grants: first, the apparent long-term decline in prevalence, and second, the advent of antenatal screening. Yet in the absence of an understanding of the initial increase in prevalence, the secular trend should bring cold comfort because a renewed and unrecognised exposure to the causative agent or agents could trigger another epidemic cycle. This possibility is particularly disturbing in the light of the apparent absence of a decline in real prevalence in Glasgow between the 1960's and 1970's. And the preventive prospects of antenatal screening may prove much more limited than is currently believed. On balance, therefore, fundamental research into aetiology should remain a high priority activity worthy of support and encouragement.

The implications for prevention are more difficult to perceive. Again, aetiological studies should be pursued since "true" or primary prevention is unlikely to be feasible until the

causation is understood. Extreme demands from either "evangelists" or "snails" should be resisted since the evidence supports neither position totally. The most constructive approach at the present time would be to stimulate an informed public debate on the merits or otherwise of serum A.F.P. screening. Both the epidemiological and ethical arguments should be brought to the forefront of the discussion. At the same time, the impact of currently operating screening programmes, including the one in the West of Scotland, should be monitored carefully for signs of the improvement in effectiveness which would require to materialize before unqualified approval to a national programme could be granted.

Finally, health care and social service provision for the victims of spina bifida and their families should be maintained at least at their current level since the condition will continue to afflict about one in 400 neonates and will continue to prove non-fatal but handicapping to the large majority of affected infants. The principle at stake here is not merely one of sensible resource allocation. It reflects our collective social attitude towards children with defects who have "slipped through the mesh" of the screening net (JOURNAL OF MEDICAL ETHICS 1978). Constant vigilance will be necessary to detect any signs of increasing social intolerance towards children with congenital malformations, for this may be one of the less palatable consequences of raising false hopes about the efficacy of screening.

LIST OF FIGURES

FIGURE 1 HEALTH BOARD AREAS IN SCOTLAND

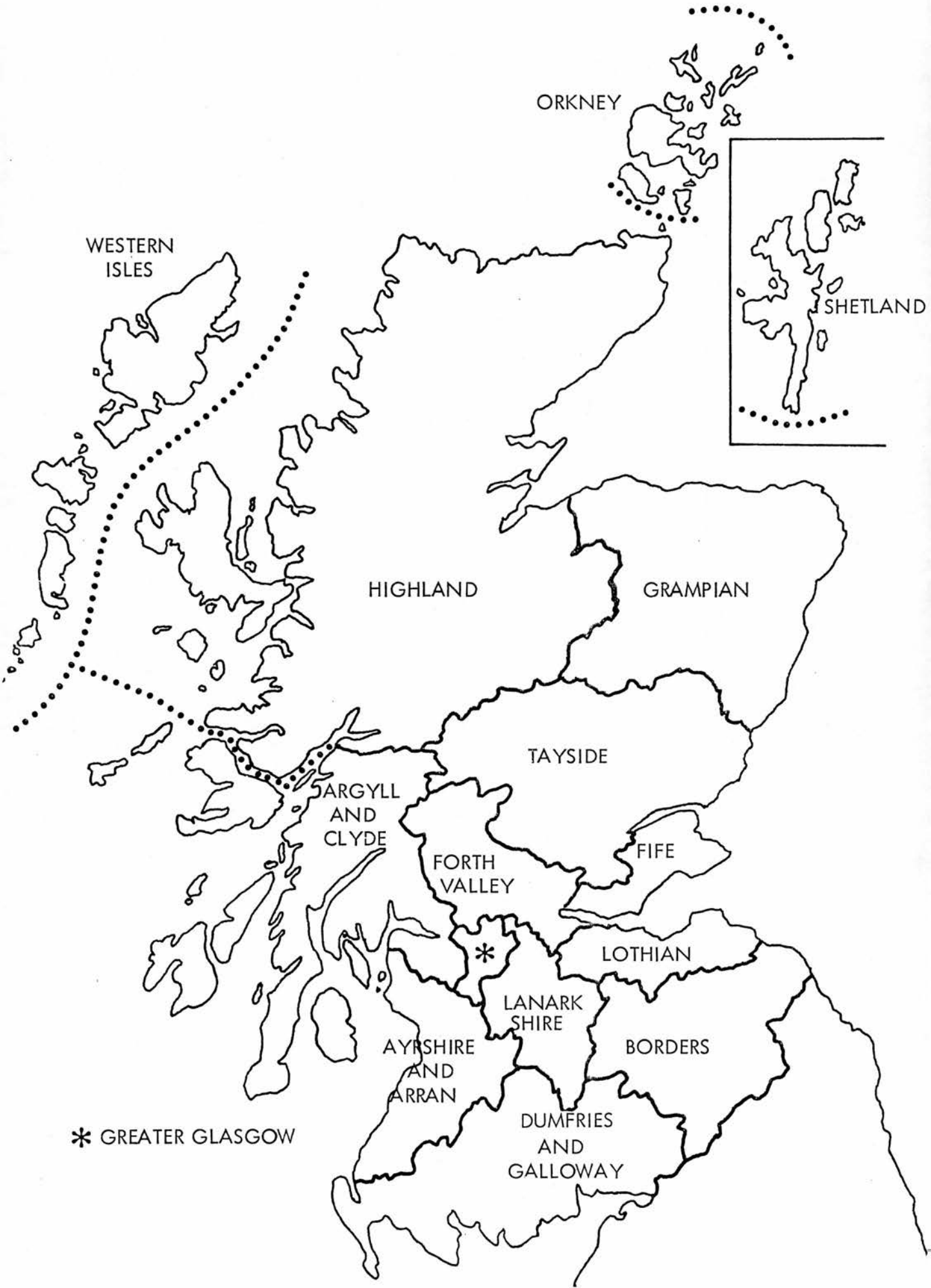
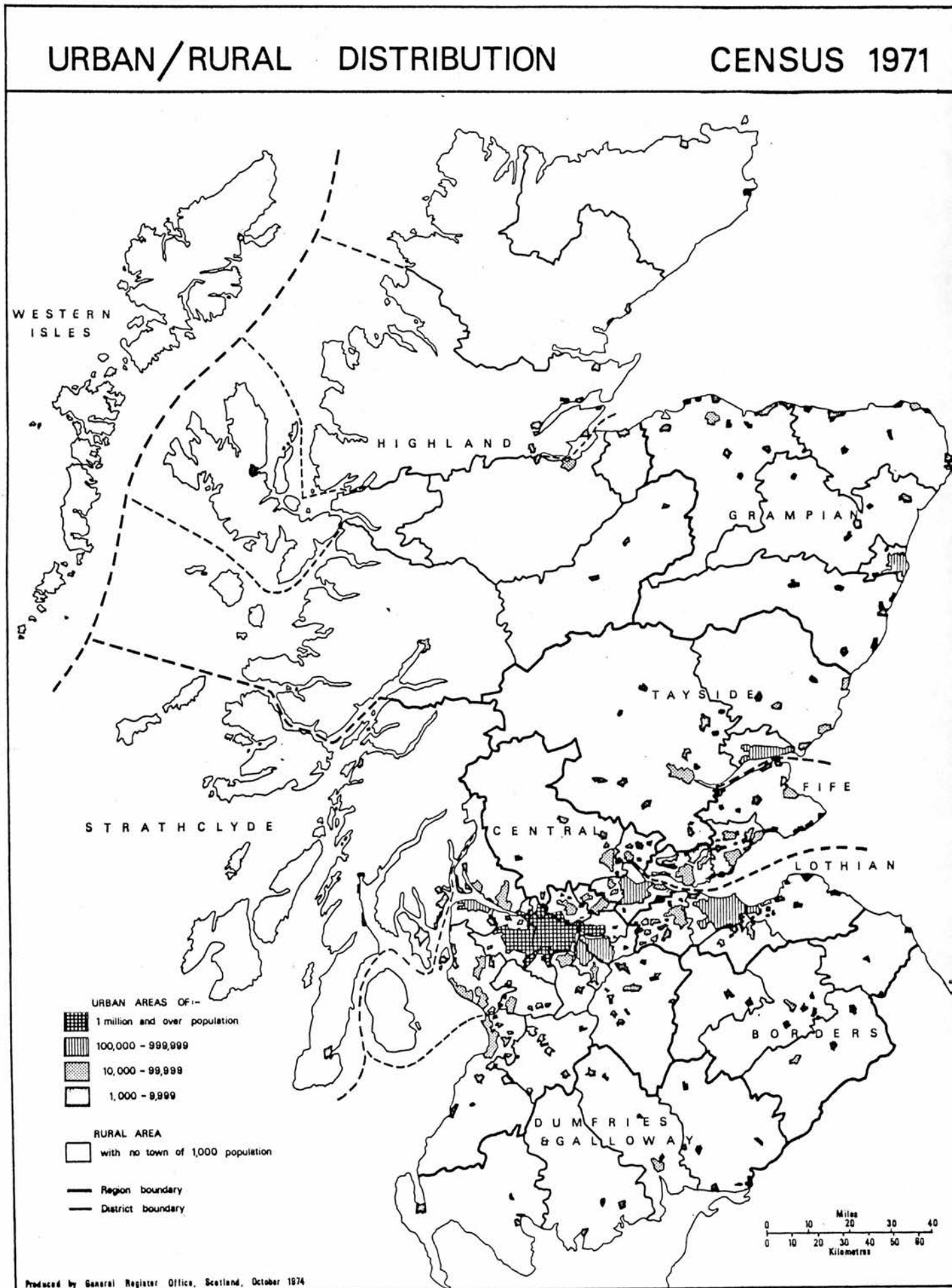


FIGURE 2



Note: Within Orkney and Shetland Islands Areas only the former small burghs of Kirkwall, Lerwick and Stromness were urban, in the 1,000 - 9,999 range.

FIGURE 3. FLOW CHART OF DATA ON ANENCEPHALUS AND SPINA BIFIDA BIRTHS

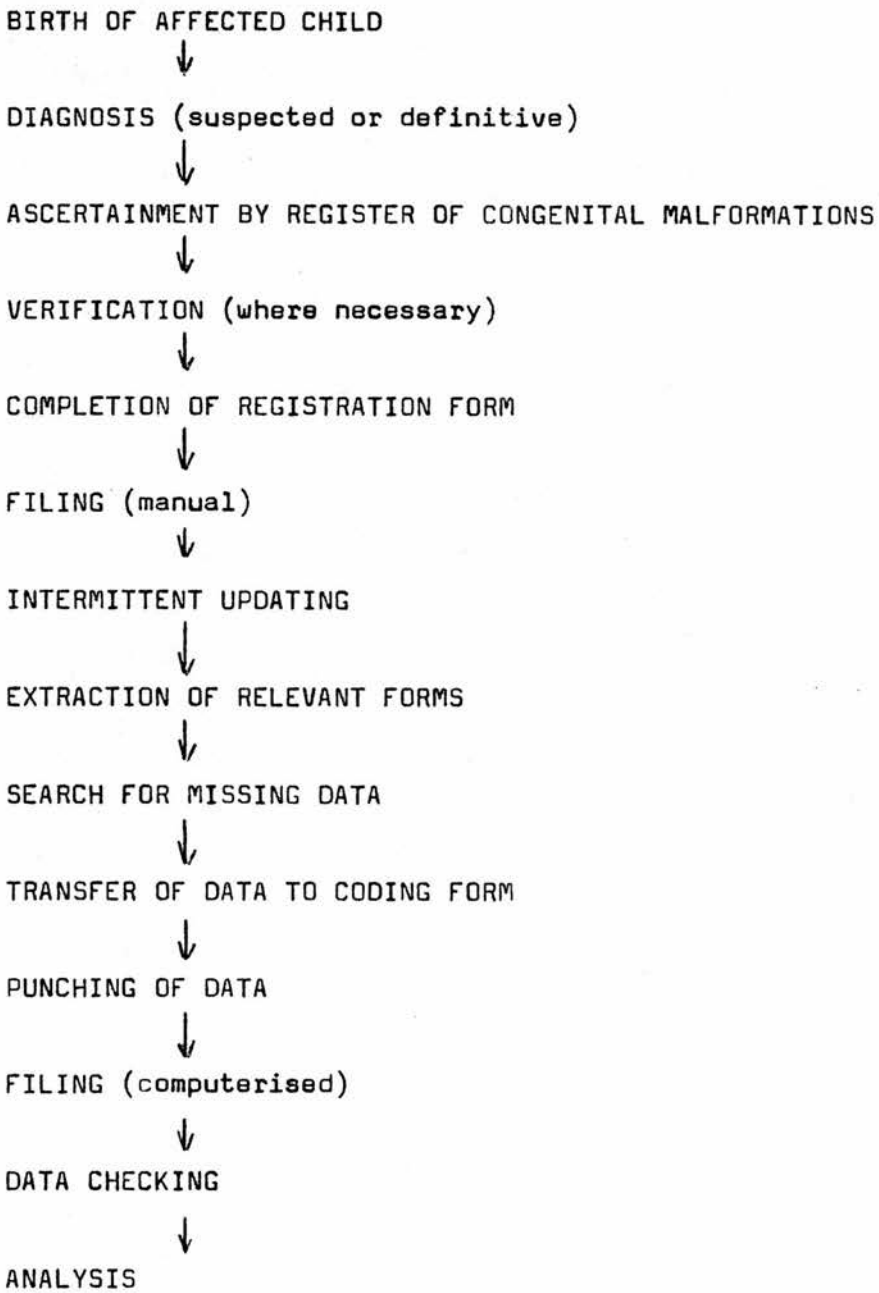


FIGURE 4. FLOW CHART OF DATA ON ANENCEPHALUS AND SPINA BIFIDA TERMINATIONS

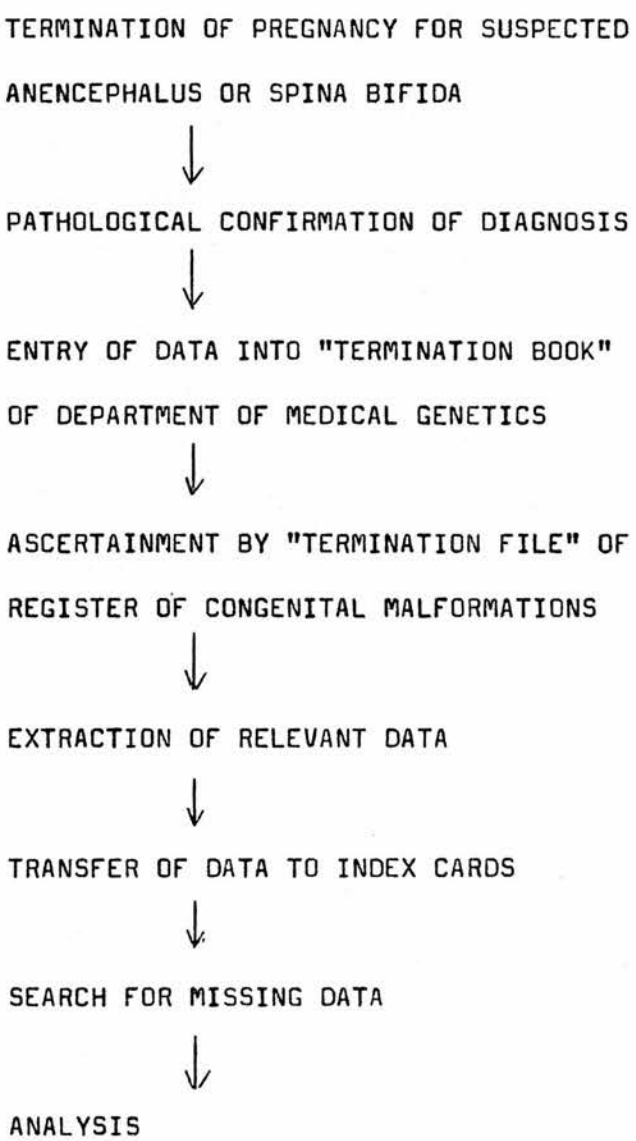
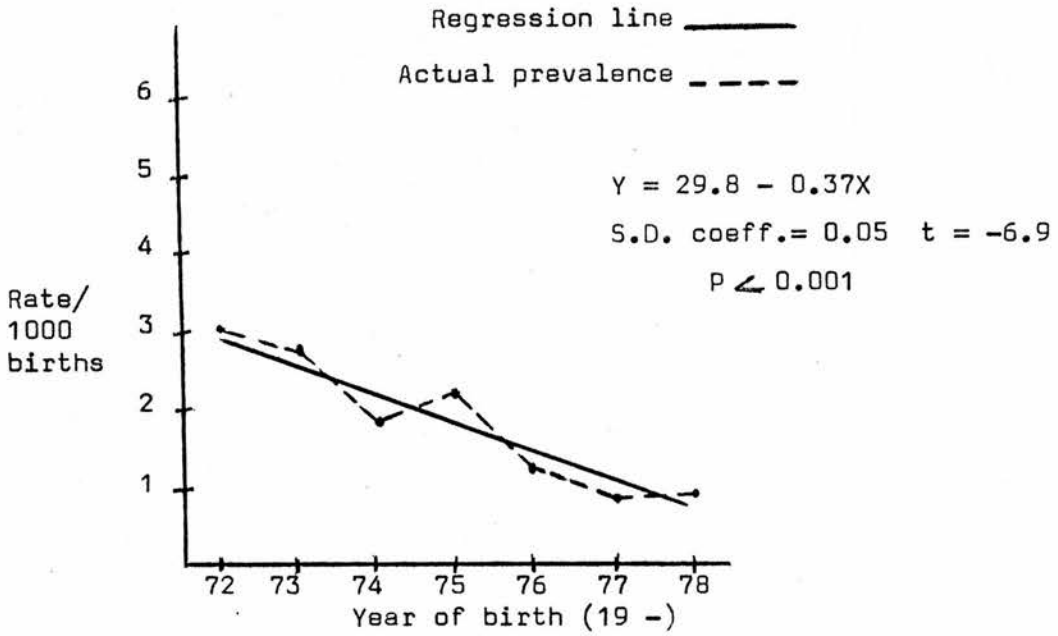


FIGURE 5. PREVALENCE OF (a) ANENCEPHALUS AND (b) SPINA BIFIDA IN GLASGOW, 1972-78 (REGRESSION ANALYSIS).

(a) ANENCEPHALUS



(b) SPINA BIFIDA

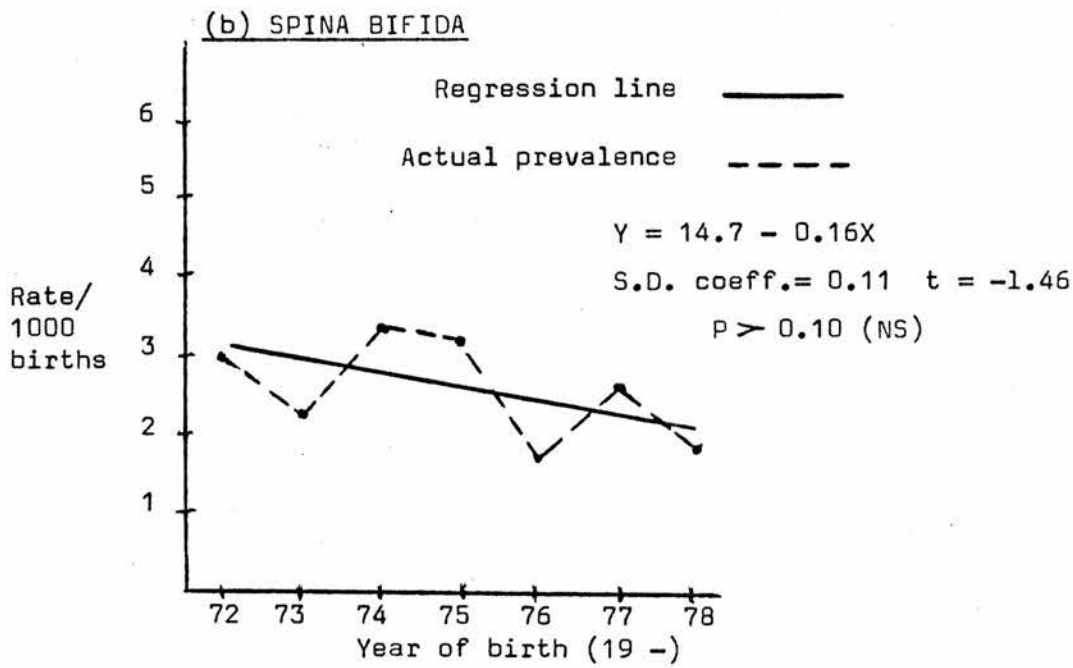


FIGURE 6. PREVALENCE OF "A.S.B." (BIRTHS AND TERMINATIONS) BY MATERNAL AGE, 1975-78.

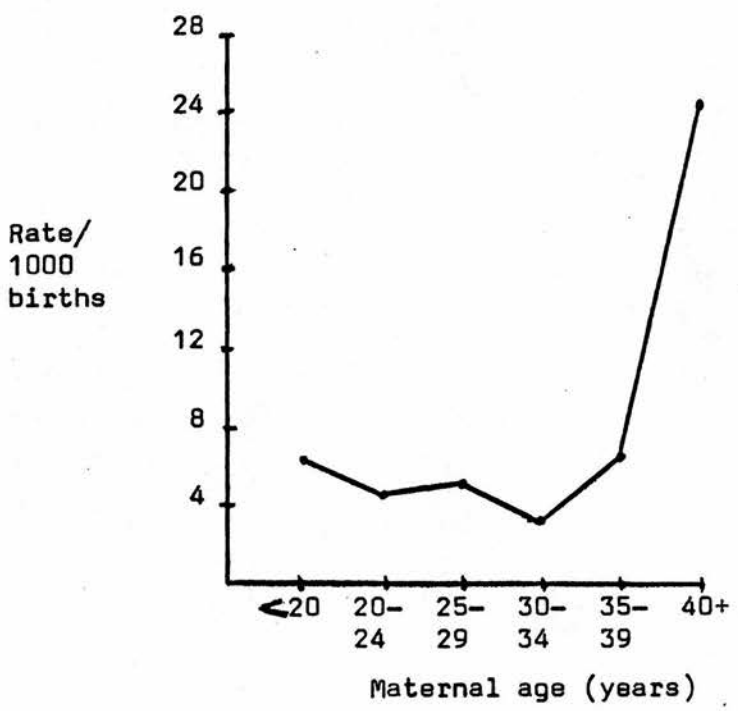


FIGURE 7. PREVALENCE OF "A.S.B." (BIRTHS AND TERMINATIONS) BY MATERNAL PARITY, 1975-78

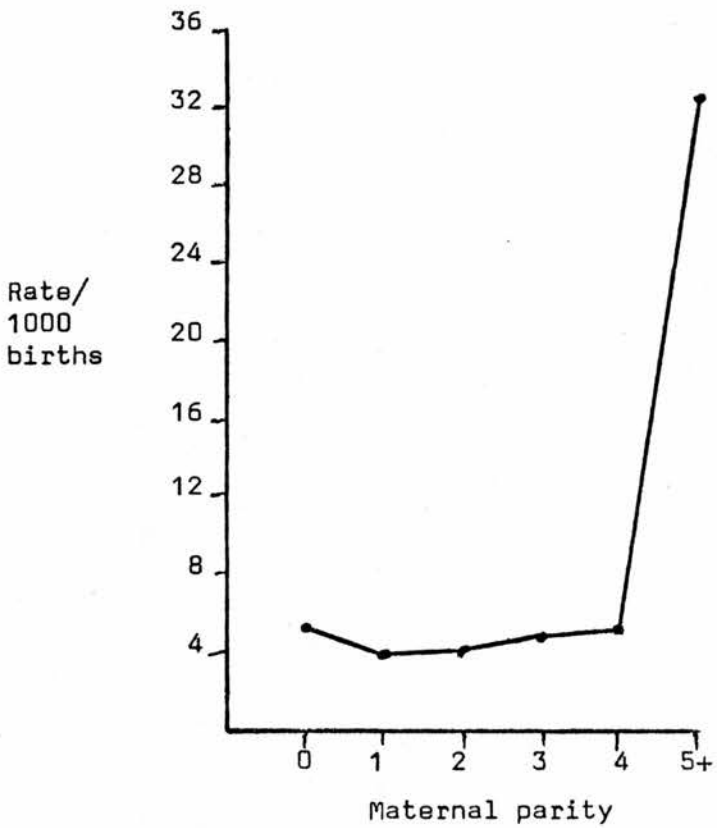


FIGURE 8. MATERNAL AGE EFFECT ON PREVALENCE OF ANENCEPHALUS (BIRTHS AND TERMINATIONS) WITHIN PARITY GROUPS, 1975-78

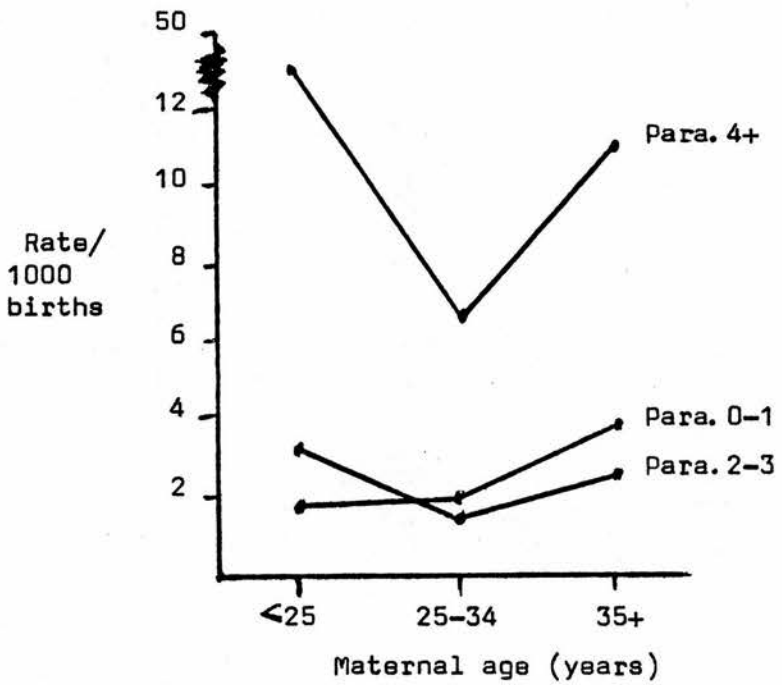


FIGURE 9. MATERNAL AGE EFFECT ON PREVALENCE OF SPINA BIFIDA (BIRTHS AND TERMINATIONS) WITHIN PARITY GROUPS

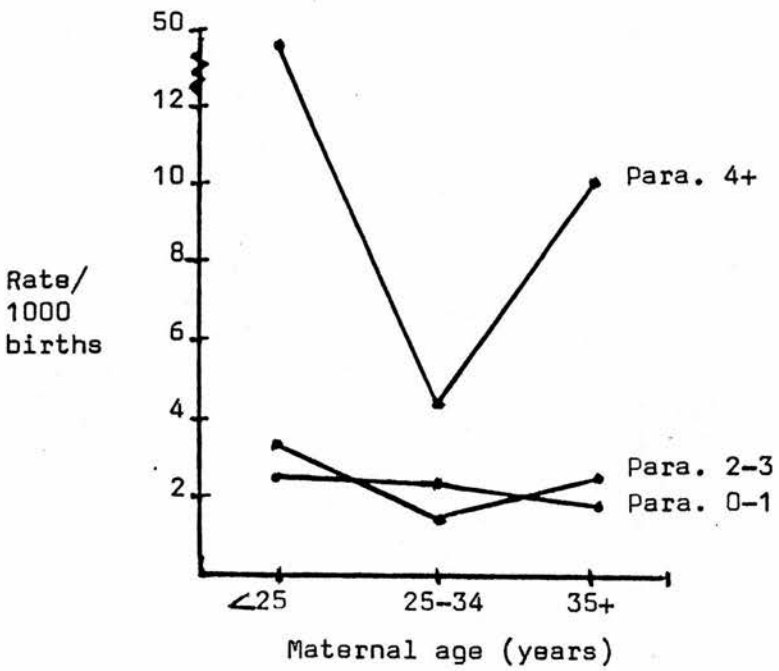


FIGURE 10. MATERNAL PARITY EFFECT ON PREVALENCE OF ANENCEPHALUS (BIRTHS AND TERMINATIONS) WITHIN AGE GROUPS, 1975–78

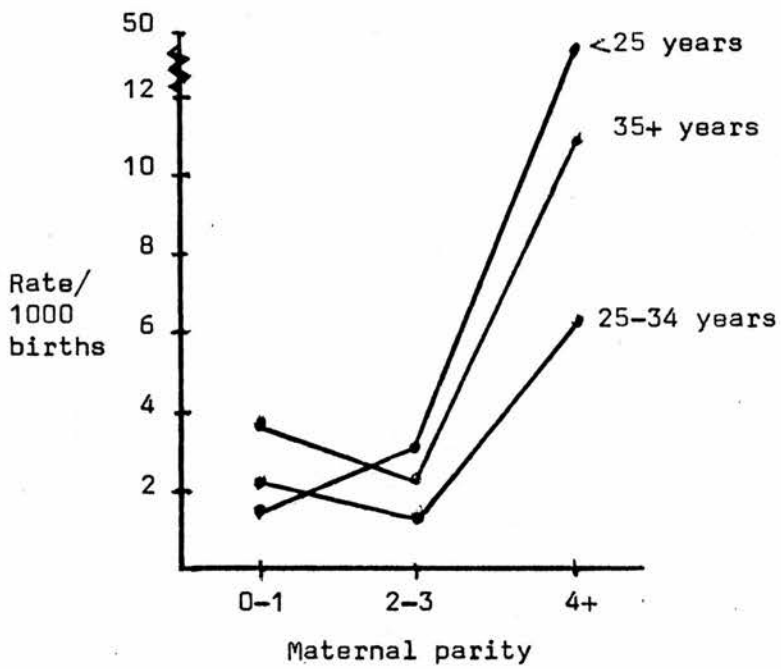


FIGURE 11. MATERNAL PARITY EFFECT ON PREVALENCE OF SPINA BIFIDA (BIRTHS AND TERMINATIONS) WITHIN AGE GROUPS, 1975-78

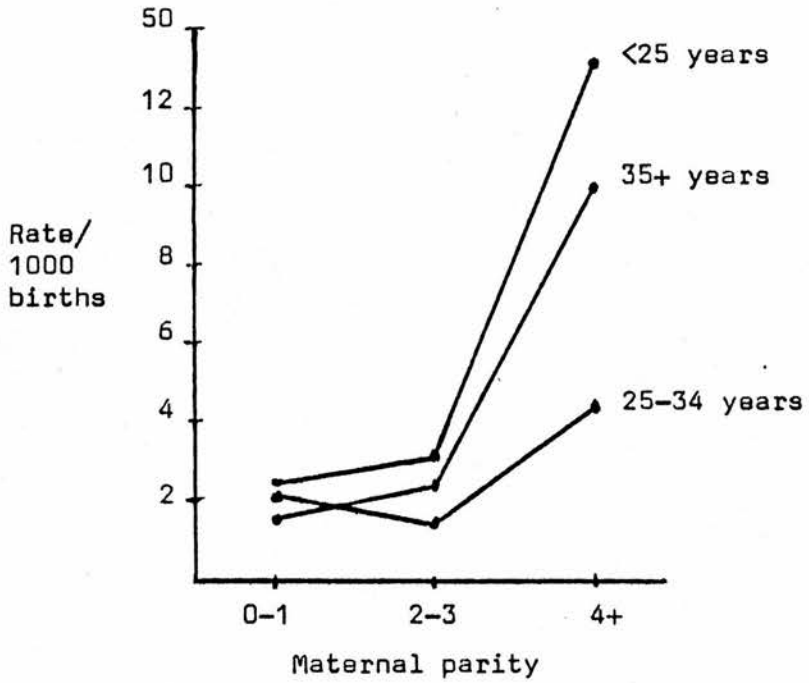
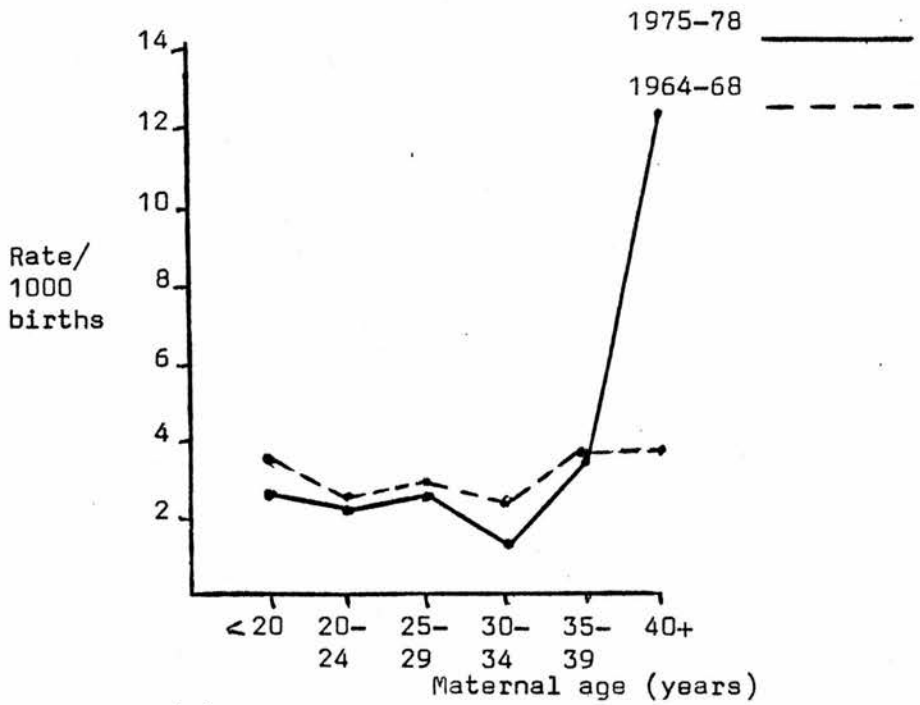


FIGURE 12. MATERNAL AGE DISTRIBUTION OF (a) ANENCEPHALUS AND (b) SPINA BIFIDA, 1964-68 AND 1975-78

(a) ANENCEPHALUS



(b) SPINA BIFIDA

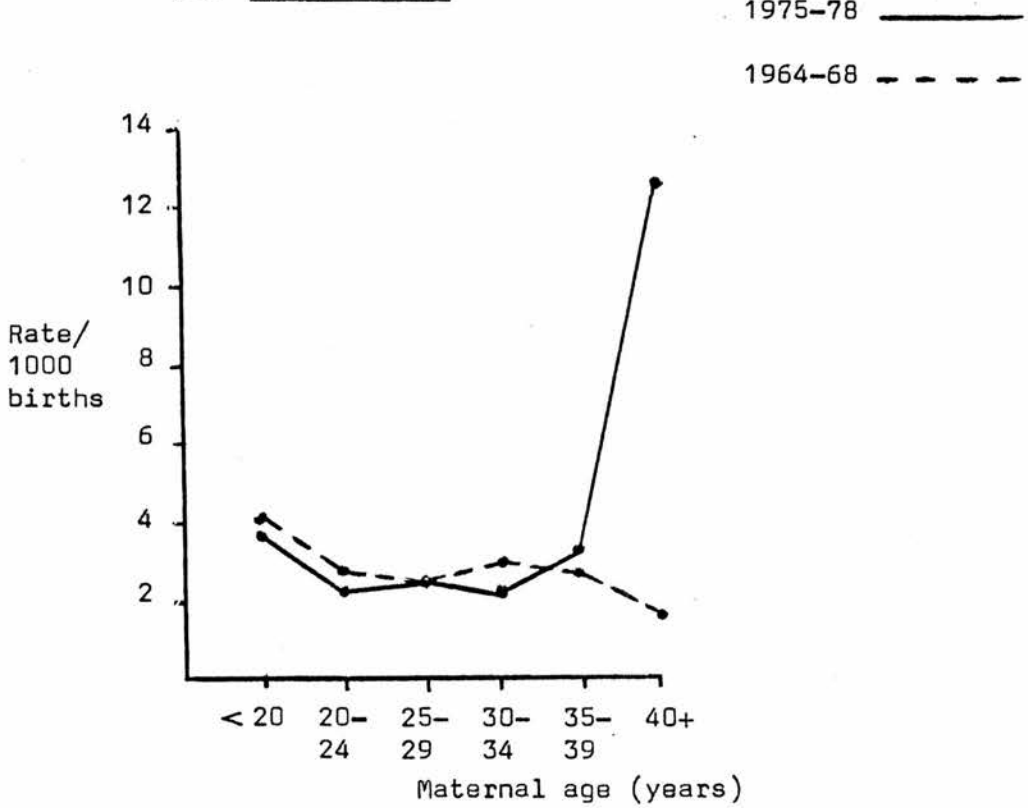
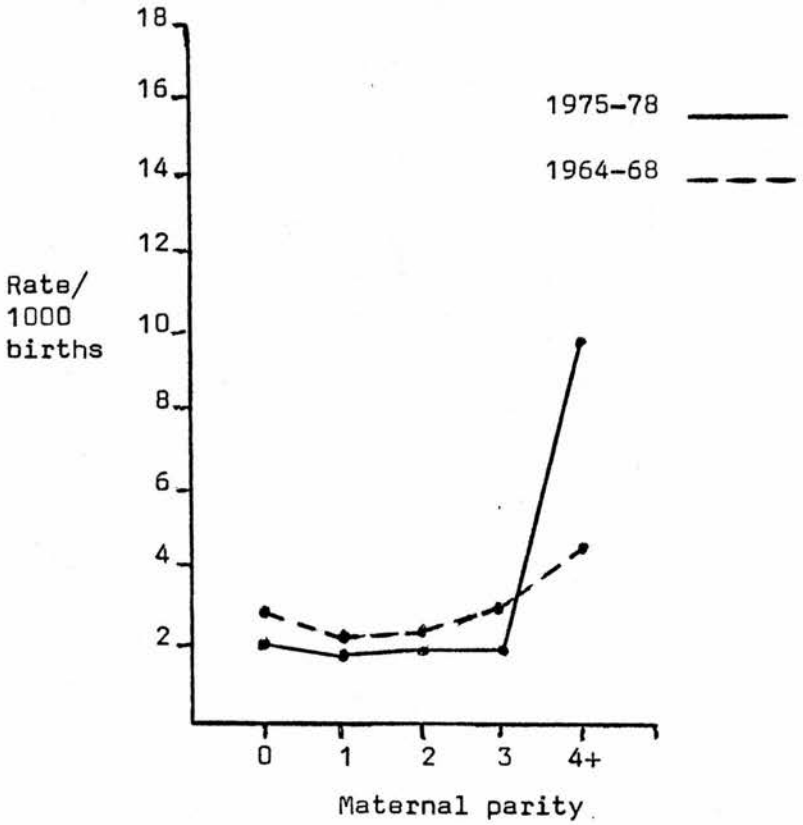


FIGURE 13. MATERNAL PARITY DISTRIBUTION OF (a) ANENCEPHALUS AND (b) SPINA BIFIDA, 1964-68 AND 1975-78.

(a) ANENCEPHALUS



(b) SPINA BIFIDA

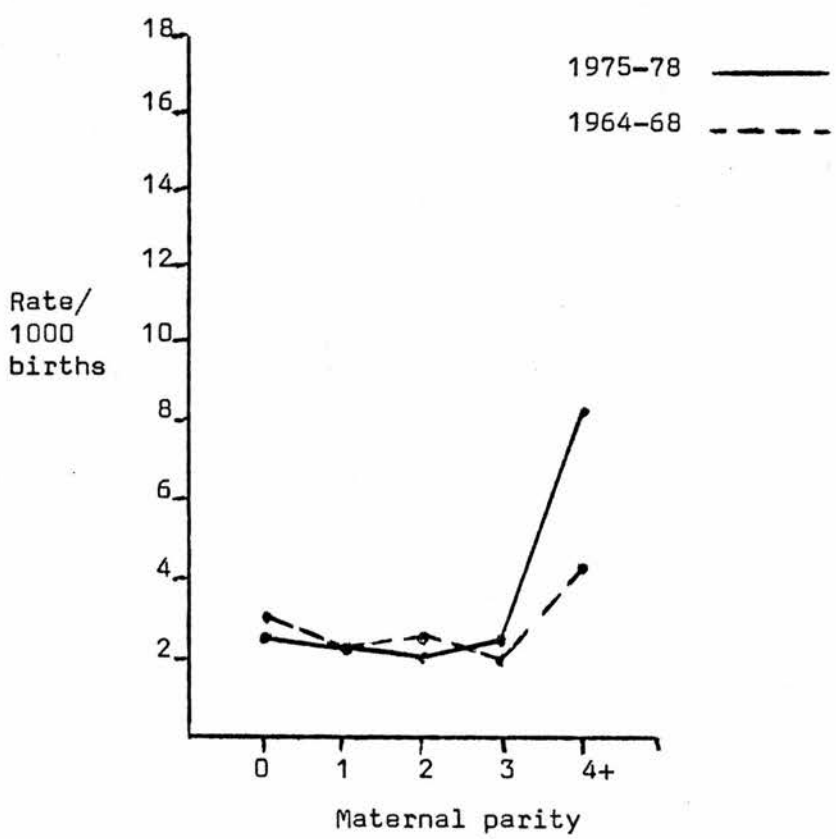
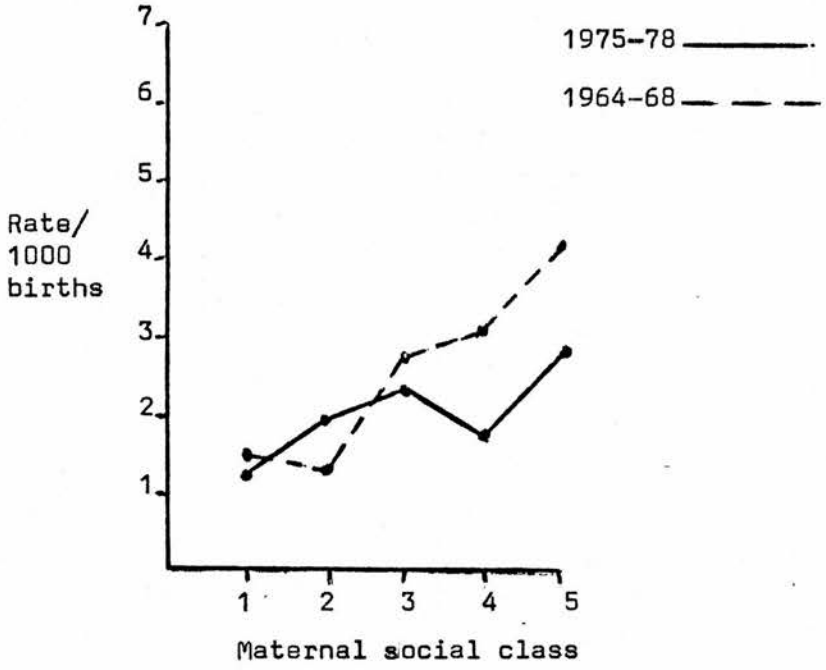


FIGURE 14. MATERNAL SOCIAL CLASS DISTRIBUTION OF (a) ANENCEPHALUS AND (b) SPINA BIFIDA, 1964-68 AND 1975-78

(a) ANENCEPHALUS



(b) SPINA BIFIDA

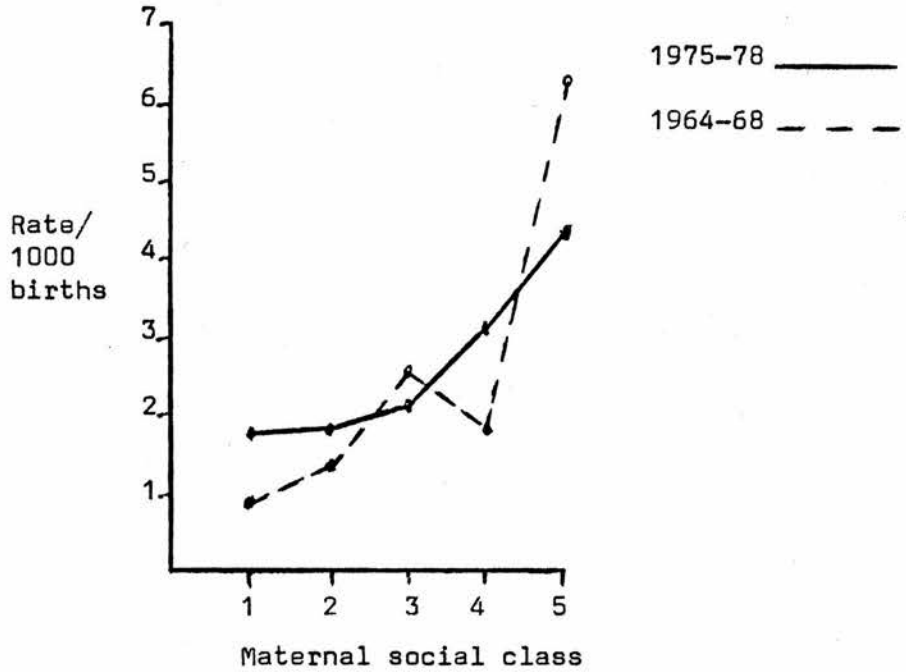


FIGURE 15

HYPOTHETICAL MODEL OF THE AETIOLOGY OF ANENCEPHALUS AND SPINA BIFIDA

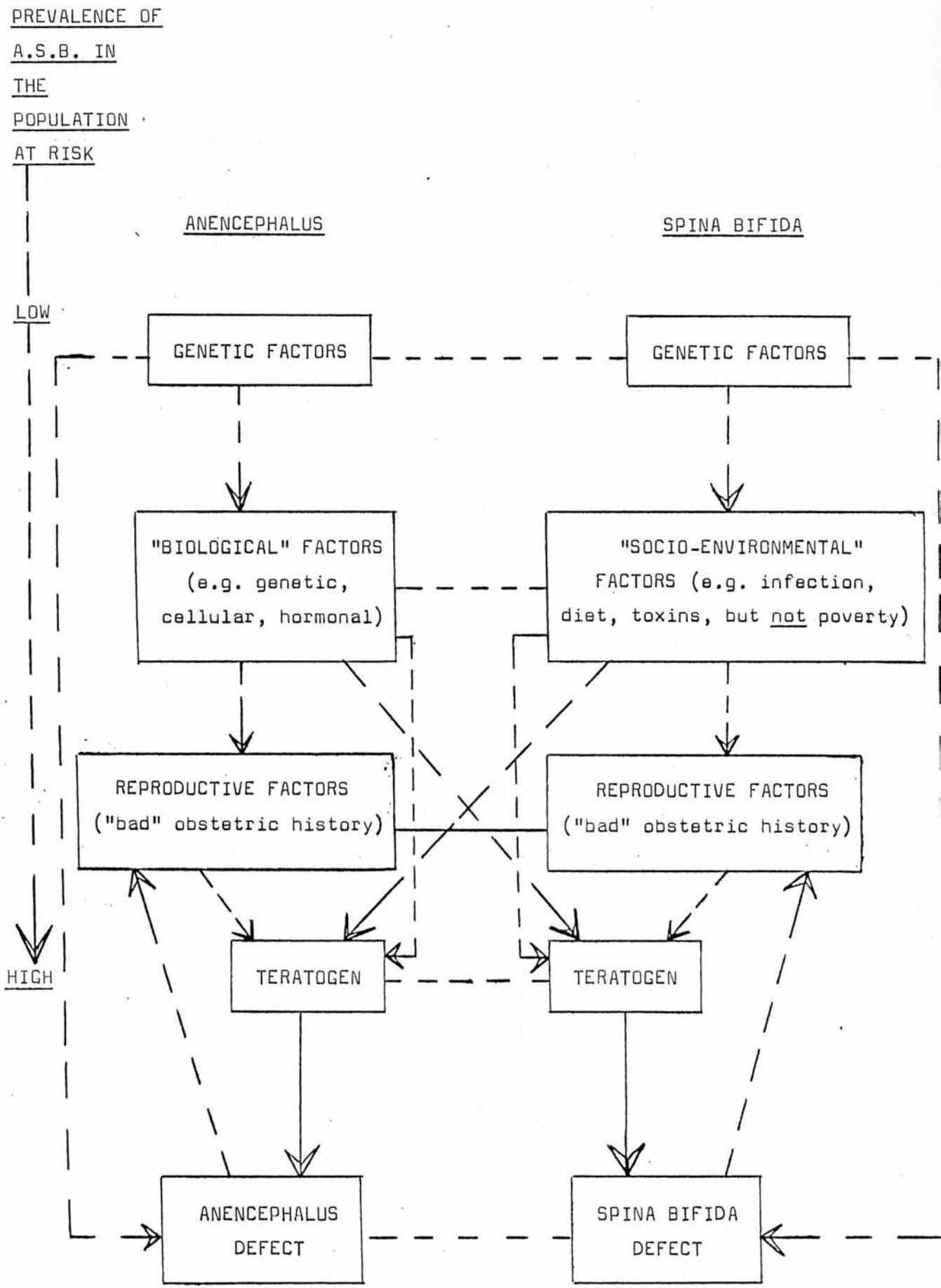


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TABLE 38. Comparison of Distribution of Glasgow Births by Maternal Social Class in 1964-68 and 1975-78.

TABLE 39. Results of Serum A.F.P. Screening (West of Scotland Programme 1975-77) : after Ferguson-Smith et al. (1978).

TABLE 1 ANNUAL CHANGES IN BIRTHS, DEATHS AND MIGRATION, 1972-78
GREATER GLASGOW HEALTH BOARD AREA (THOUSANDS)

MID-YEAR	ESTIMATED HOME POPULATION	POPULATION CHANGE	BIRTHS	DEATHS	NATURAL INCREASE	NET MIGRATION	OTHER CHANGES
1972	1,170.2	-22.7	17.1	15.0	+2.1	-25.5	+0.7
1973	1,147.5	-18.1	15.3	15.2	+0.1	-20.7	+0.5
1974	1,129.4	-23.7	14.5	14.7	-0.2	-22.8	-0.8
1975	1,105.6	-23.7	13.7	14.9	-1.1	-22.5	0.0
1976	1,082.0	-23.2	12.3	14.1	-1.8	-21.8	+0.4
1977	1,058.7	-20.7	12.4	14.6	-2.2	-18.7	+0.2
1978	1,038.0						

Source: Annual Report of the Registrar General for Scotland (1978), Edinburgh.

TABLE 2. PERCENTAGE ECONOMICALLY ACTIVE AND RETIRED MALES BY SOCIAL CLASS (1971)

SOCIAL CLASS (Registrar General's Classification)	GLASGOW	SCOTLAND	ENGLAND AND WALES
I	6.8	10.9	12.5
II	3.0	4.4	4.8
III(a)	17.0	15.6	17.3
III(b)	40.2	38.3	37.6
IV	15.3	16.4	15.0
V	13.6	10.1	7.6

Source : Millar, Ann R. (1975), Glasgow Change Exercise : An Analysis of Change 1966-71, Using Census Variables, Scottish Development Department, Edinburgh.

TABLE 3 TOTAL HOME POPULATION (MID-YEAR ESTIMATES), TOTAL BIRTHS, PERINATAL AND INFANT MORTALITY RATES OF GLASGOW (CITY OF GLASGOW, 1972-73, GREATER GLASGOW HEALTH BOARD AREA, 1974-78 AND SCOTLAND, 1972-78

YEAR	GLASGOW				SCOTLAND			
	TOTAL HOME POPULATION	TOTAL BIRTHS	PERINATAL MORTALITY RATE	INFANT MORTALITY RATE	TOTAL HOME POPULATION	TOTAL BIRTHS	PERINATAL MORTALITY RATE	INFANT MORTALITY RATE
1972	861,898	13,233	28	25	5,210,400	79,603	24	19
1973	835,622	11,947	25	21	5,211,700	75,265	22	19
1974	1,129,387	14,880	23	20	5,226,400	70,943	23	19
1975	1,105,645	14,398	23	19	5,206,200	68,708	21	17
1976	1,081,989	12,889	20	17	5,205,100	65,524	18	15
1977	1,058,743	12,487	20	18	5,195,600	64,895	18	16
1978	1,038,023	12,491	16	14	5,179,400	64,819	15	13

Source: Annual Reports of the Registrar General for Scotland (1972-78), HMSO, Edinburgh.

TABLE 4. SECULAR TREND IN THE PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA BETWEEN 1964-68[1] and 1972-78.

BIRTH YEARS	TOTAL BIRTHS	ANENCEPHALUS BIRTHS		SPINA BIFIDA BIRTHS		A.S.B. BIRTHS	
		NO.	RATE[2]	NO.	RATE[2]	NO.	RATE[2]
1964-68	103,123	292	2.83	289	2.80	581	5.63
1972-78	92,325	168	1.82	242	2.62	410	4.44

[1] Source : Wilson (1970)

[2] Prevalence is expressed as a rate per 1000 total births in this and all subsequent tables.

Anencephalus/total births X^2 (1 d.f.) = 21.15 $P < 0.001$

Spina bifida/total births X^2 (1 d.f.) = 0.59 $P > 0.1$ (NS)

TABLE 5. PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA IN GLASGOW 1972-78.

BIRTH YEAR	TOTAL BIRTHS	ANENCEPHALY BIRTHS		SPINA BIFIDA BIRTHS		A.S.B. BIRTHS	
		NO.	RATE	NO.	RATE	NO.	RATE
1972	13,233	40	3.02	40	3.02	80	6.05
1973	11,947	32	2.68	28	2.34	60	5.02
1974	14,880	26	1.75	50	3.36	76	5.11
1975	14,398	31	2.15	46	3.19	77	5.35
1976	12,889	17	1.32	22	1.71	39	3.03
1977	12,487	11	0.88	32	2.56	43	3.44
1978	12,491	11	0.88	24	1.92	35	2.80
1972-78	92,325	168	1.82	242	2.62	410	4.44

Anencephalus/total births X^2 (6 d.f.) = 30.11 $P < 0.001$

Spina bifida/total births X^2 (6 d.f.) = 12.50 $P > 0.05$ (NS)

TABLE 6. SEASONAL VARIATION OF ANENCEPHALUS AND SPINA BIFIDA BIRTHS, GLASGOW, 1972-78.

DEFECT	QUARTER OF BIRTH				TOTAL
	JAN-MAR. NO. (%)	APR-JUN. NO. (%)	JUL-SEP. NO. (%)	OCT-DEC. NO. (%)	NO. (%)
ANENCEPHALUS	37(22.02)	34(20.24)	53(31.55)	44(26.19)	168 (100)
SPINA BIFIDA	76(31.40)	49(20.25)	51(21.07)	66(27.27)	242 (100)
A.S.B.	113(27.56)	83(20.24)	104(25.37)	110(26.83)	410 (100)
TOTAL BIRTHS (1975-78 ONLY)	13,286 (25.44)	13,011 (24.92)	12,810 (24.53)	13,112 (25.11)	52,219 (100)

Anencephalus/total births X^2 (3 d.f.) = 5.68 $P > 0.10$ (NS)

Spina bifida/total births X^2 (3 d.f.) = 7.09 $P > 0.05$ (NS)

TABLE 7 PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA AROUND THE WORLD : SELECTED STUDIES

AREA	NO. OF BIRTHS	PREVALENCE (Rates per 1000 total births) OF:			AUTHORS
		ANENCEPHALUS	SPINA BIFIDA	A.S.B.	
United Kingdom					
BELFAST	41,351	4.20	4.50	8.70	Elwood and Nevin 1973
SOUTH WALES	102,786	3.55	4.13	7.68	Laurence et al 1968
LIVERPOOL	91,176	3.14	3.36	6.50	Smithells 1968
GLASGOW (1964-68)	103,123	2.83	2.80	5.63	Wilson 1970
BIRMINGHAM	190,236	2.41	2.36	4.77	Leck et al 1968
GLASGOW (1972-78)*	92,325	1.82	2.62	4.44	
LONDON	409,466	1.41	1.54	2.95	Carter and Evans 1973
Rest of World					
ALEXANDRIA	9,598	3.79	1.65	5.44	Stevenson et al 1966
NEW BRUNSWICK	49,031	1.51	2.46	3.97	Elwood and Rogers 1975
QUEBEC	656,000	1.45	1.87	3.32	Horowitz and McDonald 1969
BOMBAY	76,763	1.89	1.08	2.97	Stevenson et al 1966
BUDAPEST	692,670	1.10	1.63	2.73	Czeizel and Revesz 1970
IZMIR	44,795	1.99	0.54	2.53	Buckley and Erten 1979
BOSTON	311,437	0.98	1.26	2.24	Naggan and MacMahon 1967
ISRAEL	531,985	0.86	0.60	1.46	Naggan 1970
BRITISH COLUMBIA	135,730	0.58	0.87	1.45	Elwood and Rogers 1975
TAIWAN	25,814	1.17	0.16	1.33	Emanuel et al 1972
MELBOURNE	225,250	0.72	0.59	1.31	Stoller and Collman 1965
NEW YORK STATE	1,580,499	0.61	0.67	1.28	Janerich 1973
SWEDEN	159,500	0.37	0.72	1.09	Kallen and Winberg 1968
MOSCOW	282,336	0.33	0.41	0.74	Prytkov 1978
FINLAND	621,026	0.32	0.38	0.70	Granroth et al 1977

* PRESENT STUDY

TABLE 8. PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA BIRTHS IN THE FIVE HEALTH DISTRICTS OF GLASGOW, 1975-78.

DEFECT	HEALTH DISTRICT										ALL DISTRICTS	
	NORTH		WEST		EAST		SOUTH-EAST		SOUTH-WEST			
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
ANENCEPHALUS	16	1.73	11	0.91	19	1.68	9	0.76	15	1.94	70	1.34
SPINA BIFIDA	26	2.81	31	2.55	31	2.75	24	2.02	12	1.56	124	2.37
A.S.B.	42	4.53	42	3.46	50	4.43	33	2.78	27	3.50	194	3.71
TOTAL BIRTHS	9,267		12,134		11,293		11,858		7,713		52,265	

Anencephalus/total births X^2 (4 d.f.) = 8.81 $P > 0.05$ (NS)

Spina bifida/total births X^2 (4 d.f.) = 4.33 $P > 0.10$ (NS)

TABLE 9. "PREGNANCY" PREVALENCE (births and terminations) OF ANENCEPHALUS AND SPINA BIFIDA IN THE FIVE HEALTH DISTRICTS OF GLASGOW, 1975-78.

DEFECT	HEALTH DISTRICT					ALL DISTRICTS
	NORTH	WEST	EAST	SOUTH-EAST	SOUTH-WEST	
	NO. RATE	NO. RATE	NO. RATE	NO. RATE	NO. RATE	NO. RATE
ANENCEPHALUS	30 3.24	25 2.06	34 3.01	15 1.26	24 3.11	128 2.45
SPINA BIFIDA	27 2.91	35 2.88	34 3.01	28 2.36	13 1.69	137 2.62
A.S.B.	57 6.15	60 4.94	68 6.02	43 3.63	37 4.80	265 5.07
TOTAL BIRTHS	9,267	12,134	11,293	11,858	7,713	52,265

Anencephalus/total births X^2 (4 d.f.) = 12.70 $P < 0.05$

Spina bifida/total births X^2 (4 d.f.) = 4.15 $P > 0.10$ (NS)

TABLE 10. SEX DISTRIBUTION OF ANENCEPHALUS, SPINA BIFIDA AND TOTAL BIRTH POPULATIONS, GLASGOW, 1972–78.

DEFECT	MALES NO. (%)	FEMALES NO. (%)	TOTAL NO. (%)
ANENCEPHALUS	55 (32.7)	113 (67.3)	168 (100)
SPINA BIFIDA	108 (44.6)	134 (55.4)	242 (100)
A.S.B.	163 (39.8)	247 (60.2)	410 (100)
ALL GLASGOW BIRTHS	47,492 (51.44)	44,825 (48.56)	92,317 (100)

N.B. Births of unknown sex excluded.

Anencephalus/total births X^2 (1 d.f.) = 23.49 $P < 0.001$

Spina bifida/total births X^2 (1 d.f.) = 4.49 $P < 0.05$

TABLE 11. FREQUENCY OF SINGLETON AND MULTIPLE BIRTHS IN ANENCEPHALUS, SPINA BIFIDA AND TOTAL BIRTH POPULATIONS, GLASGOW, 1972-78

POPULATION	TYPE OF BIRTH			TOTAL NO. (%)
	SINGLETON NO. (%)	TWIN NO. (%)	OTHER NO. (%)	
ANENCEPHALIC BIRTHS	167 (99.40)	1 (0.60)	0 (0.0)	168 (100)
SPINA BIFIDA BIRTHS	240 (99.17)	2 (0.83)	0 (0.0)	242 (100)
A.S.B. BIRTHS	407 (99.27)	3 (0.73)	0 (0.0)	410 (100)
ALL GLASGOW BIRTHS (1975-78 ONLY)	50,797 (99.11)	451 (0.88)	4 (0.01)	51,252 (100)

TABLE 12. FREQUENCY OF STILLBIRTHS, FIRST WEEK DEATHS AND SURVIVING LIVEBIRTHS IN ANENCEPHALUS, SPINA BIFIDA AND TOTAL BIRTH POPULATIONS, GLASGOW, 1972-78.

POPULATION	OUTCOME			TOTAL NO. (%)
	STILLBIRTHS NO. (%)	FIRST WEEK DEATHS NO. (%)	SURVIVORS[1] NO. (%)	
ANENCEPHALIC BIRTHS	148 (88.10)	17 (10.12)	3[2] (1.79)	168 (100)
SPINA BIFIDA BIRTHS	41 (16.94)	25 (10.33)	176 (72.73)	242 (100)
A.S.B. BIRTHS	189 (46.10)	42 (10.24)	179 (43.66)	410 (100)
ALL GLASGOW BIRTHS	1,078 (1.17)	953 (1.03)	90,294 (97.80)	92,325 (100)

[1] Survivors beyond the first week of life.

[2] All three subsequently died within the first month of life.

TABLE 13 FREQUENCY OF ANENCEPHALUS, SPINA BIFIDA AND TOTAL BIRTHS ACCORDING TO BIRTH WEIGHT (grams), IN GLASGOW, 1972-78

POPULATION	BIRTH WEIGHT (grams)									
	<1500		1500-1999		2000-2499		2500+		TOTAL	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ANENCEPHALUS BIRTHS	116	(69.05)	22	(13.10)	16	(9.52)	14	(8.33)	168	(100)
SPINA BIFIDA BIRTHS	39	(16.12)	8	(3.31)	19	(7.85)	176	(72.73)	242	(100)
A.S.B. BIRTHS	155	(37.80)	30	(7.32)	35	(8.54)	190	(46.34)	410	(100)
ALL GLASGOW BIRTHS[1] (1975-77 only)	352	(0.93)	474	(1.25)	1785	(4.69)	35,254	(92.70)	38,029[2]	(100)

1 Births in Glasgow hospitals, not to Glasgow residents

2 Includes 164 births of unknown weight

TABLE 14. FREQUENCY OF ANENCEPHALUS, SPINA BIFIDA AND TOTAL BIRTHS ACCORDING TO GESTATION, GLASGOW, 1972-78.

POPULATION	ESTIMATED GESTATIONAL AGE (IN WEEKS) AT DELIVERY			
	∠ 37	37 - 41	42 +	TOTAL
	NO. (%)	NO. (%)	NO. (%)	NO. (%)
ANENCEPHALIC BIRTHS	110 (65.48)	32 (19.05)	26 (15.48)	168 (100)
SPINA BIFIDA BIRTHS	17 (7.02)	183 (75.62)	42 (17.36)	242 (100)
A.S.B. BIRTHS	127 (30.98)	215 (52.44)	68 (16.59)	410 (100)
ALL GLASGOW BIRTHS (1975-78 ONLY)	2,138 (5.14)	38,792 (93.29)	652 (1.57)	41,583 (100)

TABLE 15. DISTRIBUTION OF ANENCEPHALUS AND SPINA BIFIDA BIRTHS ACCORDING TO FREQUENCY OF ASSOCIATED MALFORMATIONS, GLASGOW, 1972-78.

NO. OF ASSOCIATED MALFORMATIONS	DEFECT		
	ANENCEPHALUS NO. (%)	SPINA BIFIDA NO. (%)	A.S.B. NO. (%)
0	144 (85.71)	194 (80.17)	338 (82.44)
1	19 (11.31)	38 (15.70)	57 (13.90)
2 or more	5 (2.98)	10 (4.13)	15 (3.66)
TOTAL	168 (100)	242 (100)	410 (100)

Anencephalus/Spina bifida X^2 (2 d.f.) = 2.11 $P > 0.10$ (NS)

TABLE 16 CONGENITAL MALFORMATIONS ASSOCIATED WITH ANENCEPHALUS AND SPINA BIFIDA, GLASGOW, 1972-78

ANENCEPHALUS				SPINA BIFIDA			
ICD[1] Code	MALFORMATION	No.	(%)	ICD Code	MALFORMATION	No.	(%)
741	Spina bifida cystica	16	(51.61)	754, 755	Limb defects	26	(41.94)
756	Spina bifida occulta	4	(12.90)	756	Spina bifida occulta	9	(14.52)
759	Unspecified anomalies	4	(12.90)	753	Congenital heart defects	8	(12.90)
749	Cleft palate and lip	2	(6.45)	742	Urinary tract anomalies	6	(9.68)
751	Digestive tract defects	1	(3.23)	745-747	CNS defects, other than S.B.	5	(8.06)
755	Congenital limb defects	1	(3.23)	751	Digestive tract defects	1	(1.61)
742	CNS defects, other than S.B.	1	(3.23)	758	Chromosomal defects	2	(3.23)
753	Urinary tract anomalies	1	(3.23)	550	Inguinal hernia	2	(3.23)
747	Congenital heart defects	1	(3.23)	744	Defects of ear, face and neck	1	(1.61)
				749	Cleft palate and lip	1	(1.61)
				685	Pilonidal cyst	1	(1.61)
	TOTAL[2]	31	(100)		TOTAL	62	(100)

1 Ninth Revision (WORLD HEALTH ORGANIZATION 1977)

2 Defects, not children

TABLE 17. PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA (BIRTHS AND TERMINATIONS) BY MATERNAL AGE AT DELIVERY (ACTUAL OR EXPECTED), GLASGOW, 1975-78.

MATERNAL AGE	DEFECT						TOTAL BIRTHS
	ANENCEPHALUS		SPINA BIFIDA		A.S.B.		
	NO.	RATE/ 1000	NO.	RATE/ 1000	NO.	RATE/ 1000	
< 20	18	2.50	27	3.74	45	6.24	7,212
20-24	37	2.24	36	2.18	73	4.41	16,540
25-29	43	2.60	40	2.42	83	5.02	16,528
30-34	10	1.31	17	2.22	27	3.53	7,653
35-39	9	3.48	8	3.09	17	6.57	2,587
40 +	9	12.30	9	12.30	18	24.60	732
Not known	2	-	0	-	2	-	-
ALL AGES	128	2.50	137	2.67	265	5.17	51,252

Anencephalus/total births X^2 (5 d.f.) = 34.15 $P < 0.001$

Spina bifida/total births X^2 (5 d.f.) = 30.80 $P < 0.001$

TABLE 18. PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA (BIRTHS AND TERMINATIONS) BY MATERNAL PARITY, GLASGOW, 1975-78.

MATERNAL PARITY	DEFECTS						TOTAL BIRTHS
	ANENCEPHALUS		SPINA BIFIDA		A.S.B.		
	NO.	RATE/ 1000	NO.	RATE/ 1000	NO.	RATE/ 1000	
0	43	1.96	57	2.60	100	4.55	21,956
1	32	1.92	35	2.10	67	4.03	16,630
2	14	1.96	15	2.10	29	4.05	7,157
3	6	2.01	7	2.34	13	4.35	2,991
4	4	3.07	3	2.30	7	5.36	1,305
5+	21	17.31	18	14.84	39	32.15	1,213
Not known	8	-	2	-	10	-	0
ALL PARITIES	128	2.50	137	2.67	265	5.17	51,252

Anencephalus/total births X^2 (5 d.f.) = 118 $P < 0.001$

Spina bifida/total births X^2 (5 d.f.) = 70 $P < 0.001$

TABLE 19. ASSOCIATION OF MATERNAL AGE AND PARITY : ANENCEPHALUS (BIRTHS AND TERMINATIONS), GLASGOW, 1975–78.

PARITY	MATERNAL AGE (YEARS)						NOT KNOWN	ALL AGES	
	< 25		25 – 34		35 +				
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	NO.	RATE
0 – 1	39	1.83	33	2.04	4	3.80	0	76	1.97
2 – 3	7	3.07	10	1.52	3	2.36	0	20	1.97
4+	5	46.30	9	6.39	11	10.95	0	25	9.91
Not known	5	–	1	–	0	–	2	8	–
ALL PARITIES	56	2.36	53	2.19	18	5.41	2	129	2.52

X^2 (4 d.f.) = 24.16 $P < 0.001$

TABLE 20. ASSOCIATION OF MATERNAL AGE AND PARITY : SPINA BIFIDA (BIRTHS AND TERMINATIONS), GLASGOW, 1975-78.

PARITY	MATERNAL AGE (YEARS)						NOT KNOWN	ALL AGES	
	< 25		25-34		35+				
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	NO.	RATE
0 - 1	54	2.53	36	2.23	2	1.90	0	92	2.38
2 - 3	7	3.07	10	1.52	3	2.36	0	20	1.97
4 +	5	46.30	6	4.26	10	9.95	0	21	8.33
Not known	1	-	1	-	0	-	1	3	-
ALL PARITIES	67	2.82	53	2.19	15	4.51	1	136	2.65

X^2 (4 d.f.) = 38.0 P < 0.001

TABLE 21. MATERNAL SOCIAL CLASS DISTRIBUTION OF ANENCEPHALUS AND SPINA BIFIDA (BIRTHS AND TERMINATIONS), GLASGOW, 1975-78.

MATERNAL SOCIAL CLASS	DEFECT						TOTAL BIRTHS
	ANENCEPHALUS		SPINA BIFIDA		A.S.B.		
	NO.	RATE	NO.	RATE	NO.	RATE	
1	5	1.26	7	1.76	12	3.02	3,973
2	13	1.95	12	1.80	25	3.75	6,670
3	63	2.44	55	2.13	118	4.56	25,864
4	18	1.83	30	3.05	48	4.88	9,839
5	16	2.91	24	4.37	40	7.28	5,498
Not known	13	-	9	-	22	-	521
ALL SOCIAL CLASSES	128	2.45	137	2.62	265	5.07	52,265

Anencephalus/total births X^2 (4 d.f.) = 4.27 $P > 0.10$ (NS)

Spina bifida/total births X^2 (4 d.f.) = 12.55 $P < 0.05$

TABLE 22. PREVALENCE OF ANENCEPHALUS AND SPINA BIFIDA IN THE 12 POST-CODE SECTOR GROUPINGS OF GLASGOW, 1975-77.

POST-CODE SECTOR GROUPINGS	ANENCEPHALUS		SPINA BIFIDA		A.S.B.		TOTAL BIRTHS
	NO.	RATE	NO.	RATE	NO.	RATE	
A	3	2.56	5	4.27	8	6.83	1.171
B	15	3.66	17	4.15	32	7.82	4,094
C	10	2.70	11	2.97	21	5.67	3,703
D	7	2.15	13	3.99	20	6.14	3,256
E	3	1.41	4	1.87	7	3.28	2,135
F	6	1.40	9	2.11	15	3.51	4,271
G	12	4.07	5	1.70	17	5.77	2,946
H	3	0.96	9	2.87	12	3.83	3,134
I	5	2.13	5	2.13	10	4.26	2,348
J	11	2.95	15	4.02	26	6.98	3,727
K	14	2,60	10	1.86	24	4.46	5,382
L	2	0.67	5	1.68	7	2.35	2,984
Others	1	-	2	-	3	-	-
ALL 12 GROUPINGS	92	2.35	110	2.81	202	5.16	39,151

Anencephalus/total births X^2 (11 d.f.) = 16.5 $P > 0.10$ (NS)

Spina bifida/total births X^2 (11 d.f.) = 13.50 $P > 0.10$ (NS)

A.S.B. /total births X^2 (11 d.f.) = 20.02 $P < 0.05$

TABLE 23. ASSOCIATION OF MATERNAL SOCIAL CLASS AND HEALTH DISTRICT OF RESIDENCE : ANENCEPHALUS (BIRTHS AND TERMINATIONS), 1975-77.

MATERNAL SOCIAL CLASS	HEALTH DISTRICT OF RESIDENCE										ALL DISTRICTS	
	NORTH		WEST		EAST		SOUTH-EAST		SOUTH-WEST			
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
1 + 2	3	2.31	3	1.21	1	1.63	2	0.81	3	3.24	12	1.54
3	16	4.78	10	2.23	10	2.30	6	1.40	3	1.01	45	2.31
4 + 5	4	2.19	5	2.33	7	1.93	3	1.45	8	4.26	27	2.34
Not known	2	-	1	-	2	-	2	-	1	-	8	-
ALL SOCIAL CLASSES	25	3.82	19	2.07	20	2.30	13	1.46	15	2.58	92	2.35

X^2 (8 d.f.) = 10.22 $P > 0.10$ (NS)

TABLE 24. ASSOCIATION OF MATERNAL SOCIAL CLASS AND HEALTH DISTRICT OF RESIDENCE : SPINA BIFIDA (BIRTHS AND TERMINATIONS), 1975-77.

MATERNAL SOCIAL CLASS	HEALTH DISTRICT OF RESIDENCE										ALL DISTRICTS	
	NORTH		WEST		EAST		SOUTH-EAST		SOUTH-WEST			
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
1 + 2	5	3.85	4	1.62	0	0.0	6	2.43	1	1.08	16	2.06
3	10	2.99	12	2.67	11	2.52	11	2.56	4	1.34	48	2.47
4 + 5	6	3.28	11	5.13	13	3.59	7	3.38	3	1.60	40	3.46
Not known	1	-	2	-	2	-	1	-	0	-	6	-
ALL SOCIAL CLASSES	22	3.36	29	3.16	26	2.99	25	2.81	8	1.37	110	2.81

X^2 (8 d.f.) = 8.86 $P > 0.10$ (NS)

TABLE 25. ASSOCIATION OF MATERNAL SOCIAL CLASS AND POST-CODE SECTOR GROUPING OF RESIDENCE : A.S.B. (BIRTHS AND TERMINATIONS), 1975-77.

POST-CODE SECTOR GROUPING	SOCIAL CLASS 1		2		3		4		5		NOT KNOWN
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.
A	0	0.00	0	0.00	6	11.15	2	8.81	0	0.00	0
B	0	0.00	0	0.00	18	8.61	5	5.13	8	12.46	1
C	4	5.51	6	6.26	8	5.03	2	6.83	0	0.00	1
D	0	0.00	1	4.39	6	3.49	6	7.72	3	6.94	4
E	0	0.00	1	4.08	2	1.87	1	2.39	2	6.83	1
F	4	5.91	3	2.80	4	2.08	3	7.5	1	5.71	0
G	0	0.00	1	8.85	9	5.95	3	3.79	3	6.49	1
H	0	0.00	1	1.73	8	5.10	1	2.35	1	4.67	1
I	0	0.00	2	8.40	2	1.61	1	1.93	4	15.21	1
J	0	0.00	0	0.00	11	5.27	5	5.60	7	17.81	3
K	1	9.43	2	6.40	14	5.26	4	3.02	2	2.20	1
L	0	0.00	3	6.44	4	2.75	0	0.00	0	0.00	0
ALL GROUPINGS	9	3.08	20	4.11	92	4.73	33	4.46	31	7.46	14
TOTAL BIRTHS	2,922		4,862		19,466		7,396		4,153		35

X^2 (8 d.f.) = 14.24 $0.10 > P > 0.05$ (NS)

TABLE 26 MULTIPLE LINEAR REGRESSION ANALYSIS : Interaction of Place of Residence, Maternal Age[1], Parity[1] and Social Class[2] on Prevalence of anencephalus and spina bifida (births and terminations), 1975-79

POST-CODE SECTOR GROUPING	% TOTAL BIRTHS			PREVALENCE RATE/1000			DENOMINATOR ERROR[3]
	PARITY 5+	MATERNAL AGE 40+ yrs.	S.C.5	ANENCEPHALUS	SPINA BIFIDA	A.S.B.	
A	2.9	1.7	7.3	2.56	4.27	6.83	3
B	3.2	2.2	15.7	3.66	4.15	7.82	16
C	1.0	1.5	3.2	2.70	2.97	5.67	159
D	2.9	1.8	13.3	2.15	3.99	6.14	119
E	3.4	1.7	13.7	1.41	1.87	3.28	53
F	1.8	1.4	4.1	1.40	2.11	3.57	613
G	4.7	2.2	15.7	4.07	1.70	5.77	189
H	1.4	1.0	6.8	0.96	2.87	3.83	1,275
I	2.8	2.1	11.2	2.13	2.13	4.26	151
J	2.4	1.2	10.5	2.95	4.02	6.98	1,113
K	3.5	1.4	16.9	2.60	1.86	4.46	518
L	1.3	1.4	5.5	0.67	1.68	2.35	73
A-L	2.6	1.6	10.6	2.35	2.81	5.16	

1 SOURCE: ad hoc analysis of SMR 2 data, 1975-77

2 SOURCE: ad hoc analysis of Greater Glasgow Health Board (Registrar General) data, 1975-77

3 Difference in total births between the two sources

TABLE 27. PREVALENCE OF ANENCEPHALUS : BIRTHS, TERMINATIONS AND "PREGNANCIES" (BIRTHS AND TERMINATIONS), GLASGOW, 1972-78.

BIRTH YEAR[1]	TOTAL BIRTHS	ANENCEPHALUS BIRTHS		ANENCEPHALUS TERMINATIONS[2]		ANENCEPHALUS PREGNANCIES	
		NO.	RATE	NO.	RATE	NO.	RATE
1972	13,233	40	3.02	0	0.00	40	3.02
1973	11,947	32	2.68	0	0.00	32	2.68
1974	14,880	26	1.75	1	0.07	27	1.81
1975	14,398	31	2.15	5	0.35	36	2.50
1976	12,889	17	1.32	11	0.85	28	2.17
1977	12,487	11	0.88	17	1.37	28	2.25
1978	12,491	11	0.88	25	2.00	36	2.88
1972-78	92,325	168	1.82	59	0.64	227	2.46

[1] Year of birth or of "expected date of delivery" (E.D.D.)

[2] Therapeutic terminations as a result of serum A.F.P. screening.

Anencephalus births/pregnancies X^2 (6 d.f.) = 15.32 $P < 0.05$

TABLE 28. PREVALENCE OF SPINA BIFIDA : BIRTHS, TERMINATIONS AND "PREGNANCIES" (BIRTHS AND TERMINATIONS), GLASGOW, 1972-78.

BIRTH YEAR[1]	TOTAL BIRTHS	SPINA BIFIDA BIRTHS		SPINA BIFIDA TERMINATIONS[2]		SPINA BIFIDA PREGNANCIES	
		NO.	RATE	NO.	RATE	NO.	RATE
1972	13,233	40	3.02	0	0.00	40	3.02
1973	11,947	28	2.34	0	0.00	28	2.34
1974	14,880	50	3.36	0	0.00	50	3.36
1975	14,398	46	3.19	0	0.00	46	3.19
1976	12,889	22	1.71	4	0.31	26	2.02
1977	12,487	32	2.56	6	0.48	38	3.04
1978	12,491	24	1.92	3	0.24	27	2.16
1972-78	92,325	242	2.62	13	0.14	255	2.76

[1] Year of birth or of "expected date of delivery" (E.D.D.)

[2] Therapeutic terminations as a result of serum A.F.P. screening.

Spina bifida births/pregnancies X^2 (6 d.f.) = 0.69 $P > 0.10$ (NS)

TABLE 29. DISTRIBUTION OF MATERNAL AGE IN A.S.B. TERMINATIONS AND BIRTHS, GLASGOW, 1972-78.

MATERNAL AGE (YEARS)	A.S.B. FETUSES		
	BIRTHS NO. (%)	TERMINATIONS NO. (%)	PREGNANCIES NO. (%)
< 20	84 (93.33)	6 (6.67)	90 (100)
20 - 24	116 (83.45)	23 (16.55)	139 (100)
25 - 29	112 (81.16)	26 (18.84)	138 (100)
30 - 34	42 (85.71)	7 (14.29)	49 (100)
35 - 39	26 (81.25)	6 (18.75)	32 (100)
40+	30 (93.75)	2 (6.25)	32 (100)
Not known	0 -	2 -	2 -
ALL AGES	410 (85.06)	72 (14.94)	482 (100)

A.S.B. births/terminations X^2 (5 d.f.) = 9.20 $P > 0.10$ (NS)

TABLE 30. DISTRIBUTION OF MATERNAL SOCIAL CLASS IN A.S.B. TERMINATIONS AND BIRTHS, GLASGOW, 1975-78[1].

MATERNAL SOCIAL CLASS	A.S.B. FETUSES		
	BIRTHS NO. (%)	TERMINATIONS NO. (%)	PREGNANCIES NO. (%)
1	8 (66.67)	4 (33.33)	12 (100)
2	14 (56.00)	11 (44.00)	25 (100)
3	85 (72.03)	33 (27.97)	118 (100)
4	41 (85.42)	7 (14.58)	48 (100)
5	32 (80.00)	8 (20.00)	40 (100)
Not known	14 (63.64)	8 (36.36)	22 (100)
ALL SOCIAL CLASSES	194 (73.21)	71 (26.79)	265 (100)

[1] Social class data not available for 1972-74.

A.S.B. births/terminations X^2 (4 d.f.) = 8.80 $0.05 < P < 0.10$ (NS)

TABLE 31. DISTRIBUTION OF MATERNAL HEALTH DISTRICT OF RESIDENCE IN A.S.B. TERMINATIONS AND BIRTHS, GLASGOW, 1975-78.

MATERNAL HEALTH DISTRICT OF RESIDENCE	A.S.B. FETUSES		
	BIRTHS NO. (%)	TERMINATIONS NO. (%)	PREGNANCIES NO. (%)
NORTH	42 (73.68)	15 (26.32)	57 (100)
WEST	42 (70.00)	18 (30.00)	60 (100)
EAST	50 (73.53)	18 (26.47)	68 (100)
SOUTH-EAST	33 (76.74)	10 (23.26)	43 (100)
SOUTH-WEST	27 (72.97)	10 (27.03)	37 (100)
ALL DISTRICTS	194 (73.21)	71 (26.79)	265 (100)

A.S.B. births/terminations X^2 (4 d.f.) = 0.60 $P > 0.10$ (NS)

TABLE 32. DISTRIBUTION OF MATERNAL PARITY IN A.S.B. TERMINATIONS AND BIRTHS, GLASGOW, 1972-78.

PARITY	A.S.B. FETUSES					
	BIRTHS NO.	(%)	TERMINATIONS NO.	(%)	PREGNANCIES NO.	(%)
0	174	(89.69)	20	(10.31)	194	(100)
1	90	(79.65)	23	(20.35)	113	(100)
2	43	(79.63)	11	(20.37)	54	(100)
3	30	(85.71)	5	(14.29)	35	(100)
4	18	(100.00)	0	(0.00)	18	(100)
5+	55	(94.83)	3	(5.17)	58	(100)
Not known	0	(0.00)	10	(100.0)	10	(100)
ALL PARITIES	410	(85.06)	72	(14.94)	482	(100)

A.S.B. births/terminations X^2 (5 d.f.) = 14.98 $P < 0.05$

TABLE 33. DISTRIBUTION OF STILLBIRTHS, FIRST WEEK DEATHS AND SURVIVING LIVE BIRTHS AMONGST ANENCEPHALIC BIRTHS, GLASGOW, 1972-74 AND 1975-78.

BIRTH YEARS	OUTCOME OF DELIVERY			
	STILLBIRTHS	FIRST WEEK DEATHS	SURVIVING LIVEBIRTHS	TOTAL
	NO. (%)	NO. (%)	NO. (%)	NO. (%)
1972-74	87 (88.78)	8 (8.16)	3 (3.06)	98 (100)
1975-78	61 (87.14)	9 (12.86)	0 (0.00)	70 (100)
1972-78	148 (88.10)	17 (10.12)	3 (1.79)	168 (100)

X^2 (2 d.f.) = 3.04 $P > 0.10$ (NS)

TABLE 34. DISTRIBUTION OF STILLBIRTHS, FIRST WEEK DEATHS AND SURVIVING LIVE BIRTHS AMONGST SPINA BIFIDA BIRTHS, GLASGOW, 1972-74 AND 1975-78.

BIRTH YEARS	OUTCOME OF DELIVERY			
	STILLBIRTHS	FIRST WEEK DEATHS	SURVIVING LIVEBIRTHS	TOTAL
	NO. (%)	NO. (%)	NO. (%)	NO. (%)
1972-74	23 (19.49)	14 (11.86)	81 (68.64)	118 (100)
1975-78	18 (14.52)	11 (8.87)	95 (76.61)	124 (100)
1972-78	41 (16.94)	25 (10.33)	176 (72.73)	242 (100)

X^2 (2 d.f.) = 1.94 $P > 0.10$ (NS)

TABLE 35 STANDARD ERRORS AND 95% CONFIDENCE LIMITS OF ESTIMATES OF ANENCEPHALUS AND SPINA BIFIDA BIRTH PREVALENCE, GLASGOW, 1972-78

YEAR OF BIRTH	ANENCEPHALUS			SPINA BIFIDA		
	PREVALENCE RATE/1000 BIRTHS	STANDARD ERROR	95% CONFIDENCE LIMITS	PREVALENCE RATE/1000 BIRTHS	STANDARD ERROR	95% CONFIDENCE LIMITS
1972	3.02	0.48	2.07 - 3.97	3.02	0.48	2.07 - 3.97
1973	2.68	0.47	1.73 - 3.63	2.34	0.44	1.46 - 3.22
1974	1.75	0.34	1.06 - 2.44	3.36	0.47	2.41 - 4.31
1975	2.15	0.39	1.38 - 2.92	3.19	0.47	2.25 - 4.13
1976	1.32	0.32	0.68 - 1.96	1.71	0.36	0.98 - 2.44
1977	0.88	0.27	0.35 - 1.41	2.56	0.45	1.66 - 3.46
1978	0.88	0.27	0.35 - 1.41	1.92	0.39	1.14 - 2.70
1972-78	1.82	0.14	1.54 - 2.10	2.62	0.17	2.28 - 2.96

TABLE 36. COMPARISON OF DISTRIBUTION OF GLASGOW BIRTHS BY MATERNAL AGE IN 1964-68 AND 1975-78.

MATERNAL AGE (YEARS)	1964-68 BIRTHS[1] NO. (%)	1975-78 BIRTHS[2] NO. (%)
<20	10,428 (9.99)	7,212 (14.07)
20 - 24	33,749 (32.33)	16,540 (32.27)
25 - 29	29,277 (28.04)	16,528 (32.25)
30 - 34	17,479 (16.74)	7,653 (14.93)
35 - 39	9,148 (8.76)	2,587 (5.05)
40+	3,025 (2.90)	732 (1.43)
Not known	1,295 (1.24)	0 (0)
TOTAL	104,401 (100)	51,252 (100)

[1] Source : Wilson (1971)

[2] Source : Information Services Unit, Greater Glasgow Health Board.

TABLE 37. COMPARISON OF DISTRIBUTION OF GLASGOW BIRTHS BY MATERNAL PARITY IN 1964-68 AND 1975-78.

MATERNAL PARITY	1964-68 BIRTHS[1] NO.	(%)	1975-78 BIRTHS[2] NO.	(%)
0	33,204	(31.80)	21,956	(42.84)
1	25,903	(24.80)	16,630	(32.45)
2	16,990	(16.27)	7,157	(13.96)
3	10,555	(10.11)	2,991	(5.84)
4+	15,345	(14.69)	2,518	(4.91)
Not known	3,434	(3.29)	0	(0)
TOTAL	104,431	(100)	51,252	(100)

[1] Source : Wilson (1971)

[2] Source : Information Services Unit, Greater Glasgow Health Board.

TABLE 38. COMPARISON OF DISTRIBUTION OF GLASGOW BIRTHS BY MATERNAL SOCIAL CLASS IN 1964-68 AND 1975-78.

MATERNAL SOCIAL CLASS	1964-68 BIRTHS[1] NO.	(%)	1975-78 BIRTHS[2] NO.	(%)
1	3,345	(3.20)	3,973	(7.60)
2	5,830	(5.58)	6,670	(12.76)
3	55,082	(52.74)	25,864	(49.49)
4	18,419	(17.64)	9,839	(18.83)
5	15,791	(15.12)	5,498	(10.52)
Not known	5,964	(5.71)	521	(1.00)
TOTAL	104,431	(100)	52,265	(100)

[1] Source : Wilson (1971)

[2] Source : Information Services Unit, Greater Glasgow Health Board.

TABLE 39. RESULTS OF SERUM A.F.P. SCREENING (WEST OF SCOTLAND PROGRAMME 1975-1977) : AFTER FERGUSON-SMITH et al. (1978).

	PHASE I	PHASE II
Cut-off point (centile)	99th	97th
Total deliveries	22,662	22,619
No. screened at recommended gestation	6,122 (27%)	11,585 (51%)
Sensitivity (proportion of affected pregnancies detected by serum A.F.P.) :		
Anencephalus	14/16 (88%)	27/27 (100%)
Open Spina bifida	10/14 (71%)	13/16 (81%)
Closed Spina bifida	0/6 (0%)	1/14 (7%)
Specificity (proportion of unaffected pregnancies with normal A.F.P.) :	98.7%	98.6%
False +ves submitted to amniocentesis	11/79 (14%)	38/161 (24%)
Neural tube defected aborted :		
Anencephalus	13/16 (81%)	26/27 (96%)
Open Spina bifida	6/14 (43%)	9/16 (56%)
Closed Spina bifida	0/6 (0%)	0/14 (0%)

A P P E N D I C E S

APPENDIX 1

(BIRTHS ON OR AFTER 1st JANUARY, 1972, GLASGOW CITY)

GREATER GLASGOW AFTER 1st APRIL, 1974.

DISTRICT: .....

Child's Surname: .....

Address: .....

.....

Sex: .....

Place of Birth: .....

.....

Place of Death: .....

.....

Maternal Age: .....

B Form No.: .....

Health Board No.: .....

Twin/Singleton: .....

Date of Birth: .....

Hospital No.: .....

LB/SB: .....

Date of Death: .....

Parity: .....

Malformations:

Health Visitor: .....

Clinic: .....

Source of ascertainment (please ring code):

1. Birth notification postcard)
2. Obstetric and social factors form) Postcards are still completed but ceased to be source in 1977 discontinued Form - August, 1977.
3. Stillbirth registration
4. Death registration
5. Handicapped register
6. Letter from hospital
7. Other (please specify)
8. Information on B form

Date: .....

Requested on Handicap Register YES/NO

PLEASE RETURN TO: Dr. F.M.W. Hamilton,
Greater Glasgow Health Board,
351 Sauchiehall Street,
Glasgow, G2 3HT.

Tel. No. 041-332-2977

APPENDIX 2.

EVALUATION OF THE GLASGOW REGISTER OF CONGENITAL MALFORMATIONS

Extracts from the Report submitted in May, 1979, for the Diploma of the Membership of the Faculty of Community Medicine (Part 2)

by

David H. Stone

1. ORIGINS OF THE STUDY

At the outset of the Study, the Register was in its seventh year of data collection. Its upkeep was laborious, time-consuming and apparently unending. Two full-time Health Board staff (a medical officer and a clerkess) divided their working hours maintaining two registers (the other being the Handicapped Children's Register). From the purely economic point of view, a review of the activities of the Register of Congenital Malformations seemed appropriate. There were, however, two additional factors which prompted the inquiry :

First, the Area Executive Group of the Greater Glasgow Health Board was planning to undertake a review of the activities of the Board to coincide with the fifth anniversary of the reorganisation of the National Health Service. The Register clearly fell within the remit of this review. And second, the Council of the European Communities had identified the field of congenital malformations as a priority area for co-operative research between member states. Glasgow had been selected as one of three U.K. centres which would pool data on congenital malformations for an initial period of three years "in order to monitor the incidence and prevalence of congenital malformations and to allow the early institution of remedial measures" (COUNCIL OF THE EUROPEAN COMMUNITIES 1974).

2. OBJECTIVES AND OVERALL DESIGN OF THE STUDY

The broad aim of the study was to evaluate the past, current and potential uses of the Glasgow Register of Congenital Malformations.

More specifically, the following objectives were formulated :

1. To review the operation and uses of the Register from 1972 to 1977 inclusive in the light of its original stated objectives.

2. To evaluate the past, current and potential uses of the Register as a source of data on congenital malformations by means of an investigation into the validity of the data.

3. To demonstrate the potential role of the Register as a research and planning tool by undertaking a detailed study of a specific group of defects (congenital heart disease) with a view to elucidating aspects of (a) its descriptive epidemiology, and (b) its natural history.

In pursuit of these objectives, four studies were designed, namely :

(i) A critical review of the success or otherwise with which the Register had fulfilled its objectives between 1972 and 1977 (the Review Study).

(ii) An assessment of the validity of the data held by the Register (the Validity Study).

(iii) An attempt to measure the prevalence at birth of congenital heart disease in Glasgow from 1972 to 1975 inclusive (the Prevalence Study).

(iv) A five-year follow-up study of all cases (both registered and unregistered) of congenital heart disease diagnosed in children born to Glasgow residents in 1972 (the Cohort Study).

Each of these four studies represents the means of meeting study objectives 1, 2, 3(a) and 3(b) respectively.

As will become apparent, none of the studies can be viewed in isolation from the others. In particular, the results of study (ii) were found to influence profoundly the outcome of (i), (iii) and (iv).

3. MATERIALS AND METHODS

1. THE REVIEW STUDY.

The aim of the Review Study was to examine critically the operation of the Register from 1972 to 1977 inclusive and to assess the extent to which its original stated objectives had been fulfilled.

The methodological approach involved observation, discussion and a literature review :

(a) Observation

The stages of data ascertainment, registration, verification, storage and analysis were observed for a period of one year (from January 1978 to December 1978). The researcher was based in close physical proximity to the Registry and was in daily contact with Registry staff. Careful attention was paid to difficulties which arose in relation to data handling and processing.

(b) Discussion

Both formal and informal discussions were held with Registry staff, health board officers, paediatricians, nurses, records officers and others concerned with some aspect of congenital

malformations and their ascertainment. Issues relating to the objectives, operation and uses of the Register were explored and the perceived successes and failures of the Register were noted.

(c) Literature Review

Between 1972 and 1977 the Registry staff and other ad hoc research workers had analysed registered data for various purposes. The resultant body of literature, published and unpublished, was collated and reviewed in an attempt to establish the range of written material which had emerged from the Register.

Arising out of these three methods, an assessment of the operation and uses of the Register from 1972 to 1977 inclusive was possible, if somewhat subjective. Since the data were largely descriptive, few statistical analyses were necessary. The activities of the Register, as identified by the Review Study, were compared and contrasted with the defined objectives of the Register.

2. THE VALIDITY STUDY.

The objective of the Validity Study was to assess both the accuracy of registered data (item validity) and the success with which eligible cases had been ascertained (case validity). Accordingly, a series of sub-studies was designed :

(i) Item Validity Study - Measurement of the Completeness and the Accuracy of Registered Data

The intention of this study was to attempt to quantify the extent to which errors in the communication, transcription or recording of individual items of data had arisen. To this end, various items of data on the Registration Form were extracted from the Register and compared with an independent, external

source - namely, a hospital case-record. (The "independence" of a hospital case-record may be questioned; although the case-record itself was very rarely used as a primary source of registered defects, many of the other sources were themselves secondary to it. Because the hospital case-record was the source of data for comparison, it was necessary to study the registration data of hospital-born children with defects which could reasonably be expected to be identified at, or within a few days of birth. A list of these defects, drawn up in collaboration with a consultant paediatrician, is shown in the Annexe.)

The following sampling method was employed : all registered children born between 1972 and 1977 in any of the four major Glasgow maternity units (which delivered almost 80 per cent of all births to Glasgow residents) with any of the listed defects were identified on the Register. (Stillbirths were excluded). There were 409 children in this category. To reduce this number to manageable proportions, a one in four random sample, stratified by year and hospital of birth, was selected using a table of random numbers. For each of these cases (N = 105), an attempt was made to trace and examine a case-record (either neonatal paediatric or maternity) from which the following items were recorded : name, address, date of birth, sex, whether single or multiple birth, maternal age and parity, and diagnosis. These items, with the exception of the identifying details (name, address and date of birth) were then compared with the same items on the Register and the concurrent validity (or concordance) of each pair of items calculated.

(ii) Case Validity Studies - Comparison with Other Sources.

(a) Comparison with Other Registers

This was the crudest level of "case validation" since it was almost impossible to establish whether or not varying prevalence rates between different registers reflected varying "true" prevalence or varying recording, classification or analytical procedures. Although unsatisfactory as a form of validation in itself, such a comparison was felt to be worthwhile as a general guide to the level of ascertainment of the Register.

The methodology was straightforward : prevalence rates of specific defects or group of defects recorded by the Glasgow Register were tabulated and compared with the published rates of other Registers in Great Britain.

(b) SMR11 Study

The Computerised Neonatal Record - Form SMR11 - is a readily available source of data on disorders diagnosed in the neonatal period. The analysis was therefore restricted to those defects which could reasonably be expected to have been diagnosed at or shortly after birth (ANNEXE). Stillbirths, of course, were excluded.

Unfortunately, two further factors acted as major constraints on the scope of the study. First, as the form was a relative newcomer to Scottish Medical Records, data were available for only two complete calendar years in Glasgow, 1976 and 1977. Second, only two of the four

major maternity hospitals in Glasgow routinely completed the forms. In one of those, the SMR11 had been used as an occasional source of ascertainment by the Register, thereby effectively confining its status as "an independent external criterion" to one hospital (the Glasgow Royal Maternity Hospital). An unavoidable (but unquantifiable) degree of bias was therefore introduced.

To obtain the data, SMR11 printouts displaying the names of children, their diagnoses (coded according to the International Classification of Disease, Eighth Revision) and dates of birth were requested from the central SMR11 file (at the Tayside Computing Centre) for the years 1976 and 1977 at the Glasgow Royal Maternity Hospital. Maternal home addresses were identified using the Birth Register and children born to non-Glasgow residents were excluded. The SMR11 data were then compared with registered data for the same years, defects and hospital.

(ii) (c) SMR1 Study

An SMR1 form is completed for every discharge or death from a Scottish non-psychiatric hospital.

As with the SMR11 Study, an ad hoc request was made to the central SMR1 file (in this case located at the Information Services Division of the Common Services Agency of the Scottish Health Service. In order to preserve comparability, the malformations selected for this exercise were the same as those used in the SMR11 study

(ANNEXE). The ensuing printout contained details of children discharged from Scottish hospitals between 1972 and 1977 inclusive who fulfilled the following criteria :

(1) one of the listed diagnoses had been recorded;

(2) the date of birth was 1972; and

(3) the home address was Glasgow. (It was assumed that a child resident in Glasgow at the time of hospitalisation had been born to a Glasgow resident. Since Glasgow is a city of net emigration, any error arising from this assumption was likely to have been more than counterbalanced by the "loss to observation" of children born to Glasgow mothers who subsequently migrated).

By restricting the analysis to 1972-born children, the potential of the SMR1 in identifying subsequent hospital discharges was maximised.

SMR1 data have several disadvantages as a source of validation : diagnostic information may be incomplete, inaccurate or misleading; many cases may be "missed" because of the high emigration rate from Glasgow; and some of the most clinically severe cases may never have received hospital care. These reservations must be borne in mind when comparing SMR1 data with those of the Register.

(ii) (d) Study of Service Records

Children with congenital defects are liable to come into contact with a variety of health services, including

hospital in-patient and out-patient departments and school health clinics. And children who die either from a congenital or related disorder may be necropsied in pathology departments. The case-records of such agencies offered a potential source of data with which the Register could be compared. Their disadvantages were recognised: situated in diverse locations they often contained incomplete or misleading data, and were suspected of having "missed" many clinically significant cases. Despite these objections, there was no satisfactory alternative method of obtaining data on children whose defects may not have been diagnosed in the immediate post-natal period.

A comprehensive search of health service records for all children known to have a congenital disorder would have proved impractical. A single group of disorders - congenital heart disease - was therefore selected for detailed examination. (Congenital heart disease was selected for two reasons. First, it was the single most prevalent group of registered malformations; and second, the notorious difficulties associated with its ascertainment were perceived as likely to "stretch" the capabilities of the Register to the utmost).

An attempt was made to identify all children born in 1972 (to Glasgow residents) with a diagnosis of congenital heart disease. The following sources of data were used :

(1) the SMR1 file (I.C.D. codes 746-747), as described above;

(2) the patient index cards of attenders at the two Cardiac Clinics run in Glasgow by paediatric cardiologists;

(3) the diagnostic index cards (and relevant case-records) of the two largest neonatal units in Glasgow;

(4) the post-mortem reports of the four major pathology departments providing a paediatric service in Glasgow;

(5) computer print-outs (requested from the Information Services Division of the Common Services Agencies) of children with congenital heart disease diagnosed at the School Entry Health Examination (which most children born in 1972 should have received by 1977).

The names, dates of birth, sex and address of children so identified were then "linked" (manually) with the Birth Register for 1972, which was held by the Greater Glasgow Health Board. If the maternal address at birth was within the City of Glasgow, the child was included in the study.

By "pooling" the data on children identified from the various sources, it was possible to compare the completeness of the ascertainment of congenital heart disease achieved by searching "service records" with that of the Register.

3. THE PREVALENCE STUDY.

The intention of both the Prevalence Study and Cohort Study (4. below) was to demonstrate the potential uses and limitations of the Register as a source of data for research and planning purposes.

The Prevalence Study was designed to establish the descriptive epidemiology of congenital heart disease in Glasgow from 1972 to 1975 inclusive. (By limiting the data to those years, more cases whose diagnosis had been delayed were likely to have been ascertained). The basic data required for this exercise (date of birth, sex, diagnosis, etc.) were available on the Registration Forms.

The analyses were performed manually. Their purpose was to indicate the numerical dimensions of congenital heart disease, the frequency of specific diagnoses and the effect on the estimate of prevalence of including in the analysis unregistered cases which had come to light in the course of the Validity Study.

4. THE COHORT STUDY.

The objective of this study was to attempt to delineate the natural history of congenital heart disease from birth to school entry. To achieve this, a cohort of children born in 1972 and notified to the Register as having congenital heart disease was identified and "followed up" (retrospectively) for five years. The features of the natural history which were observed were : outcome of pregnancy (whether live-born or still-born), time of ascertainment of congenital heart disease, survival, handicap and hospitalisation. This conceptual framework was developed partly on theoretical grounds and partly as a pragmatic response to the availability of appropriate data.

The cohort consisted of a total sample of children born in 1972 to Glasgow mothers and registered as having congenital heart disease (i.e. all heart defects, specified or unspecified, present at birth). Details of names, addresses, diagnoses, etc., were transcribed onto a proforma. The Register itself provided only a proportion of the data, the remainder being obtained from the Handicapped Children's Register (Forms HS23 and SMR7) and the SMR1 file data (as requested for the Validity Study).

As with the Prevalence Study, the analysis was repeated to include unregistered cases discovered in the course of the Validity Study.

4. THE RESULTS AND THEIR IMPLICATIONS.

1. The Operation and Uses of the Register, 1972-77.

This part of the study consisted of an assessment of the organisation and functioning of the Register as well as an examination of the uses made of its data. Three methods were employed - direct observation of the work of the Registry staff, discussion with both Registry staff and other interested individuals, and a review of published and unpublished literature which had emanated from the Register. A number of impressions were gained about the activities of the Register : these may be expressed in terms of its "apparent strengths and weaknesses". Inevitably, these comments are subjective and are influenced to some extent by the knowledge of the results which emerged from other parts of the evaluation.

Apparent Strengths of the Register.

1. In general, data on children with congenital malformations were transmitted efficiently and accurately from the source of ascertainment through the various stages of the registration process.

2. Despite the clerical burdens imposed, detailed annual tabulations of the prevalence rates of specific malformations were compiled and circulated, usually within the first quarter of the succeeding year.

3. Any requests for ad hoc information about a particular aspect of the registered data received a prompt, courteous and interested response.

4. The attitude of the staff towards the data was consistently one of exemplary conscientiousness and professionalism.

5. The quality of working relationships within the Registry and between the Registry and other individuals, medical and clerical, was of an impressively high order.

Apparent Weaknesses of the Register.

1. The physical isolation of the Registry from its clinical sources of ascertainment resulted in an over-dependence on formal written communication to and from the sources. This may have contributed to incomplete ascertainment.

2. The loss of two useful sources of data (the Birth Notification Postcard in 1976 and the Obstetric and Social Factors Form in 1977) had not been sufficiently counterbalanced by the introduction of new sources.

3. Criteria for the registration of defects were inadequate. For example, an arbitrary assessment of "severity" was often made, with the risk that some significant but apparently "trivial" defects may have been mistakenly excluded. In practice, the onus for registration was often placed on the sources of the data although there was little evidence of any attempt to standardise the criteria employed by each source.

4. Similarly, criteria for the registration of multiple defects in order of importance were inadequate. The choice of the "principal malformation" was often quite arbitrary.

5. The Registration Form itself was not entirely suited to its purpose. The use of adhesive coloured stars, for example, to indicate "handicap" and "death" caused unnecessary practical difficulties.

6. The entire process of registration was manual, thereby imposing perpetual clerical demands of a time-consuming and tedious nature on Registry staff.

7. The storage of Registration Forms in bulky cardboard box files rendered the data vulnerable to loss, destruction and breaches of confidentiality.

8. The scope for analysis of the data in accordance with the objectives of the Register was severely limited by the lack of automated data processing. In consequence, the uses made of the data for research, planning and service provision were modest. Some potential users expressed the view that the objectives themselves were too limited and that these should be reviewed. Others, including those who acted as clinical sources of notification, believed that "feedback" of analyses was meagre or inappropriate to their needs. The Registry staff were faced with the formidable task of attempting to satisfy the widely divergent aspirations of potential users while lacking the administrative, scientific or technical support with which to do so.

2. The Validity of Registered Data.

(i) Item Validity

The items of data on the Registration Form were examined from the points of view of completeness and concordance (with a hospital case-record). The main findings may be summarised as follows :

The items of registration data relating to the child were complete on almost 100 per cent of the forms; those concerning the mother (namely maternal age and parity) were grossly under-recorded (only 40 per cent of the forms being complete in these respects).

The concordance of the items of data with those recorded on case records was of a high order (between 86 per cent and 99 per cent of the forms) with the exception of maternal age (77 per cent of the forms) and the number of recorded malformations (78 per cent of the forms).

These were reassuring findings in the main; however, the incompleteness of the maternal information caused concern since these factors are often important in the statistical analysis of malformation data. A possible solution to this problem will be outlined later.

(ii) Case Validity

(a) Comparison with Other Registers

The comparison of the prevalence rates of congenital defects by the Glasgow Register with those reported by other British registers established a *prima facie* case for accepting the validity of the Glasgow data (Table A1). The infant malformation rate for Glasgow between 1972 and 1976 was 30.9 per 1,000 total births, a figure higher than that of Liverpool (1960-64) and Birmingham (1950-54) but lower than that of Devon (1967-70) and South Wales (1964-66). Thus the Glasgow prevalence lay exactly in the middle of

the range of prevalence, if these are ranked from highest to lowest.

When the same technique was applied to the nine individual diagnostic groups, an interesting pattern emerged. For three diagnoses (hydrocephalus, cardiac defects and congenital dislocation of the hip), the Glasgow prevalence ranked second of the five, that is, nearer the upper end of the series. For another three diagnoses (urogenital defects, talipes and cleft palate and/or lip), Glasgow ranked bottom of the series. And for the remaining three (anencephaly, spina bifida and Down's Syndrome), the Glasgow prevalence ranked third, that is in the middle of the series.

It is important not to overemphasise the significance of this comparison which was far from comprehensive and potentially highly misleading (as discussed below). Nevertheless, the following broad generalisations seemed justified :

1. The infant malformation rate (for all defects) recorded by the Glasgow Register was comparable with that reported by other British registers.

2. The prevalence of individual defects recorded by the Glasgow Register was comparable with other registers for most of the major diagnostic groups; some malformations (namely urogenital defects, talipes and oral clefts) were probably less completely ascertained by the Glasgow Register than by other registers.

(ii) (b) The SMR11 Study

The correlation between the Register and the SMR11 form was fairly strong in terms of the numbers of children with selected defects ascertained by each source. A large minority of these children, however, were uniquely identified by one or other of the sources, as indicated by the "overlap" rate of only 55 per cent (Table A2). That the close numerical correlation was superficial was also suggested by the fairly low "sensitivity" (66.1%) and "true positive rate" (77.1%) of the Register when validated against the "reference test" of the SMR11. (Table A3). The distorting effect of the low prevalence of the defects on the estimates of "specificity" and the "true negative rate" has been commented upon elsewhere.

The pattern of ascertainment of specific defects revealed by this analysis provides some confirmation of the results of the comparison of the Glasgow data with other registers (discussed above); hypospadias, bowel defects and oral clefts were more often "missed" by the Register than by SMR11. These defects may have been less successfully ascertained by the Register because of their low stillbirth and mortality rates, and their likelihood of successful surgical repair. The three bottom-ranking groups of defects in the "league-table" of British registers were similarly "surgical" in nature - urogenital defects, talipes and oral clefts.

The SMR11 form represented the external criterion of validation which was closest in time to the birth of a child

under "observation"; the other two criteria, the SMR1 form and "service records" were further removed (in time) from birth and this factor may have been partly responsible for the even less impressive performance of the Register when validated against them.

(ii) (c) The SMR1 Study

The correlation between the numbers of malformed children who were ascertained by the Register and the SMR1 was less convincing than in the SMR11 study. The "overlap" (the proportion of all children ascertained by both sources) was even smaller (38%) (Table A4) as were the "sensitivity" (62%) and "true positive rate" (49%) (Table A5). As with the SMR11 study, the Register appeared more likely to "miss" bowel defects than the SMR1. On the other hand, the two sources ascertained hypospadias and oral clefts at a similar rate, and Down's Syndrome was strikingly more completely ascertained by the Register. Arguably, this diagnostic pattern was at least compatible with the findings of both the SMR11 study and the comparison with other registers in that "surgical" disorders (such as bowel defects) were less completely ascertained by the Register than non-surgical defects (such as Down's Syndrome).

It must be conceded, however, that this explanation is mere hypothesis, for neither the numbers of cases nor the range of reference criteria were large enough to justify a firm conclusion of this kind. Moreover, the peculiar biases operating within each reference source

(discussed later) render comparisons between the validity studies somewhat hazardous.

In summary, a distinct general trend was observed in the results of the validity studies: the comparison with other registers broadly indicated that the Glasgow Register was reasonably valid, while the more detailed local studies of selected defects suggested a much lesser degree of validity, with a progressively weakening correlation between the Register and the reference criteria observed as the criteria become more remote, temporarily, from the birth of the population under "observation". This trend was confirmed, albeit in the context of a single diagnostic group (congenital heart disease), by the findings of the study of service records.

(ii) (d) The Study of Service Records

The search for cases of congenital heart disease was conducted more intensively and using a greater diversity of sources than any of the other validity studies. It is perhaps not surprising, therefore, that the yield of unregistered cases should have been greater than in the other studies. The most productive sources of data were the two forms, SMR1 and SMR10 (completed at the school entry medical examination) and the records of the two paediatric cardiology out-patient clinics in Glasgow (Table A6). Twenty-two (20%) of the 110 cases found in the course of the search were identified in post-mortem reports; this was a larger number than expected in view of the use made by the Register of certified deaths from

congenital defects for ascertainment purposes. The small number (15) of cases found in the records of special care nurseries is a reflection of the diagnostic difficulties associated with congenital heart disease, particularly in the neonatal period. Only 38 (35%) of the 110 cases identified from service records were registered; of the remaining 72, 57 (79%) were found in one source only (Table A7), emphasising the importance of casting the case-finding net as widely as possible.

When the ascertainment rates achieved by the Register and the service records were compared, the Register appeared to have "missed" 72 cases (50%) of the "pooled" total (144) (Table A8). While a detailed lesion-specific analysis was not possible (because of the small numbers and insufficient diagnostic data) the Register appeared especially liable to fail to record ventricular septal defects. The poor correlation between the cases ascertained by the Register and service records was underlined by the small proportion (26%) of all cases which was recorded by both sources (the "overlap"), the low "sensitivity" (34.5%) of the Register, its high "false positive rate" (47.2%) and low "true positive rate" (52.8%) (Table A9).

The conclusion was inescapable : the Register appeared to have performed poorly as a means of ascertaining children with congenital heart disease. Yet there were a number of factors which may have exerted a distorting effect on the results and which must be taken into account

in assessing the significance of the findings. These will be outlined below.

3. Uses of the Register : The Example of Congenital Heart Disease

(i) The Prevalence Study

Between 1972 and 1975, congenital heart disease was the single most prevalent diagnosis recorded on the Register. The prevalence rate of 6.52 per 1000 total births was comparable with prevalence rates reported elsewhere. The Handicapped Children's Register was the most fruitful source of ascertainment of cases over the four-year period, although the Obstetric and Social Factors Form was becoming progressively more important and by 1975 had supplanted the Handicapped Children's Register as the largest single contributor of data. Although only a small proportion (23%) of heart defects was ascertained in the neonatal period, almost three-quarters (74%) had been ascertained by the age of six months. (In a similar study in the United States, Yerushalmy, 1970, observed that only a third of registered cases had been ascertained at birth while more than four-fifths had been ascertained by the age of three months).

Two points are worth making about the ascertainment of congenital heart disease. First, the withdrawal of the Obstetric and Social Factors Form in 1977 was bound to have adversely affected the completeness of ascertainment of heart defects; second, the existence and use of the SMR11 (neonatal discharge) form will have compensated only partially for this loss because of the relatively high rate of ascertainment in the post-neonatal period.

The sharp rise in the prevalence of congenital heart disease in 1974 could not be attributed entirely to the effects of the reorganisation of the National Health Service in that year, for the increase in the prevalence of heart defects was out of proportion to the increase in the prevalence of registered malformations generally (Table A10). By 1975, however, the rate had declined again and it is possible that some unidentified local administrative factor was operating.

Undoubtedly, the most significant finding of the prevalence study was the discovery of the effect of including unregistered cases identified in the course of the validity study of service records (Table A11). Although confined to a single year (1972), the doubling of the prevalence rate (from 5.4 to 10.8 per 1000 total births) for that year cast serious doubt on the prevalence estimates for the remaining years.

The "revised" prevalence rate of 10.8 per 1000 total births may, of course, have been an overestimate; it was certainly well in excess of the upper end of the range of prevalences reported by other British registers. As Hoffman (1968) had observed, however, registry studies tend to report lower prevalence rates than those of more intensive studies, the results of some of which are presented in Table A12. If the Glasgow estimate of 10.8 per 1000 total births was accurate, it represents one of the highest prevalence rates of congenital heart disease reported anywhere in the world.

The implications of this finding are considerable. If Glasgow is indeed prone to an exceptionally high prevalence of

congenital heart disease, an intensive epidemiological search for the explanation should be carried out. And health service planners may have to revise their projections of demand for the entire range of clinical, laboratory and institutional services appropriate to the management of congenital heart disease.

From the point of view of the potential user of the Register, however, one stark conclusion stands out : the Register in itself is an inadequate source of data for the study, whether for research or planning purposes, of the prevalence of at least one group of defects, congenital heart disease. This rather negative statement is not as discouraging as it seems, for as a corollary it should be emphasised that the Register is an invaluable baseline from which to launch an intensive search for data on the prevalence of congenital heart disease in Glasgow.

(ii) The Cohort Study

Most studies of the natural history of congenital heart disease have concentrated on its prevalence (at birth and in later years) and mortality. Reports of morbidity are conspicuous by their absence.

The mortality experienced by the 1972 cohort of Glasgow children with registered heart defects was not as high as that reported by McMahon, McKeown and Record (1953) in an early study based on the Birmingham registry : by the age of one month, 29 per cent of the Glasgow cohort had died compared with 34 per cent of the Birmingham children at the same age. By one year of age, 42 per cent of the Glasgow children had died, the equivalent figure for Birmingham being 61 per cent. And by five years of age, 47 per cent of the Glasgow children and 62 per cent of the

Birmingham children were dead.

Hoffman (1968) has pointed out that the mortality rates reported by intensively followed series are lower than those of others, since the former tend to include more cases of milder, non-fatal congenital heart disease.

The accuracy of Hoffman's observation was confirmed by estimating the impact of including unregistered cases in the Glasgow cohort study. The revised Glasgow survival curve was much closer to the more optimistic findings of other intensive studies than to those of the early Birmingham series. Similarly, the prevalence of handicap (51 per cent of the registered cohort were placed on the Handicapped Children's Register at some time in the first five years of life) was halved (to 26%) when unregistered cases were added to the cohort.

It appeared, therefore, that the prognosis for children with congenital heart disease was substantially "improved" when unregistered cases were included in the analysis. Again, potential users of the Register should be aware of its bias towards the more severe cases; nevertheless, the Register did appear to be a useful starting point for natural history studies provided that it was augmented by data obtained from other relevant sources.

5. CONCLUSIONS AND PROPOSALS

1. CONCLUSIONS.

This study had three main objectives which were, briefly :

(1) to review the operation and uses of the Register from 1972 to 1977 in the light of its objectives;

(2) to investigate the validity of registered data; and

(3) to demonstrate the potential role of the register as a research and planning tool by elucidating the prevalence and natural history of congenital heart disease.

To meet these objectives, a series of sub-studies was undertaken. From their results, which have been presented and discussed in detail, the following broad conclusions (complementing the study objectives) were reached :

(1) Between 1972 and 1977, the Register fulfilled only one of its original stated objectives - namely, the calculation of prevalence rates. This in itself was a formidable achievement given the enormous scope of the Register, the multiplicity of sources of ascertainment and the absence of automated data processing.

(2) The individual items of data on the Registration Form were recorded with an impressive degree of completeness and accuracy with the exception of maternal data which were frequently totally absent. The success with which the Register ascertained cases varied considerably, depending on the lesion. There was some suggestion that the Register was poor at ascertaining defects (such as bowel disorders, oral clefts and hypospadias) which necessitated surgical repair. In addition, congenital heart disease, which may be typical of defects posing diagnostic difficulties at birth or later, was very incompletely ascertained.

(3) The Register may be regarded as a useful starting-point for the study of specific defects for research or planning purposes. If registered data alone are used, however, seriously misleading results may be obtained. For example, the prevalence of congenital heart disease appeared unremarkable on the basis of the registered data; when augmented by data obtained by examining other sources, the estimated prevalence was doubled to a level which, if accurate, would indicate that Glasgow has one of the highest prevalence rates of congenital heart disease in the world.

2. PROPOSALS.

The following proposals have been formulated :

(a) An Advisory Group should be established to provide relevant epidemiological, clinical, administrative and computing support to the Registry staff on a continuing basis. This group should meet at regular intervals, perhaps two or three times per year, to review the objectives, operation and uses of the Register. Initially, it should probably consist of a small number of officers of the Greater Glasgow Health Board; subsequently, other members with specific skills and interests could be co-opted.

(b) A closer relationship should be encouraged between the Registry and both its providers and users of data. An appropriately structured Advisory Group could contribute to this process but other steps may be necessary, such as the more effective communication of "feedback" data to clinicians, health visitors, records officers and other relevant groups.

(c) The processing of registration data should be automated and an expanded version of the Registration Form should be designed for computing purposes. (Preliminary discussions to implement this proposal have taken place at the time of writing). Particular attention should be paid to the more efficient acquisition of maternal data, possibly by means of a record linkage exercise with the Scottish Maternity Discharge Form, SMR2.

(d) Specific criteria should be established for :

(i) the inclusion of "trivial" and ill-defined defects on the Register; and

(ii) the ranking of multiple defects in order of "importance".

(e) New sources of ascertainment should be sought urgently to compensate for the withdrawal of the Obstetric and Social Factors Form. One possibility is the SMR11 form; others are forms SMR1, SMR10, the records of specialised clinics and laboratories, and post-mortem reports.

(f) More extensive planning and research use of the data should be encouraged by the highlighting of trends in prevalence, the formulation of hypotheses and the epidemiological investigation of specific defects. The most effective catalyst for activities of this kind might be the preparation and widespread circulation of an Annual Report for which the Advisory Group would be responsible.

It should be emphasised that some of these proposals have been implemented while others are under discussion. An ad hoc Steering Committee has been formed to advise and assist the Registry staff on problems arising from the participation of Glasgow in the European study of congenital malformations; this Committee is not far removed from the Advisory Group envisaged in the first Proposal. Given the continued dedication and enthusiasm of the Registry staff, a firm organisational framework for professional and administrative support, and a modicum of good-will, the future of the Glasgow Register of Congenital Malformations is assured.

ANNEXE

SELECTED DEFECTS IDENTIFIABLE AT BIRTH

CARDIFF CODE	DIAGNOSIS
524.02	Pierre Robin Syndrome
551.10	Exomphalos
551.11	Umbilical Hernia
551.12	Paraumbilical Hernia
741.00	Spina Bifida with Hydrocephalus
741.90	Spina Bifida without Hydrocephalus
743.00	Meningoencephalocoele
744.30	Congenital Cataract
749.00	Cleft Palate
749.10	Cleft Lip
749.20	Cleft Lip and Palate
750.20	Oesophageal Atresia
750.21	Oesophageal Atresia with Fistula
750.22	Oesophagotracheal Fistula without Atresia
751.05	Persistent Vitelline Duct
751.10	Duodenal Atresia
751.11	Intestinal Atresia
751.20	Imperforate Anus
751.23	Imperforate Anus excluding Stenosis/Ectopic
752.20	Hypospadias
753.00	Renal Agenesis
755.20	Reduction Deformity Upper Limb
755.30	Reduction Deformity Lower Limb
755.40	Reduction Derformity Unspecified Limb
756.005	Mandibulo Facial Dysotosis (Treacher Collins)
756.15	Congenital Scoliosis
756.50	Fragilitas Ossium (not Tarda)
756.86 (551.3)	Diaphragmatic Hernia
759.3	Down's Syndrome

TABLE A1 PREVALENCE (RATES PER 1,000 TOTAL BIRTHS) OF CONGENITAL MALFORMATIONS RECORDED BY FIVE REGISTERS : GLASGOW, BIRMINGHAM, LIVERPOOL, SOUTH WALES AND DEVON.

MALFORMATION	GLASGOW 1972-76	BIRMINGHAM 1950-54	LIVERPOOL 1960-64	SOUTH WALES 1964-66	DEVON 1967-70	RANGE (Excluding Glasgow)
Anencephaly	2.25	2.01	3.14	3.09	1.38	1.38 - 3.14
Spina Bifida (without anencephaly)	3.33	2.18	3.36	3.92	2.56	2.18 - 3.92
Hydrocephalus (without spina bifida)	0.90	1.39	0.55	0.90	-	0.55 - 1.39
Cardiac Defects	7.02	4.23	5.03	4.38	8.06	4.23 - 8.06
Urogenital Defects	1.94	3.86	2.62	2.66	2.48	2.48 - 3.86
Talipes	2.10	5.72	2.65	3.42	7.67	2.65 - 7.67
Congenital Dislocation of Hip	1.38	0.91	0.67	0.85	2.99	0.67 - 2.99
Down's Syndrome	1.44	1.61	1.43	0.99	1.45	0.99 - 1.61
Cleft Palate and/or Lip	1.16	1.98	1.54	2.06	1.77	1.54 - 2.06
Total Number of Affected Infants	2,058	2,527	2,182	3,242	1,185	
Total Number of Births	66,634	94,474	91,176	90,921 (singletons only)	25,432	
Infant Malformation Rate per 1,000 Total Births	30.9	26.7	23.9	35.7	46.6	23.9 - 46.6
Minimum Period of Follow-up	2 yrs.	6 yrs.	5 yrs.	2 yrs.	5 yrs.	

TABLE A2 COMPLETENESS OF ASCERTAINMENT OF MALFORMED CHILDREN (SELECTED DIAGNOSES) BY REGISTER AND SMR11 : NOS. (%) AND RATES PER 1000 TOTAL BIRTHS, 1976-77, GLASGOW ROYAL MATERNITY HOSPITAL (LIVE BIRTHS ONLY).

PRINCIPAL MALFORMATION	REGISTERED CASES			SMR11 CASES			OVERLAP			TOTAL		
	No.	(%)	Rate	No.	(%)	Rate	No.	(%)	Rate	No.	(%)	Rate
Hypospadias	12	(54.4)	1.9	18	(81.8)	2.9	8	(36.4)	1.3	22	(100)	3.5
Down's Syndrome	11	(78.6)	1.8	14	(100.0)	2.2	11	(78.6)	1.8	14	(100)	2.2
C.N.S. Defects[1]	8	(100.0)	1.3	5	(62.5)	0.8	5	(62.5)	0.8	8	(100)	1.3
Bowel Defects[2]	4	(57.1)	0.6	6	(85.7)	1.0	3	(42.9)	0.5	7	(100)	1.1
Cleft lip and/or palate	4	(66.7)	0.6	6	(100.0)	1.0	4	(66.7)	0.6	6	(100)	1.0
Diaphragmatic Hernia	4	(100.0)	0.6	4	(100.0)	0.6	4	(100.0)	0.6	4	(100)	0.6
Reduction Deformity of limb	2	(66.7)	0.3	3	(100.0)	0.5	2	(66.7)	0.3	3	(100)	0.5
Renal Agenesis	2	(100.0)	0.3	0	(0.0)	0.0	0	(0.0)	0.0	2	(100)	0.3
Osteogenesis Imperfecta	1	(100.0)	0.2	0	(0.0)	0.0	0	(0.0)	0.0	1	(100)	0.2
TOTAL	48	(71.6)	7.7	56	(83.6)	9.0	37	(55.2)	5.9	67	(100)	10.7

1 C.N.S. Defects = spina bifida ± hydrocephalus
encephalocoele

2 Bowel Defects = oesophageal atresia
duodenal atresia
imperforate anus
exomphalos

TABLE A3. NO. OF MALFORMED CHILDREN (SELECTED DIAGNOSES) IDENTIFIED BY REGISTER AND SMR11, 1976-77, GLASGOW ROYAL MATERNITY HOSPITAL (LIVE-BIRTHS ONLY)

		MALFORMED CHILDREN : SMR11		
		YES	NO	TOTAL
MALFORMED CHILDREN :	YES	37 (a)	11 (b)	48 (a+b)
	NO	19 (c)	6178 (d)	6197 (c+d)
	TOTAL	56 (a+c)	6189 (b+d)	6245 (a+b+c+d)

VALIDITY OF REGISTER AGAINST SMR11 :

"SENSITIVITY"	= a/a+c	=	66.1%
"SPECIFICITY"	= d/b+d	=	99.8%
"FALSE POSITIVE RATE"	= b/a+b	=	22.9%
"FALSE NEGATIVE RATE"	= c/c+d	=	0.3%
"TRUE POSITIVE RATE" (i.e. POSITIVE PREDICTIVE VALUE)	= a/a+b	=	77.1%
"TRUE NEGATIVE RATE" (i.e. NEGATIVE PREDICTIVE VALUE)	= d/c+d	=	99.7%

TABLE A4 COMPLETENESS OF ASCERTAINMENT OF MALFORMED CHILDREN (SELECTED DIAGNOSES) BY REGISTER AND SMR1 : NOS. (%) AND RATES PER 1,000 TOTAL BIRTHS, CITY OF GLASGOW RESIDENTS, 1972 BIRTHS

PRINCIPAL MALFORMATION	REGISTERED CASES			SMR1 CASES			OVERLAP			TOTAL		
	No.	(%)	Rate	No.	(%)	Rate	No.	(%)	Rate	No.	(%)	Rate
Hypospadias	10	(62.5)	0.7	10	(62.5)	0.7	4	(25.0)	0.30	16	(100)	1.2
Down's Syndrome	19	(86.4)	1.4	4	(18.2)	0.3	1	(4.5)	0.1	22	(100)	1.6
C.N.S. Defects[1]	48	(85.7)	3.6	36	(64.3)	2.7	28	(50.0)	2.1	56	(100)	4.2
Bowel Defects[2]	16	(53.3)	1.2	25	(83.3)	1.9	11	(36.7)	0.8	30	(100)	2.2
Cleft lip and/or palate	19	(82.6)	1.4	18	(78.3)	1.3	14	(60.9)	1.0	23	(100)	1.7
Diaphragmatic Hernia	2	(100.0)	0.1	0	(0.0)	0.0	0	(0.0)	0.0	2	(100)	0.1
Reduction Deformity of limb	3	(100.0)	0.2	0	(0.0)	0.0	0	(0.0)	0.0	3	(100)	0.2
Renal Agenesis	3	(100.0)	0.2	1	(33.3)	0.1	1	(33.3)	0.1	3	(100)	0.2
Osteogenesis Imperfecta	1	(50.0)	0.1	1	(50.0)	0.1	0	(0.0)	0.0	2	(100)	0.1
TOTAL	121	(77.1)	9.1	95	(60.5)	7.1	59	(37.6)	4.4	157	(100)	11.8

1 C.N.S. Defects = spina bifida ± hydrocephalus
encephalocoele

2 Bowel Defects = oesophageal atresia
duodenal atresia
imperforate anus
exomphalos

TABLE A5. NO. OF MALFORMED CHILDREN (SELECTED DIAGNOSES) IDENTIFIED BY REGISTER AND SMR1, CITY OF GLASGOW RESIDENTS, 1972 BIRTHS.

		MALFORMED CHILDREN : SMR1		
		YES	NO	TOTAL
MALFORMED CHILDREN :	YES	59 (a)	62 (b)	121 (a+b)
REGISTER :	NO	36 (c)	13203 (d)	13239 (c+d)
	TOTAL	95 (a+c)	13265 (b+d)	13360 (a+b+c+d)

VALIDITY OF THE REGISTER AGAINST SMR1 :

"SENSITIVITY"	= a/a+c	=	62.1%
"SPECIFICITY"	= d/b+d	=	99.5%
"FALSE POSITIVE RATE"	= b/a+b	=	51.2%
"FALSE NEGATIVE RATE"	= c/c+d	=	0.3%
"TRUE POSITIVE RATE" (i.e. "POSITIVE PREDICTIVE VALUE")	= a/a+b	=	48.8%
"TRUE NEGATIVE RATE" (i.e. "NEGATIVE PREDICTIVE VALUE")	= d/c+d	=	99.7%

TABLE A6. SEARCH OF "SERVICE RECORDS" FOR CASES OF CONGENITAL HEART DISEASE, 1972 BIRTHS : CONTRIBUTION OF VARIOUS SOURCES.

SOURCE	TOTAL NO. OF CASES FOUND (%)	NO. OF UNREGISTERED CASES (%)
Form SMR1	44 (40.0)	22 (30.6)
Form SMR10	35 (31.8)	26 (36.1)
Paediatric Cardiology Clinic Records ...	39 (35.5)	21 (29.2)
Records of Neonatal Special Care Units	15 (13.6)	7 (9.7)
Post-Mortem Reports ...	22 (20.0)	11 (15.3)
TOTAL	110[1] (100)	72[1] (100)

[1] Some cases were identified from more than one source.

TABLE A7. FREQUENCY DISTRIBUTION OF NUMBER OF SOURCES IDENTIFYING CASES OF CONGENITAL HEART DISEASE (1972 BIRTHS) FOUND IN COURSE OF SEARCH OF "SERVICE RECORDS".

NO. OF SOURCES IDENTIFYING EACH CASE	TOTAL NO. OF CASES FOUND (%)	NO. OF UNREGISTERED CASES (%)
1	75 (68.2)	57 (79.2)
2	25 (22.7)	13 (18.1)
3	10 (9.1)	2 (2.8)
TOTAL	110 (100)	72 (100)

TABLE A8 COMPLETENESS OF ASCERTAINMENT OF CHILDREN WITH CONGENITAL HEART DISEASE (V.S.D., SPECIFIED DEFECT OTHER THAN V.S.D. AND UNSPECIFIED DEFECT) BY REGISTER AND SERVICE RECORDS : NOS. (%) AND RATES PER 1,000 TOTAL BIRTHS, CITY OF GLASGOW RESIDENTS, 1972 BIRTHS

PRINCIPAL MALFORMATION	REGISTERED CASES			CASES IDENTIFIED FROM SERVICE RECORDS			OVERLAP			TOTAL		
	No.	(%)	Rate	No.	(%)	Rate	No.	(%)	Rate	No.	(%)	Rate
V.S.D.	17	(37.8)	1.3	40	(88.9)	3.0	12	(26.7)	0.9	45	(100)	3.4
Other Specified Defect	32	(53.3)	2.4	51	(85.0)	3.8	23	(38.3)	1.7	60	(100)	4.5
Unspecified Defect	23	(59.0)	1.7	19	(48.7)	1.4	3	(7.7)	0.2	39	(100)	2.9
TOTAL	72	(50.0)	5.4	110	(76.4)	8.2	38	(26.4)	2.8	144	(100)	10.8

TABLE A9. NO. OF CHILDREN WITH CONGENITAL HEART DISEASE IDENTIFIED BY REGISTER AND SERVICE RECORDS, CITY OF GLASGOW RESIDENTS, 1972 BIRTHS.

		CHILDREN WITH C.H.D. : SERVICE RECORDS		
		YES	NO	TOTAL
CHILDREN WITH C.H.D. REGISTER	YES	38 (a)	34 (b)	72 (a+b)
	NO	72 (c)	13216 (d)	13288 (c+d)
	TOTAL	110 (a+c)	13250 (b+d)	13360 (a+b+c+d)

VALIDITY OF THE REGISTER AGAINST SERVICE RECORDS (CONGENITAL HEART DISEASE) :

"SENSITIVITY"	= a/a+c	=	34.5%
"SPECIFICITY"	= d/b+d	=	99.7%
"FALSE POSITIVE RATE"	= b/a+b	=	47.2%
"FALSE NEGATIVE RATE"	= c/c+d	=	0.5%
"TRUE POSITIVE RATE" (i.e. "POSITIVE PREDICTIVE VALUE")	= a/a+b	=	52.8%
"TRUE NEGATIVE RATE" (i.e. "NEGATIVE PREDICTIVE VALUE")	= d/c+d	=	99.5%

TABLE A10. PREVALENCE OF REGISTERED CONGENITAL HEART DISEASE IN GLASGOW

YEAR	TOTAL BIRTHS [1]	CONGENITAL HEART DISEASE			
		CHILDREN	RATE / 1000 TOTAL BIRTHS	DEFECTS	RATE / 1000 TOTAL BIRTHS
1972	13,360	72	5.39	77	5.76
1973	12,032	56	4.66	59	4.90
1974	13,863	119	8.59	128	9.24
1975	14,440	103	7.13	107	7.41
1972-75	53,695	350	6.52	371	6.91

[1] i.e. Total births to Glasgow residents.

TABLE A11. IMPACT OF UNREGISTERED CASES ON PREVALENCE, SEX RATIO, PROPORTION OF STILLBIRTHS AND PROPORTION OF MULTIPLE BIRTHS (CONGENITAL HEART DISEASE, 1972 BIRTHS).

C.H.D. CASES	PREVALENCE NO.	PREVALENCE RATE/1000 TOTAL BIRTHS	SEX RATIO M : F	STILLBIRTHS NO. (%)	MULTIPLE BIRTHS NO. (%)
Registered	72	5.39	1.0	0 (0.0)	0 (0.0)
Unregistered	72	5.39	1.0	4 (5.6)	1 (1.4)
TOTAL	144	10.75	1.0	4 (2.8)	1 (0.7)

TABLE A12. REPORTED PREVALENCE OF CONGENITAL HEART DISEASE : VARIOUS STUDIES

AUTHORS	TOTAL NO. OF BIRTHS	RATE PER 1000	REFERENCE
McMAHON et al. (1953)	194,418	3.2	British Heart Journal, 15, 121.
RICHARDS et al. (1955)	6,053	8.3	Pediatrics, 15, 12.
CARLGREN (1958)	58,105	6.4	British Heart Journal, 21, 40.
YERUSHALMY (1970)	19,000 (live births only)	10.8	In Fraser, F.C. and McKusick, V.A. (eds.), Congenital Malformations. Amsterdam, Excerpta Medica.
MITCHELL et al. (1971)	56,109	8.1	Circulation, 43, 323.
KENNA et al. (1975)	163,692	6.6	Quarterly Journal of Medicine, 44, 17.

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PENDIX 3

NFIDENTIAL

GREATER GLASGOW HEALTH BOARD

REGISTER OF CONGENITAL MALFORMATIONS

AND CONGENITAL DEFECTS

IDENTIFICATION CARD [1] 1

G.H.B. NUMBER (1st 6 digits = D.O.B.) [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] 2-11

GISTER NUMBER.....

RNAME.....

TERNAL ADDRESS.....

.....

ST CODE [G][ ][ ][ ][ ][ ][ ] 12-18

ALTH DISTRICT (of maternal address) [ ] 19
1 Northern 2 Western 3 Eastern 4 South East 5 South West

ACE OF DELIVERY (Specify.....) [ ][ ][ ][ ][ ] 20-24

X 1 Male 2 Female 3 Indeterminate 9 Not Known [ ] 25

TCOME OF PREGNANCY [ ] 26
1 Livebirth (surviving) 2 Stillbirth 3 Livebirth died < 7 days.

STATION (weeks) nk = 99 [ ][ ] 27-28

RTH WEIGHT (gms) nk = 0000 [ ][ ][ ][ ] 29-32

NGLE OR MULTIPLE BIRTH: 1 Single 2 Twin 3 Triplet [ ] 33
4 Multiple 9 Not Known

TERNAL DATA: AGE AT BIRTH OF MALFORMED CHILD (years) nk = 99 [ ][ ] 34-35

PARITY (previous viable births) nk = 99 [ ][ ] 36-37

OCCUPATION OF PARENT (R.G. Classification) [ ][ ][ ] 38-40
nk = Default code 223.

SOCIAL CLASS nk = 6 [ ] 41

FIDENTIAL

MALFORMATION CARD [2] 1

.H.B. NUMBER [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] 2-11

NCIPAL MALFORMATIONS
rdiff Code, ICD 9th Revision)

1).....[ ][ ][ ][ ][ ][ ][ ] 12-18
2).....[ ][ ][ ][ ][ ][ ][ ] 19-25
3).....[ ][ ][ ][ ][ ][ ][ ] 26-32
4).....[ ][ ][ ][ ][ ][ ][ ] 33-39
5).....[ ][ ][ ][ ][ ][ ][ ] 40-46
6).....[ ][ ][ ][ ][ ][ ][ ] 47-53

Recognised Syndrome [ ][ ][ ][ ][ ][ ][ ] 54-60

RCE OF ASCERTAINMENT (REGISTER)
er 1=Yes, Blank=No. Enter 2 = Initial Source

Birth Notification Postcard [ ] 61

Obstetric and Social Factors Form [ ] 62

Stillbirth Registration [ ] 63

Death Registration [ ] 64

Handicapped Children's Register [ ] 65

Obstetric Case Record/Dismissal Letter [ ] 66

Computer Neonatal Record (SMR11) [ ] 67

Health Visitor Record [ ] 68

Other (Specify.....) [ ] 69

E OF INITIAL REGISTRATION [ ][ ][ ][ ][ ][ ] 70-75

HANDICAPPED CHILDREN'S REGISTER (FORM SMR7)
Yes 2 = No 9 = not relevant. [ ] 76

a Proforma completed .....

tials .....

Dr. F.M.W. Hamilton,
Greater Glasgow Health Board,
351 Sauchiehall Street,
Glasgow G2 3HT.
041.332.2977.

'IDENTIAL

DEATH CARD [3] 1

H.B. NUMBER [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] 2-11

OF DEATH [ ][ ][ ][ ][ ][ ] 12-17

CIPAL CAUSE OF STILLBIRTH

..... [ ][ ][ ][ ][ ][ ][ ] 18-24

OT STILLBORN, UNDERLYING CAUSE OF DEATH

..... [ ][ ][ ][ ][ ][ ][ ] 25-31

R CAUSES

a)..... [ ][ ][ ][ ][ ][ ][ ] 32-38

b)..... [ ][ ][ ][ ][ ][ ][ ] 39-45

c)..... [ ][ ][ ][ ][ ][ ][ ] 46-52

E OF DEATH (Specify) ..... [ ][ ][ ][ ][ ] 53-57

A POST MORTEM PERFORMED?

No 2 = Yes 3 = Expected 9 = Not Known [ ] 58

Proforma completed .....

ials .....

Dr. F.M.W. Hamilton,
Greater Glasgow Health Board,
351 Sauchiehall Street,
Glasgow G2 3HT.

041.332.2977.

APPENDIX 4.

The Twelve Post-Code Sector Groups

For the purpose of sub-dividing the Greater Glasgow Health Board geographically, aggregates of post-code sectors were found to be useful for three reasons :

(1) the flexibility of the post-code sector in varying the number and size of the sub-divisions according to requirements;

(2) the virtual coterminosity of the boundaries of the Greater Glasgow Health Board with the boundaries of post-code sectors; and

(3) the availability of post-code sector data for both numerators and denominators.

Twelve groups of post-code sectors were selected. This represented a compromise between the desire to subdivide the city into a meaningful number of units and the need to retain a reasonable number of annual births within each geographical unit for statistical purposes. The twelve groups were identified by aggregating contiguous post-code sectors (starting with G1 at the city centre and moving peripherally). An attempt was made to maintain the internal homogeneity of each group by avoiding the aggregation of post-code sectors containing markedly contrasting social and environmental characteristics. This resulted in two non-contiguous sectors being aggregated into a single group (Group G). While this method of sub-dividing the city was essentially arbitrary, it proved its "validity" by successfully fulfilling the analytical functions required of it.

TABLE A13 lists the twelve groups of post-code sectors. FIGURE A1 is a map on which individual sectors may be identified.

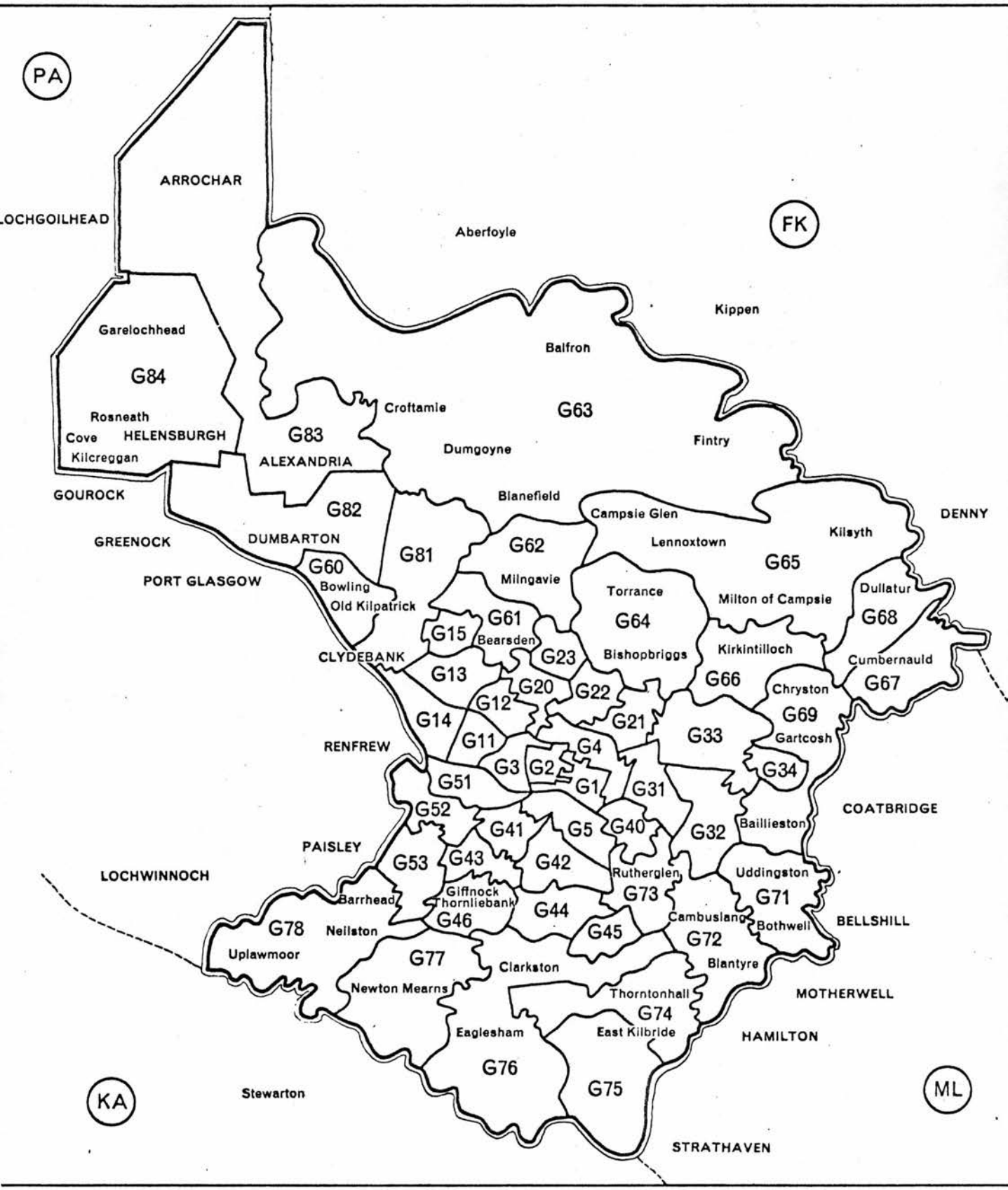
APPENDIX 4.

TABLE A13. The Twelve Post-Code Sector Groups (A - L)

Group[1]	Post-Code Sectors (G--)
A	1, 2, 3, 4.
B	20, 21, 22.
C	23, 61, 62, 64, 66.
D	31, 32, 40.
E	5, 42.
F	41, 43, 44, 46, 77.
G	45, 53.
H	72, 73, 76.
I	51, 52.
J	15, 60, 81.
K	33, 34, 69.
L	11, 12, 13, 14.

[1] All Glasgow (G) post-code sectors were included except : 63, 65, 67, 68, 71, 74, 75, 78, 82, 83 and 84.

IGURE A1



This map does not include all places in the area. It shows the main code areas and places near the boundaries.

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