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EVALUATION OF ANTENATAL SCREENING FOR  
NEURAL TUBE DEFECTS IN GLASGOW 1976-1986

AN EPIDEMIOLOGICAL STUDY

by

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Thesis submitted for the Degree of Ph.D.  
to the University of Glasgow  
Faculty of Medicine

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TO THE MOTHERS OF GLASGOW

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## STATEMENT OF ORIGINALITY

I hereby declare that this thesis was my own composition, the content, study design and analysis done by myself with partial recourse to the assistance of statistical and computing when required.

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## LIST OF ABBREVIATIONS

1. AN Anencephaly
2. SB Spina Bifida
3. ASB Anencephaly and Spina Bifida
4. NTD Neural Tube Defects
5. AFP Alpha-fetoprotein
6. Ms AFP Maternal serum Alpha-fetoprotein
7. Am AFP Amniotic fluid Alpha-fetoprotein
8. AchE Acetylcholinesterase
9. Amino Aminocentesis for amniotic fluid, Alpha-  
phetoprotein and acetylcholinesterase
10. Ultra Ultrasound
11. MOM Multiple of the Median
12. EUROCAT European Registration of Congenital Anomalies  
and Twins
13. GGHB Greater Glasgow Health Board
14. MRC Medical Research Council
15. BPD Biparietal diameter

## ABSTRACT

Glasgow suffers one of the highest prevalence rates of congenital neural tube defects in the world. There have been reports of a long-term decline in the prevalence of neural tube defects although the reasons for it are unclear. Anencephaly is always fatal while, even with active treatment, spina bifida is associated with high rates of early infant mortality and a high degree of physical and mental impairment in the survivors. Antenatal screening followed by induced abortion is the only available means of avoiding such births.

The purpose of the study was to evaluate the effectiveness of antenatal screening for neural tube defects in the context of changing epidemiological patterns and the growing use of ultrasound. The impact of screening on the population frequency of the defect during 1976-1986 was investigated. The data were obtained from several sources including the Glasgow Register of Congenital Malformations and the Department of Medical Genetics at the Royal Hospital for Sick Children, Yorkhill, Glasgow.

There was a statistically significant decline in both the birth and pregnancy prevalence of anencephaly and a statistically significant decline in birth prevalence of spina bifida over the study period. Antenatal screening made a considerable impact on both anencephaly and spina bifida birth prevalence particularly the former.



The effectiveness of antenatal screening was influenced by three factors: the proportion of affected pregnancies screened; the proportion of affected pregnancies detected and the proportion of affected pregnancies terminated when detected. The interaction of these factors can be expressed arithmetically.

The proportion of pregnancies screened was higher in Glasgow than in the west of Scotland as a whole. A high proportion of those not screened were women under twenty years of age, multipara and those from lower social class. The effectiveness of antenatal screening improved with the combined use of maternal serum AFP and ultrasound. The combined screening approach had a high sensitivity, specificity and efficacy.

In conclusion, antenatal screening for neural tube defects has contributed to the reduction of both anencephaly and spina bifida birth prevalence but there is substantial scope for improving the efficiency and consequently the effectiveness of screening for spina bifida. Until primary prevention is possible, antenatal screening for neural tube defects in Glasgow will continue to play a major role in avoiding affected births.

## DEFINITIONS\*

EPIDEMIOLOGY: The study of the distribution and determinants of health-related states or events in a specified population, and the application of this study to the control of health problems

CONGENITAL MALFORMATION: An abnormality of structure attributable to faulty development (Leck et al. 1968)

INCIDENCE 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 OF A CONGENITAL MALFORMATION: The proportion of births (live and still, delivered from 28 weeks gestation) with the malformation during a specified period of time. (Some studies in the literature refer to this as an "Incidence Rate".)

The term "prevalence" of a congenital malformation is shorthand for "prevalence at birth" (Pharoah 1990) usually defined as the number of instances of the disorder per 1000 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.

\* Definitions from Last, 1983 - unless stated otherwise.

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 to master patient files and record linkage systems, which provide the means of collecting, storing and retrieving information on many topics not predetermined or limited in scope.

REGISTRY: Place where a register is kept

EVALUATION: 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.

Screening is an initial examination only and positive responders require a second diagnostic examination. The initiative for screening usually comes from the investigator or the person or agency providing care rather than from a patient with a complaint.

There are different types of medical screening each with its own aim:

Mass screening simply means the screening of whole populations. Multiple or multiphasic screening involves the use of a variety of screening tests on the same occasion.

Prescriptive screening has as its aim the early detection in presumptively healthy individuals of disease that can be controlled better if detected early in its natural history.

**SENSITIVITY:** Is the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test. Sensitivity is a measure of the probability of correctly diagnosing a case or the probability that any given case will be identified by the test (Syn : true positive rate)

**SPECIFICITY:** Is the proportion of truly non-diseased persons who are so identified by the screening test. It is a measure of the probability of correctly identifying a non-diseased person with a screening test. (Syn : true negative rate)

**FALSE POSITIVE:** Positive test result in a subject who does not possess the attribute for which the test is conducted. The labelling of a healthy person as diseased when screening in the detection of disease.

**FALSE NEGATIVE:** Negative test result in a subject who possesses the attribute for which the test is conducted. The labelling of a diseased person as healthy when screening in the detection of disease.

**Predictive value of positive test:** the proportion of true positive (i.e. diseased individuals) among all those who have positive tests. (The probability that a person with a positive test does have the disease.)

**Predictive value of negative test:** the proportion of non-diseased individuals among all those who have negative test result. (The probability that a person with a negative test does not have the disease.)

**EFFICIENCY:** The end results achieved in relation to the effort expended in terms of money, resources and time.

**EFFECTIVENESS:** The extent to which a specific intervention, procedure, regimen, or service, when deployed in the field, does what it is intended to do for a defined population.

**EFFICACY OF ANTENATAL SCREENING:** The proportion of those with the disorder in the study population detected and terminated as a consequence of screening procedure. (Roberts et al. 1983.)

**PARITY:** The number of full term infants previously born to a woman, excluding miscarriages or abortions in early pregnancy, but including still birth

**SOCIAL CLASS:** A stratum in society composed of individuals and families of equal standing.

Social class based on Classification of the Registrar General:-

Social Class I: Higher professional and administrative occupation

Social Class II: Employees in industry and retail trades  
the "lesser" professions (intermediate occupations)

Social Class III: Skilled occupation

Social Class IV: Partly skilled occupation

Social Class V: Unskilled occupation

(Office of Population Censuses and Surveys, 1980)

**SECULAR TREND:** Changes over a long period of time, generally years or decades.

**COST-BENEFIT ANALYSIS:** An economic analysis in which the costs of medical care and the loss of net earnings due to death or

disability are considered. The general rule for the allocation of funds in a cost-benefit analysis is that the ratio of marginal benefit (the benefit of preventing an additional case) to marginal cost (the cost of preventing an additional case) should be equal to or greater than one.

**COST-EFFECTIVENESS ANALYSIS:** This form of analysis seeks to determine the cost and effectiveness of an activity or to compare similar alternative activities to determine the relative degree to which they will obtain the desired objectives or outcomes. The preferred action or alternative is one that requires the least cost to produce a given level of effectiveness or provides the greatest effectiveness for a given level of cost.

**SECTION I: INTRODUCTION**



## SECTION I: INTRODUCTION

### 1.1 HISTORICAL NOTE

Ferembach (1963) reported a prehistoric human skeleton with spina bifida occulta excavated in North America. Brothwell and Power (1968) found prehistoric skeletons with spina bifida cystica from the Roman, Anglo-Saxon and Medieval periods in England.

The teratological records of Chaldean clay tablets covered with cuneiform script, excavated near the River Tigris in the nineteenth century, contain descriptions of several types of human malformation. Ballantyne (1894) suggested that these tablets were a good source of information for congenital malformations in the past.

The concept of congenital malformations, including anencephaly and spina bifida, has evolved throughout history. From prehistory to the end of the nineteenth century, the term monsters (derived from a Latin verb *moneo* meaning to warn) was used to include all types of congenital malformations. Congenital malformations were regarded as an indication of divine warning to the parents or society and believed to be a result of supernatural intervention. (Warkany 1971)

In medieval Christian societies it was thought that supernatural anger at the community frequently led to abnormal infants who were regarded as portents of major events.

Many cultures believed that unions between members of different species could produce monstrous offspring, this being linked with the centaur of Greek mythology and the Hindu belief in transmigration of the soul from man to animal and vice versa. The theory of Hippocrates and Aristotle, that the narrowing of the womb and excessive pressure are causes of abnormalities, are still popularly accepted as explanations of postural deformities. The wide acceptance of "maternal impression" as a cause of malformed births, due to similarities in appearance between malformed infants and real and imaginary animals, gave rise to the belief that it was dangerous for a pregnant woman to look at monkeys for fear of producing a similar monstrous infant. (Kenen 1980)

Infanticide was widespread in many ancient cultures. Deformed infants were killed as were many normal female children in times of hardship. An especially brutal infanticidal eugenic policy was that of the Spartans who threw rejected offspring into a deep chasm on Mount Taygetus. The Romans drowned unwanted infants in the River Tiber. Infanticide was also widespread throughout medieval Europe. Christian societies in England during the fifteenth century practised infanticide, as is indicated by the large excess of male children in parish records of medieval England (Russell, 1948). At the end of the seventeenth century, London was a centre for exhibiting every variety of unusual human form, displayed like circus animals.

Subsequently, anatomists, surgeons and pathologists began to document their experiences of such conditions. In Amsterdam, Nicholase Tulp (1637), a successful surgeon, gave the first detailed description of spina bifida (Brocklehurst, 1976).

The second era of development in teratology came during the late nineteenth and early twentieth centuries with the publication of Darwin's "The Origin of the Species" (1859). He argued that selective forces produced changes over many generations. This led to renewed interest in congenital malformations in terms of their biological importance as a matter of natural variation. The science of genetics started to develop during this period and some scientists encouraged the more intelligent and successful members of society to have large families for eugenic reasons.

During the third era of development (from the middle of the twentieth century) it was discovered that specific environmental factors predisposed to congenital defects (including x-rays and vitamin deficiencies). During this period experimental work and human observational work has gone hand in hand. The dramatic change in the pattern of disease, with decreases in the frequency and impact of infectious disease as causes of infant deaths, has been accompanied by advances in genetics and experimental teratology. All these disciplines have investigated congenital abnormalities which are becoming relatively more important clinically with the passage of time. The advances in genetic understanding of the most common defects has led to the

development of the concept of multifactorial inheritance. Most congenital defects are probably due to a combination of genetic and environmental factors.

Toward the end of the 1970's the fourth era was initiated by discovery of methods for examining and analysing maternal serum and amniotic fluid to detect and diagnose a number of congenital abnormalities prenatally. This is linked with the use of induced abortion of the abnormal fetus as a legally and ethically accepted procedure in many countries.

## 1.2 EMBRYOLOGY, ANATOMY AND CLASSIFICATION

### EMBRYOLOGY

Normally the brain and spinal cord develop from the neural plate, a thickening of the outer germ layer, the ectoderm of the embryonic central nervous system. This runs the length of the embryo in the midline dorsally, and rapidly forms a groove called the neural groove. The groove deepens and is bounded on either side by the neural folds. The edges of the neural folds fuse with each other to form the neural tube, when the embryo has six to seven somites at about twenty-two days.

The fusion commences in the cervical region and extends in both cranial and caudal directions leaving temporary canals or neuropores connecting the central neural canal to the amniotic cavity which is the last point to close. This process is normally completed by twenty-six days of gestation which is approximately four weeks after conception (Shepard, 1976).

The neural tube consists of a single layer of cells which proliferate at the cephalic end to form the various structures of the brain, while the remaining cells of the tube proliferate to form ependyma, neurones, glial cells and pyramidal cells. The mesoderm surrounding the tube segments into somites which develop into vertebral bodies and arches. The meninges, the pia, arachnoid and dura are also formed from the mesenchyme at the time of separation of the neural tube from the ectoderm. The

lesions of anencephalus and spina bifida are believed to be due to the failure of some part of the foregoing process.

Marin-Paddilla (1966) suggested that vitamin A excess in hamsters acts primarily by retarding mesodermal development and points out that the deformity produced is similar to that seen in humans with various degrees of neural tube defects. Wilson, Jordan and Brent (1954) concluded that radiation-induced anencephalus is due to rupture of a necrotic area of the closed tube.

Kallen (1968) and Warkany (1971) agree that the pathogenesis of neural tube defects is due to a disturbance of the neural-mesodermal interaction and that the cause of this is unknown.

Vogel and McClenahan (1952) and Vogel (1961) demonstrated anomalous vasculature in anencephalic specimens and suggested that the cerebral vessels never become connected to the systemic circulation, preventing adequate nutrition to the cranial neural tissue resulting in anencephaly.

Stevenson et al (1987) demonstrated abnormalities of the arterial supply to the region of spine defect. Because embryologically these arteries develop prior to closure of the neural tube, he suggested that vascular disturbance limited nutrition to the developing neural tissue and supporting structures, preventing appropriate growth and closure.

In summary, although conflicting hypotheses have been proposed, there is a general agreement among embryologists that the key to the pathogenesis of N.T.D lies in the disturbance of the neural-mesodermal interaction.

#### ANATOMY

Anencephaly: failure of fusion of the neural tube at the cephalic end prevents development of the fore brain and as a consequence the vault of the skull does not develop leading to anencephaly (Morison, 1970).

In anencephaly the fore brain is replaced by a mass of haemorrhagic fibrovascular tissue containing some neural elements called cerebrovasculosa (Warkany, 1971). The brain stem is usually present as eyes and optic nerves which end blindly at the base of the skull, but the mid-brain and cerebellum may be normally developed or absent.

There is an abnormality in the shape of the bones at the base of the skull particularly the sphenoid and petrous temporal bones. The cranial vault bones, the parietal frontal, squamous temporal and the occipital are present but rudimentary.

The facial bones are normal but look deformed because of their articulation with an abnormal skull base. In anencephalus the lesion may extend through the cranium and sometimes through the cranium and the spine; this is called craniorachischisis which is

rare in humans (Warkany, 1971).

The abnormality is incompatible with life and most infants are stillborn, but if the respiratory centre is intact liveborn infants may survive for a few days.

Anencephaly may be associated with other abnormalities, the commonest being spina bifida (Elwood and Nevin, 1973). Others include exomphalos, congenital heart disease, cleft palate and urinary tract defects (David and Nixon, 1976). There are other conditions leading to herniation of brain tissue through a defect in the skull but they are much rarer and should be distinguished from anencephaly. They include cranial meningocele, encephalocele and hydroencephalocele, in which there is a herniation of the meninges only, meninges and brain tissue, meninges and brain tissue and part of the ventricular system respectively.

Anencephaly is usually distinguished from exencephaly and iniencephaly.

Exencephaly is an overgrowth of the cerebral hemispheres accompanied by normally developing cranial nerves, midbrain and hindbrain. The overgrowing material expands from the cranial base, cranial vault being open in the midline and cerebral material is everted, the ventricular surface being exposed.

Iniencephaly: failure of closure of the neural tube in the cervical and upper thoracic region.



Spina bifida: Failure of embryonic fusion caudally causes a dorsal defect in the vertebral arches leading to spina bifida which shows considerable variation in severity.

Spina bifida occulta: This is the least serious form of spina bifida. There is a localised defect in one or more vertebral arches due to the failure of fusion of the halves of the vertebral arches. The meninges and nervous tissue remain within the vertebral canal, with no associated disorders. The only external evidence of underlying bony maldevelopment is the presence of changes in overlying skin in the form of a dimple, patch of hair, pigmentation, a lipoma or a dermoid.

Spina bifida cystica: This occurs when vertebral arches are deficient and there is external herniation of the meninges and nervous tissue. It includes meningocele (herniation of the meninges out of the spinal canal while the cord remains in its position) and myelomeningocele (in which there is a filled cystic swelling formed by meninges protruding through a defect in the vertebral arches under the skin, the spinal cord and nerve roots are carried out into the fundus of the sac). Myelocoeles, myelocytocoeles, hydromyelocoeles, syringomyelocoeles and localised rachischisis are all essentially the same lesion and best regarded as myelocoeles.

In all these lesions vertebral arches are deficient and neural plate material spreads out on the surface, sometimes in a shallow

depression, more commonly over a cystic swelling of the meninges with some degenerative changes at birth. The lesion is seen as a bluish semitransparent membranous sac due to the accumulation of cerebrospinal fluid which gives it its cystic nature.

Spina bifida cystica, in which there is skin cover, is called a closed defect. When there is no skin cover it is called open or aperta.

Hydrocephalus nearly always co-exists with a spina bifida defect, due to the Arnold-Chiari malformation (in which the medulla of the fourth ventricle and cerebellum are dragged caudally into the foramen magnum with consequent obstruction of the cerebro-spinal fluid pathway).

As with any other congenital defects there may be multiple developmental anomalies, talipes equinovarus, cleft lip or palate, cardiac lesions or supernumary digits.

In summary, failure of fusion of the neural tube at the cephalic end leads to anencephaly, and at the caudal end to spina bifida. Because of the multiplicity of anatomical variants and associated defects which can occur, a clear and unambiguous system of classification is necessary as a precondition of scientific research into these defects.

Classification: There is no universally agreed classification but the International Classification of Diseases (ninth revision) (World Health Organisation, 1977) is widely used for classification of anencephaly and spina bifida. Anencephaly with spina bifida is most commonly included in the anencephaly group. Exencephaly, encephalocele and iniencephaly are separated from anencephaly.

Spina bifida includes open and closed cystica defects but does not include spina bifida occulta. Any abnormality secondary to or associated with spina bifida is classified under spina bifida (except for encephalocele).

In summary, 'anencephaly' includes anencephaly with or without spina bifida, and excludes exencephaly, iniencephaly and encephalocele. 'Spina bifida' includes open and closed cystica defects (along with secondary defects such as hydrocephalus) but excludes spina bifida occulta.

### 1.3 AETIOLOGY AND NATURAL HISTORY

#### Aetiology:

In spite of extensive studies of neural tube defects, there is no consensus about their causation. Epidemiological studies suggest that anencephaly and spina bifida may result either from genetic factors, environmental factors or by the combined action of genetic and environmental factors, so-called multifactorial aetiology. Each of these will be considered in turn.

#### Genetic Factors:

There is some evidence for the operation of genetic factors in the aetiology of neural tube defects. The preponderance in one or other sex is a pointer to a genetic cause. The number of affected females in the population of neural tube defects has been noted to be consistently greater than the number of affected males (Carter, 1974; Stone, 1981). The reason for this female predominance remains unclear. It could be due to selective prenatal loss but this has not been established.

There is a degree of stability of the prevalence rate in certain ethnic and racial groups. British and Sikh populations have high prevalence rates (up to eight per 1000) of neural tube defects (Carter, 1974). Although the rate decreases somewhat after migration of these groups to regions of low prevalence, a relatively high prevalence rate persists (Carter, 1974; Baird, 1983). Some African populations appear to have a low prevalence rate of neural tube defects (e.g one per 1000 in Lagos - Carter,

1974). This low rate persists even after migration to an area of high prevalence such as Great Britain (Carter, 1974).

There is an excess rate of neural tube malformation if the parents are related (Carter, David and Laurance, 1968; Carter and Evans, 1973a; Leck, 1983). This indicates a polygenic determination of neural tube malformation, since consanguineous marriage implies a degree of assortive mating leading to a predisposition to the malformation (Carter, 1974).

There is a higher concordance rate among monozygotic than dizygotic twin pairs (James, 1972; Windham and Sever, 1982). This provides strong evidence for a genetic component. There is a higher risk (up to 6%) of neural tube defects to siblings of affected individuals (Carter and Evans, 1973) than that for the general population, although with the recent decline in prevalence it is now likely to be only 1-2% in the United States (Holmes, Driscoll and Atkins, 1976). The risk to an offspring of either affected mother or father is approximately 3% (Carter and Evans, 1973a).

It has been suggested that this genetic susceptibility may not be specific for neural tube defects but may reflect a more general susceptibility to any defect involving the midline of the developing embryo. The planes of fusion of tissue or the midline of the embryo may be a developmental field under specific chromosomal control (Opitz and Gilbert, 1982). This theory is

supported by studies which have shown an increased risk of hydrocephalus (Robertson et al, 1981), tracheo-oesophageal dysraphism, cleft lip and palate (Fraser, Czeizel and Hanson, 1982), diaphragmatic hernia and omphalocele (Czeizel, 1981) in families of individuals with neural tube defects. The presence of multiple anomalies such as congenital heart disease (Ferguson, Rouse and Lockhart, 1983), omphalocele, vertebral fusion defect (Jones, Jones and Chernoff, 1982) in individuals with neural tube defects is further evidence of a non specific mid-line involvement.

#### Environmental Factors:

While the following studies suggest that environmental factors increase the risk of neural tube defects they do not necessarily establish an environmental agent as the primary aetiology.

There has been a decline in the prevalence of neural tube defect over a time (Macmahon and Yen, 1971; Owens et al, 1981). Most studies now show a fall in prevalence which cannot be attributed to prenatal screening (Khyoury, Erickson and James, 1982a; Windham and Edmonds, 1982; Stone et al, 1988).

Neural tube defects show a striking geographical variation both between and within countries. Neural tube defects are commoner in Europe than in Asia or Africa (Leck, 1974).

In the British Isles the prevalence rate is high in the north-

west and low in the south-east (Carter, 1974). Similar variability has also been noted in the United States with high rates in the east and low rates in the west (Khoury, Erickson and James, 1982a).

In Great Britain infants conceived in March, April or May (Carter, 1974) appear to be at highest risk, while in Canada September and October conception appear to result in the highest rate of neural tube defect (Dallaire et al, 1984). The majority of affected children are born to mothers younger than 20 years or older than 35 years (Carter and Evans, 1973a; Stone, 1981). Most studies show an excess of first born children in the affected population (Carter, 1974). Some have shown a higher prevalence rate in lower socio economic classes as determined by the father's occupation (Carter, 1974; Stone, 1981).

Various dietary factors have been suspected of causing neural tube defects in man. Associations have been reported between neural tube defects in offspring and excessive tea drinking (Fedrick, 1974), and consumption of icecream, white bread loaves, canned meat, canned peas and corned beef (Knox, 1972) by the mothers during pregnancy. Knox suggested the nitrites and nitrates used for preserving canned food may be teratogens.

Penrose (1957) observed that areas in the United Kingdom where the prevalence of neural tube defects were the highest were also those areas where the drinking water was soft, rather than hard,

and suggested that the presence or absence of certain trace elements may be an important causation. Fedrick (1970) and Wilson (1971) found no relation between the type of water supply and the prevalence of neural tube defects.

Renwick (1972) suggested that the causal agent of neural tube defects was an unidentified substance occurring in blighted potatoes and that if women avoided ingesting such potatoes they would not have neural tube defects in their offspring. Nevin and Merret (1975) advised all parents of infants with anencephaly and spina bifida born at Belfast hospital from July 1972 onwards to avoid potatoes as soon as they decided on another pregnancy. They found there is no significant reduction in the incidence of neural tube defects in women who avoid potatoes.

Zinc deficiency appeared to be associated with anencephaly in Turkey (Cavdar et al, 1980) and in London (Buamah and Russel, 1984). Low plasma zinc may operate at the time of conception and during early embryogenesis (Soltan and Jenkins, 1982).

It has been noted that serum and RBC folate are low in mothers of children with neural tube defects compared to controls (Smithells, Sheppard and Schorah, 1976). Trials of supplementing high risk mothers with folic acid (Laurence et al, 1981) or multivitamins (Smithells et al, 1981; Seller, 1985) have shown lower than expected frequency of neural tube defects in their offspring. These studies have been compromised, however, by poor



compliance and unsatisfactory methodology. The role of folic acid in neural tube defects remains unsettled.

A study by Yates et al (1987) confirmed that red cell folate is depressed in women who have had offspring with neural tube defects; since this cannot be entirely attributed to lower dietary intake of folate, there could be an unidentified inherited disorder of folate metabolism.

Maternal vitamin B12 levels were found to be low in fetuses with neural tube defects (Schorah, Smithells and Scott, 1980).

A significant increase in the risk of neural tube defect has been observed among the offspring of women who have had gastric bypass operations for morbid obesity (Haddow et al, 1986; Martin et al, 1988). These women are at risk of nutritional deficiencies, especially for iron, calcium, vitamin B12 and folate (Printer and Scott, 1982; Shilling, Gohdes and Hardie, 1984; Amaral et al, 1985). This provides support for recent studies linking diet and neural tube defects (Smithells, Sheppard and Schorah, 1976) and the association between folate and vitamin B12 deficiencies and neural tube defects found by Laurence et al (1981).

Parkinson and Tan (1982) found vitamin A concentration of amniotic fluid is significantly greater in the presence of a fetus with neural tube defect, but suggest that vitamin A should not be included in supplements until there is definite evidence

that it is harmless.

Maternal illness has been implicated as a factor in some neural tube defects. It was found that febrile illness during the first trimester of pregnancy was associated with congenital malformation (Miller, Smith and Sheppard, 1978; Lady, Edmonds and Erickson, 1980). During pregnancy a silent infection with an unknown teratogenic organism may take place, or involve exposure not during the affected pregnancy (Kalter and Warkany, 1983).

Diabetic mothers with poorly controlled diabetes mellitus before and during early pregnancy are at increased risk of having a malformed baby (Miller et al, 1981; Cousins, 1983). The mechanism of teratogenesis is unknown; however, altered metabolic control with associated hyperglycemia during organogenesis is considered causative (Pedersen, Tygstrups and Pedersen, 1964; Kalter and Warkany, 1983).

Some drugs have a potential teratogenic effect. Accutane is used for treating severe acne and is isotretinoin, a vitamin A analogue. When mothers used this drug in early pregnancy some had babies with malformation of the central nervous system and other systems (Rosa, 1983; Braun et al, 1984; Lammer et al, 1985). The cause is thought to be a deleterious effect on cephalic neural-crest cell activity. Benditin, called Debendox in the United Kingdom, which contains anti-histamine was often given to pregnant women as an anti-emetic and may cause

neural tube defects (Harron, Griffith and Shank, 1980).

Anti-convulsant drugs such as phenytoin and phenobarbital lead to an increased frequency of congenital malformation in epileptic women taking such drugs during pregnancies (Montouris, Fenichol and McLain, 1979). Also exposure to valproic acid during first trimester of pregnancy is reported to be associated with spina bifida (Bjerkedal et al, 1982; Staunton, 1989).

Other possible neural tube teratogens are aminopterin, a powerful folic antagonist which sometimes is taken by women to induce abortion (Emerson, 1962); antimetabolic cancer chemotherapeutic agents such as Methotrexate (Milunsky and Gaynor, 1968) and Busulfan (Abramovici, Shaklai and Pinkhas, 1978). Alcohol abuse in the first month of pregnancy has been reported in several mothers of infants with neural tube defects (Castro-Gago et al, 1984).

#### Multifactorial Aetiology

The vast majority of neural tube defects occur as isolated malformations and are believed to be multifactorial in origin. The teratogenic effect is attributed to the combination of several minor gene abnormalities and environmental factors. Their precise number and nature have not been determined (Carter and Evans, 1973; Leck, 1974). Others suggest monogenic inheritance with a large influence of environmental factors

(Demenais et al, 1982). Kalter and Warkany (1983) suggest a multigenic inheritance with environmental influence.

The malformation is believed to occur during the first stage of development by environmental factors acting on the fetus when it is susceptible through inherited characteristics carried on several genes (Carter, David and Laurence, 1968; Carter, 1974).

A number of factors may be responsible; some of these factors may act as trigger mechanisms when certain threshold levels are reached, others may act only when deficient. Aminopetrin, a folic acid antagonist, now rarely used, has been shown to produce neural tube defects in man (Thiersch, 1952). This suggests that folic acid may act as a deficiency factor when the available concentration falls below certain thresholds.

Seller (1983) suggests that the cause of neural tube defects in man is due to a basic metabolic defect in the bio-synthesis pathway of DNA, folate, vitamin B12, zinc and other vitamins are intimately involved directly or indirectly in biosynthesis of DNA.

Holmes, Driscoll and Atkins (1976) suggest that there is aetiological heterogeneity within neural tube defects which expresses itself in the form of multiple anomalies. This might represent 6% (Martin, Fineman and Jonde, 1983) to 20% (Khoury, Erickson and James, 1982a) when associated with chromosomal

abnormality such as trisomies 13, 18 and 21 (Khoury, Erickson and James, 1982a). They have been reported as a disorder of major mutant genes with family patterns of x-linked recessive (Baraitzen and Burn, 1984), autosomal recessive (Robertson et al, 1981) and autosomal dominant (Sever, 1983); it occurs in specific phenotype of unknown aetiology Meckels syndrome, cloacal extrophy (Holmes, Driscoll and Atkins, 1976).

The group with multiple anomalies varies from the group with isolated neural tube defect by showing equal involvement of male and female, lack of geographic variability, failure to decrease in prevalence over time and lack of predominance in white over black (Khoury, Erickson and James, 1982a). The potential heterogeneity in the aetiology of neural tube defects must be carefully considered in counselling parents about the risk of subsequent children being affected (Holmes, Driscoll and Atkins, 1976).

In summary, there appears to be a genetic component in up to 10% of births associated with NTD but there is no consensus about the aetiology of the remainder which is the vast majority.

The most promising aetiological hypothesis relates to diet and particularly to the role of vitamin deficiency.

### Natural History:

Neural tube defect is one of the commonest abnormalities found at birth in the United Kingdom and is also one of the commonest abnormalities found in abortuses. The true rate of conception is difficult to estimate as some women are unaware that either a conception or an abortion has taken place.

Spontaneous abortion may be regarded as a natural screening method for the elimination of abnormal fetuses. Failure of this natural process leads to births of abnormal infants. It is possible, however, that the factor causing the malformation also causes the abortion (Sentrakul and Potter, 1966). The risk of spontaneous abortion is higher in women with previous spontaneous abortion and women who have given birth previously to a malformed baby (Warburton and Fraser, 1964). The incidence of neural tube defects in early pregnancy might be constant in different populations and the geographical variation in prevalence at birth might be due to differing rates of spontaneous abortion (Roberts and Lloyd, 1973).

Creasy and Alberman (1976) in London found that neural tube defects occurred in 3% of all spontaneous abortions and estimated that one quarter of conceptuses at eight weeks gestation with neural tube defects will be stillbirths, one quarter live births and half spontaneous abortions. They suggested that screening should be carried out on pregnancies subsequent to spontaneous abortion. Knowledge about the diagnosis of spontaneously aborted

fetuses increases the accuracy of genetic counselling services. In Edinburgh a study by Bell and Gosden (1978) found an incidence rate (2.7%) of neural tube defects among conceptuses which are spontaneously aborted.

The great majority of fetuses with anencephaly (88%) are stillborn while the remainder (10%) result in death within the first week of life and only 2% survive beyond the first week (Stone, 1981).

The proportions of anencephalic infants which are stillborn or live born appeared to vary from area to area. The live born proportions varied from about 19% in Belfast, 10% in Glasgow and 1.5% in Aberdeen (Elwood and Mackenzie, 1971). Very occasionally a child with anencephaly may survive several months (Milunsky, 1979). For this reason parents of anencephalic infants should not be informed that the child will die immediately.

Roberts and Powell (1975) in Wales found that 9% of anencephalic fetuses had other congenital malformations outside the central nervous system. In Glasgow 14% of anencephaly fetuses had other congenital malformations (Stone, 1981).

Spina bifida is most commonly lumbosacral with associated paralysis of the legs and sphincters. About 15-20% have covering of intact skin and are known as "closed" spina bifida (Connor and Ferguson-Smith, 1987). About one third of infants with closed

spina bifida were severely disabled and a further third were moderately disabled (Wald and Cuckle, 1984).

Hydrocephalus occurs in about 80% of spina bifida cases (Conner and Ferguson-Smith, 1987); 20% of spina bifida fetuses are known to have other congenital malformations. The most frequent defects associated with spina bifida were deformities of the limb (Stone, 1981).

Wilson (1971) carried out a study in Glasgow and reported about 19% stillborn and a survival rate after one year of 32.9%. Of those, 33.7% survived with minimal disability and 57.9% with severe disability. In a later Glasgow study Stone (1981) found that 17% of spina bifida were stillborn, 10% died within the first week of life and 73% survived beyond the first week. This proportion of stillbirths is slightly lower than in previous studies, while the survival rate is more favourable (Stone, 1981).

#### Role of Treatment:

There has long been a controversy regarding the appropriate treatment of spina bifida cases. Before the late 1950's non-surgical treatment of infants with spina bifida was the rule as the risks of immediate operation were excessive. Closure of the defect was considered at 12-18 months of age to give time for hydrocephalus to be stabilised. Epithelisation of the sac had occurred by this time and the operative risk decreased.



The development of the mechanical valved shunt system for hydrocephalus (Nulsen and Spitz, 1951) provided a means of controlling hydrocephalus. Owing to the observation that spina bifida children survived in a state of paraplegia, hydrocephalus, mental retardation, incontinence and severe recurrent renal infection, changes in neonatal neurosurgery with early closure of open lesions became widespread and led to improved survival rate. Sharrard et al (1963) realised that muscle function tended to be preserved with early closure of the sac; but improved survival was associated with an increase in the proportions of severely disabled children among the survivors.

Studies from other centres demonstrate indirectly the effect of treatment. In Birmingham about 24% survived one year and 22% were stillborn (Knox, 1967). In Liverpool 36% survived one year and 23% were stillborn (Rickham and Mawdsley, 1966). In Belfast 43% survived at one year and 16% were stillborn (Elwood and Nevin, 1973).

This period of active surgical treatment has been assessed by Lorber (1971; 1972) who established the major adverse neonatal criteria for non-treatment. These included the presence of a thoracolumbar lesion, severe paralysis of the legs, advanced hydrocephalus, kyphosis or scoliosis, severe congenital defect or birth injury. A large number of children survived after non-selective early surgery with incapacitating mental and physical disabilities, thus limiting the success of this therapeutic approach

(Richards and McIntosh, 1973).

Various neonatal criteria have been used to select the more promising children for early treatment. Shurtleff et al (1974) proposed his own selection criteria which predicted poor prognosis and indicated non-treatment. These were similar to the Lorber criteria but additionally considered the social circumstances and the presence of the central nervous system, infection or haemorrhage.

An alternative approach has been proposed by Stein, Schut and Ames (1975). This takes into consideration the presence of an absence of lacunar skull deformity which appears useful in predicting intelligence. These lesions which are present on the neonatal skull x-ray during the first month of life disappear from x-rays of older children. Early surgery is not recommended for children with lacunar skull deformity along with at least two of Lorber's major adverse neonatal criteria.

Opinions differ on where to strike the balance between active surgical intervention and simple nursing care. The most widely adopted approach is a selective one in which only those infants whose prognosis seems most promising are selected for surgery and active treatment. As a result of this the mortality rate for children with spina bifida appears to have increased with a decline in the proportion of survivors (Weatherall and White, 1976).

Later the approach shifted toward early closure with appropriate shunting of hydrocephalus (Chervenak, 1984). Adopting such treatment policy, one third of infants with open spina bifida lesions survived for five years, 84% of these being severely disabled, 10% moderately disabled and only 6% with no disability (Althouse and Wald, 1980).

McLaughlin et al (1985) found a significant improvement over time in the survival of newborn receiving early surgical care regardless of whether the initial prognosis was good or poor.

Others have suggested that early closure has no advantage over non-closure, in terms of the incidence of hydrocephalus mortality and ventriculitis. Non-closure is safe, spares the neonate a major operation and reduces the number of shunt operations needed in those babies who have limited life expectancy. It also gives time to the family to make their choice regarding the operation and allows time for the medical team to assess the baby fully (Deans and Boston, 1988).

Medical, social and educational services are needed for the survivors; the majority (more than 80%) have some degree of disability whether physical, mental or both (Wilson, 1970).

In summary, different rates of spontaneous abortions in different geographical areas may be responsible for some of the variation in birth prevalence of NTD.

In the case of anencephaly, those which are not spontaneously aborted are either stillborn or die early, usually during the first week of life. Some Spina bifida cases which are not spontaneously aborted are stillborn while some are born alive with consequent physical and mental disabilities of varying degrees. Several approaches to treatment of the survival of spina bifida cases have been reported, and these have changed over the years. Even with active treatment, spina bifida is associated with high rates of early infant mortality and a high degree of physical and mental disability in the survivors whether surgical treatment is carried out early or late.

#### 1.4 EPIDEMIOLOGY

##### Prevalence of Anencephaly and Spina Bifida:

There is a continuing controversy about whether to use the term prevalence or incidence in expressing the frequency of neural tube defect. Most authors now use the term prevalence rather than incidence. This is because the true incidence is unknown since it is probable that many severely malformed fetuses are aborted early in pregnancy (Biggar, Montimer and Haughie, 1976).

Prevalence rates are widely quoted in the literature and are expressed as the number of affected individuals divided by the total number of births (live and still). The proportions of newborns with the defect recognised at birth are referred to as prevalence rates at birth, and have the characteristics of point prevalence rates in being simultaneously influenced by both incidence and duration (Lowry and Thunem, 1988; Pharoah, 1990). They are observations of the frequency of defects at birth because the events that led to those defects may have occurred six months or more before birth. The proportion of new born (live and still birth) and fetuses (terminated as a result of prenatal diagnosis) with the defect recognised at any time during pregnancy are referred to as adjusted prevalence or pregnancy prevalence.

The prevalence of neural tube defects within the British Isles may be represented as a gradient of decreasing prevalence from the relatively high risk regions of Ireland, Scotland and Wales

to the relatively low risk south-east of England (Stocks, 1970). The reason for this pattern is likely to be related to both genetic and environmental factors.

In Dublin in 1900 the prevalence of anencephaly was 1 per 1000 livebirths. There was a peak in 1938-1941, and after 1950 there was a persistent increase, reaching a remarkable peak in prevalence of 8 per 1000 in 1960-1961, which continued at a high level to 1964-1965 (Windham and Edmond, 1982). Thereafter the prevalence of both anencephaly and spina bifida started to decline and the adjusted prevalence for 1980-1986 in Dublin fell to about 3.28 per 1000 total births (Eurocat, 1989).

In the United Kingdom the highest prevalence of neural tube defects has been reported from Belfast and is probably the highest in the world (Elwood, 1970). It is about three times greater than that in London (Carter and Evans, 1973) and 20% above the prevalence in south Wales (Laurence, Carter and David, 1967). It has recently started to decline - the adjusted prevalence in 1980-1986 was 3.09 per 1000 total births (Eurocat, 1989).

It seems that in Dublin as well as in Belfast and Scotland the prevalence has increased since 1950 with a 1960-1961 peak occurring in the three areas at the same time (Elwood and Warnock, 1969). The prevalence of anencephaly and spina bifida in Glasgow in 1972-1978 was estimated by Stone (1981); the

prevalence of anencephaly was found to be 1.82 per 1000 total births and that for spina bifida 2.62 per 1000 total births.

Windham and Edmond (1982) studied the trends up to 1975 in the United Kingdom particularly Edinburgh and Glasgow and suggest that the prevalence for anencephaly has been declining steadily.

In Liverpool a study of the epidemiology of neural tube defects between 1961-1979 shows a decline in prevalence from 1974 onwards. This was more marked for anencephaly than for spina bifida, but overall there was a significant decrease in the incidence of both anencephaly and spina bifida over the nineteen years (Owens et al, 1981). The adjusted prevalence in Liverpool declined to about 2.19 per 1000 total births during the period 1980-1986 (Eurocat, 1989). In England and Wales the prevalence has been high since 1932 with a peak in 1942-1943, followed by a second peak in 1954-1955 (Rogers and Morris, 1971). This was followed by a steady decline in prevalence to about 0.39 per 1000 for anencephaly and 1.1 per 1000 for spina bifida (Leck, 1983).

It seems that the birth prevalence of anencephaly and spina bifida during the period 1971-1982 in Northern Ireland exceeded that for Scotland, England and Wales. While the birth prevalence of both defects in Scotland initially exceeded that in England and Wales, after 1978 similar rates are reported from both countries. But there has been a marked decline in birth prevalence in Northern Ireland, Scotland, Glasgow, and England

and Wales (Carstairs and Cole, 1984).

Elsewhere in Europe no such clear-cut decline in prevalence is as evident as the one in the British Isles. Some European countries including Italy, Belgium, Netherlands and France, have actually experienced a rise in the prevalence rate (Eurocat, 1986).

In North America, the prevalence of neural tube defects is high in the east and decreases towards the west coast. In Canada the prevalence rate of anencephaly and spina bifida is about 4 per 1000 in the east and 1.5 per 1000 in the west (Elwood and Elwood, 1980). The prevalence rate began to rise in British Columbia to a peak in 1950-1954, followed by a subsequent decline and then started to peak again in the early 1960's (Elwood and Elwood, 1980). In the United States the prevalence of neural tube defects is similar to that in Canada, generally decreasing from the east to the west, with a four-fold difference between the highest risk region of the south-east and the lowest risk regions in Nevada and Montana (Elwood and Elwood, 1980).

The prevalence of anencephaly and spina bifida in Boston, Massachusetts, and Providence rose reaching a peak in 1930 followed by a marked decline between 1930-1945 until another peak occurred in 1950-1954, followed by a steady decline thereafter (Naggan, 1969; MacMahon and Yen, 1971).



In New York the prevalence rate declined until about 1955. In the last two decades (1955 to 1974) the rate has remained in the range 1 to 1.5 per 1000. During that period the rates of anencephaly and spina bifida remained approximately equal and parallel (Janerich, 1973a). It seems that the epidemic ended in New York State sometime during the early to mid-1950's (Janerich and Piper, 1978).

In Brooklyn, during 1968-1979, there was a significant decline in the prevalence of myelomeningocele, which is relatively consistent with a linear decline over the past 50 years in the north-eastern region of the United States (Stein et al, 1982). In New England the rate of anencephaly and spina bifida was about 3 per 1000 births in the early years of this century and peaked to almost 10 per 1000 births in the 1930's; the rate had reached a level of 2-3 per 1000 births by 1960 (MacMahon and Yen, 1971).

Reports of NTD epidemiology outside of Europe and North America have been sporadic and have not demonstrated any consistent pattern. In 1981-1987 the prevalence rate (adjusted prevalence) of anencephaly and spina bifida in Australia was 1.2 per 1000 total births (National Perinatal Statistics Unit, University of Sydney, 1989). In Bursa, Turkey, the prevalence of anencephaly and spina bifida was about 5.8 per 1000 total births in the years 1983-1986. In the first six months of 1987 there was an apparent increase in the prevalence rate to 20 per 1000 total births (Akar, Cavdar and Ancasoy, 1988). This raised the possibility

that the Chernobyl disaster of May 1986 might have resulted in an elevation of the rate in an already susceptible population, associated with poor nutrition and/or zinc deficiency. The impact of radiological contamination from the Chernobyl accident was evaluated in relation to central nervous system and eye defects in nine countries of Western Europe (Eurocat Working Group, 1988). The results do not suggest an increase in the frequency of these malformations in the countries of Western Europe.

In summary, the highest rates of NTD in the world have been reported for the British Isles, particularly Ireland. There has been a decline in prevalence of NTD in the British Isles, but no such a decline has occurred in Europe, or large parts of the U.S.A. This provides strong evidence of environmental factors in the aetiology of NTD but does not establish any specific agent as the primary teratogen.

#### Pregnancies at Increased Risk of Neural Tube Defects:

Some women are at increased risk of having a child with neural tube defects, most frequently because of family history. This group constitutes up to 10% (Main and Mennuti, 1986) of all NTD pregnancies.

The recurrence risk for neural tube defects depends on a number of factors, in particular the population prevalence (Nevin, 1980). In the United Kingdom the frequency of N.T.D. shows a

marked geographical variation which steadily increases from the south and east to the north and west (Carter, 1974).

In British surveys from Greater London during 1965-68 (Carter and Evans, 1973), Southampton (Williamson, 1965), South Wales during 1956-67 (Carter, David and Laurence, 1968), Glasgow during 1964-68 (Richards, McIntosh and Sweeney, 1972), Northern Ireland (Elwood and Nevin, 1973), the recurrence rates were reported as 4.45%, 5.63%, 5.18%, 5.64% and 8.87% respectively. The risk of recurrence varies according to the population prevalence of neural tube defects and is high in Northern Ireland and low in Greater London; the recurrence risk also varies according to social class with mothers in higher socio-economic groups (I and II) having a lower recurrence risk (5.5%) than those in groups III, IV and V (9.0%) (Nevin, 1980).

The recurrence risk (calculated retrospectively) in the United States, has been estimated as 1.7%-1.8% (Holmes, Driscoll and Atkins, 1976; Janerich and Piper, 1978), while in a prospective study of women undergoing prenatal diagnosis due to a previously affected fetus or infant the recurrence risk was 1.5%-3.0% (Milunsky, 1980; Crandall and Matsumoto, 1984).

If parents are affected with neural tube defects the recurrence risk is the same as for full sibling recurrence rate (Connor and Ferguson-Smith, 1987).

When there are two affected siblings, the recurrence risk for neural tube defects rises to 10% in the United Kingdom (Connor and Ferguson-Smith, 1987) and 5.7% in the United States (Milunsky, 1980).

The recurrence risk for half siblings should be lower than full siblings (Janerich and Piper, 1978). There is a high recurrence rate observed among mother's sister's children (Williamson, 1965). The recurrence risk for second degree relatives is 1.4% and for third degree relatives is 0.7% (Connor and Ferguson-Smith, 1987).

There is a tendency for concordance of the defects within families, but there is a possibility of discordance of the defect (Carter, 1974). The recurrence of these anomalies in sibships is as likely to be due to persistent or recurrent environmental factors as to a common genetic inheritance (Yen and Macmahon, 1968). The birth prevalence of neural tube defects has been declining recently in many parts of the world (Elwood and Elwood, 1980) and especially in the United Kingdom (Windham and Edmonds, 1982; Stone, 1987); the recurrence rate is also expected to have fallen. Seller (1981) calculated the recurrence rate of neural tube defects within a genetics centre population in the south-east of England during 1972-79 when the recurrence rate was 3.2% (1 in 32) and calculated the rate for 1980-mid 1984 and it fell to 2.8% (1 in 35), concluding that as the birth prevalence declines the recurrence rate also declines (Seller and Hancock,

1985).

Spina bifida occulta of single vertebra in parents does not seem to indicate an increased risk of neural tube defect in their offspring (Main and Mennuti, 1986). Spina bifida occulta affecting multiple vertebrae in the same individual has been observed in the parents of children with neural tube defects (Wynne-Davies, 1975). If an index patient has multiple vertebral anomalies and spina bifida occulta, the proportion of siblings affected with neural tube malformation is as high as if the index patient had had spina bifida cystica or anencephaly.

If the index patient had multiple vertebral anomalies alone, the proportion of siblings with spina bifida or anencephaly is rather less, but still five times higher than in the general population (Wynne-Davies, 1975).

Siblings of patients with sacrococcygeal tumours (Teratomas, hamartomas) appear to have an increased risk of neural tube defects (Lemire, 1983).

There are other reported pregnancy risks to the fetus for neural tube defects. Valproic acid taken during the first trimester of pregnancy is associated with a 1%-2% risk (Main and Mennuti, 1986). An increased number of NTD were reported both in children whose mothers had been treated with clomiphene used to induce ovulation (Cornel et al, 1989), and among children born after in

vitro-fertilisation (Lancaster, 1987). Maternal diabetes mellitus is associated with a 2% risk of having a child with neural tube defect (Milunsky et al, 1982; Ylinen et al, 1984).

It was found that women with a bad obstetric history, such as spontaneous abortion, stillbirth or child death from causes other than NTD., appear to be at a higher risk and if these events occur more than once the risk is higher again (Elwood and Elwood, 1980).

In summary, the risk of NTD depends on the prevalence in the general population. Other factors may contribute to the increased risk such as the social class of the mother, family history of NTD (up to 10%), the presence of parental vertebral defects, drugs during pregnancy and bad obstetric history.

However we do not have precise enough estimates of the risk to enable subgroups to be targeted with specific public health measures.

## 1.5 PREVENTION

It is widely accepted that neural tube defects have a multifactorial aetiology involving genetic predisposition and environmental triggering factors (Carter, 1969; Leck, 1974). Since there is little hope of being able to modify the genetic component in most cases, the primary prevention of neural tube defects depends ultimately on identifying the environmental factors so they can either be removed from the environment or avoided (Laurence, James and Campbell, 1983).

Methods of prevention of neural tube defects are applied either before conception (primary prevention) or after conception.

### BEFORE CONCEPTION:

#### 1 - Genetic counselling:

This is the major approach. It involves communication of information and advice about inherited conditions and associated risk of the disorder in the offspring of prospective parents. The West of Scotland has a population of about 3 million of whom at least 3000 families are in need of genetic counselling. Each year only about 1000 of these families are formally counselled although some of the remainder are adequately counselled by other health professionals (Connor and Ferguson-Smith, 1987).

About 10% of neural tube defects occur in families with a previous history of neural tube defects or a near relative who have also had a child with neural tube defect. These families need information and advice about the nature and prognosis of the

disorder they are confronted with, and be informed about the recurrence risk and this should be understood properly by the parents (Carter et al, 1971; Morris and Laurence, 1976). It is also important to explain that every couple has, with each pregnancy, a 1 in 40 risk of having a child with serious abnormality (Carter et al, 1971; Leonard, Chase and Childs, 1972). Provided that genetic counselling is given sympathetically at an appropriate time most couples with high risk either postpone pregnancy or avoid it altogether.

With the increasing availability of antenatal diagnosis some families may now choose to have further unaffected children if they are prepared to undergo therapeutic abortion. By this means the number of children placing a burden on the family and society can be reduced (Carter, 1974). Up to 80% of families with neural tube defects that attended counselling reported that they were positively influenced in their decision to have more children by the information received during the counselling sessions (Swerts, 1987).

## 2 - Prenatal precautions:

All women who have decided on pregnancy and those already pregnant should reduce the use of drugs or preferably avoid the use of drugs during this period. This is believed to reduce the risk of congenital malformations including neural tube defects.



Greenberg et al (1977) found an association between the use of the hormonal pregnancy test during the first trimester of pregnancy and central nervous system defects. Winship et al (1984) performed a case control study on women prescribed drugs during the trimester before the last menstrual period and the first trimester of pregnancy. There was a statistically significant difference overall between the numbers of mothers who were prescribed drugs in the study and control groups during the trimester before the last menstrual period, But no such difference was found for the first pregnancy trimester, nor was there a significant difference for any specific group of drugs. The same was found for non-steroid anti-inflammatory drugs, salicylates and sulphasalazine. Pregnant women are advised to avoid contact with possible sources of infection like influenza during the first trimester of pregnancy due to the observed association between pyrexia during the first trimester of pregnancy and congenital malformations (Lady, Edmonds and Erickson, 1980).

### 3 - Vitamin supplementation:

Intensive epidemiological and clinical studies in man have only recently produced evidence of specific environmental factors which might be of aetiological importance. Vitamin deficiency has been considered as a possible factor in the occurrence of neural tube defects. The following studies are the basis for the notion that preconception vitamin supplement may decrease the incidence of neural tube defects.

In a prospective study of blood vitamin levels in the first trimester of pregnancy, vitamin A, red cell folate, red cell riboflavin, white cell vitamin C, were low in lower social classes and lower still in women who later gave birth to infants with neural tube defects than in the controls (Smithells, Sheppard and Schorah, 1976). There was a significant social class difference in nutrient intake in women in the first trimester of pregnancy (Smithells et al, 1977). Laurence et al (1980) used a questionnaire to assess first trimester dietary intake retrospectively in mothers of neural tube defect infants. A relation undoubtedly exists between social class and maternal diet; he concluded that improving the quality of diet during early pregnancy in women at risk of fetal neural tube defects reduces the recurrence risk.

The evidence from the above studies, though not yet clear cut, suggests that minor deficiencies of one or more vitamins may be implicated in the causation of neural tube defects. These data justify intervention studies designed to reduce or eliminate the recurrence of neural tube defects by vitamin supplementation. A preliminary study carried out by Smithells et al (1980) suggested that neural tube defects might be prevented by maternal vitamin supplementation. Later a multicentre study was performed by Smithells et al (1981a); the supplement used was Pregnavite forte F (Bencard - the compound contains ten vitamins or cofactors, the dose 'of each ingredient' being either identical with or slightly lower than the current United States recommended daily intake).

The vitamins were given before and after conception to women with a history of fetal neural tube defects and a highly significant reduction in the recurrence rate (0.5%) was observed in the supplemented group when compared with the recurrence rate (4.3%) of unsupplemented. This study was neither randomised, double blind nor controlled by a placebo group, but the result suggests that this multivitamin preparation might reduce the risk of recurrence of neural tube defects although there is no way of knowing which particular ingredient has this beneficial effect.

Extending the original study Smithells et al (1981b; 1983) showed that 0.7% of women who took the supplement had fetuses with neural tube defects compared with 4.7% of women who did not get the supplement; the recurrence rate after two or more previous neural tube defect pregnancies were 2.3% in the supplemented group and 9.6% in the unsupplemented. They examined the factors which might influence recurrence rates such as maternal age, social class, previous reproductive history. None was a contributory factor to the difference between supplemented and the unsupplemented groups.

Smithells' study is open to several criticisms (Stone, 1980; Wald, 1983; Wald and Polani, 1984) not only because of the numbers but also because of the choice of controls who consisted of those women who were already pregnant when it was ascertained who, for one reason or another, were not supplemented or did not want supplementation.

Laurence et al (1981) offered a supplementation on a random basis, folic acid or placebo, to women who had a child with neural tube defects. The results suggest that folic acid deficiency may be an important factor in the causation of these malformations. This study was criticised because of small numbers and because non-compliers with folic acid treatment were utilised (Seller, 1982; Wald and Polani, 1984).

Comparison of the effectiveness of preconceptional vitamin supplementation for prevention of neural tube defects in two areas - the south-east of England (low prevalence area) and Northern Ireland (high prevalence area) - showed beneficial effects of supplementation are apparent in both areas, but were more marked in the high prevalence area (Seller and Nevin, 1984).

Wild et al (1986) assessed the influence of various factors such as area of residence, number of previous pregnancies with neural tube defects, prior miscarriages and inter-pregnancy interval on the recurrence risk in supplemented and unsupplemented mothers. They found a highly significant difference in the recurrence rate between supplemented and unsupplemented mothers. Mulinare et al (1988) found differences in neural tube risk between preconceptional vitamin users and non-users and suggested that it is not possible to say whether this difference is due to multivitamin use or the result of other characteristics of women who use multivitamins. Although there were no reported adverse

effects reported in these studies, it is not safe to assume that there would be no harmful effects if large numbers were involved. Since most vitamins have been reported to cause adverse effects when ingested in excessive doses this should be considered before embarking upon the use of high dose vitamin therapy for which scientific evidence of efficacy has not been provided (Oversen, 1984). All vitamin preparations, except those containing folic acid, are freely available and can be bought without doctor's prescription. Before considering the possible advantage of supplementing the diet of the whole population with vitamins or folic acid further evidence is needed that neural tube defects would be prevented by these means.

Since there are unidentified factors influencing the risk of neural tube defects only a randomised clinical trial can provide the assurance that these do not bias the assessment of vitamin supplementation (Wald and Polani, 1984). In an attempt to resolve the issue the Medical Research Council ran a multicentre, controlled randomised and double blind trial designed to establish whether multivitamin supplementation (including folic acid) in high risk women can help to reduce the number of recurrences of neural tube defects (Wald and Polani, 1984). The supplement was one of four kinds - minerals and folic acid (4 mg); minerals, folic acid and multivitamins; minerals and multivitamins but no folic acid; minerals only (calcium and iron). There is also a placebo group. The design of the trial enabled an analysis of whether folic acid alone is sufficient to

prevent neural tube defects or whether multivitamins without folic acid are effective in preventing recurrence. The result of the study confirms that a supplementation of folic acid before conception is effective in reducing the number of neural tube defects in those women who have had previous NTD pregnancies and are therefore considered to be at high risk. (MRC Vitamin Study Research Group 1991.)

The other current trial is a study which has been started in Dublin where antenatal diagnosis and induction of abortion are largely unacceptable. In this trial women receive either multivitamins and folate, folate alone or multivitamins alone.

In summary, primary prevention of congenital defect is the most desirable objective. Genetic counselling may be offered to parents who have had an affected child, since they appear to be exposed to a recurrent risk. Prenatal precautions, such as reduction in use drugs once decided on pregnancy and avoidance of contact with possible sources of infection, should be taken.

Another form of primary prevention is the use of preconceptional folic acid supplementation.

#### AFTER CONCEPTION:

The only method of prevention of neural tube defects is prenatal diagnosis. A prenatal test is offered as a screening procedure

for those with a previous history of neural tube defects or because of clinical suspicion of fetal abnormality. The parent should be informed about the limitations of the test, since no single test can exclude all known fetal abnormalities.

If the test is positive, selective termination of pregnancy is offered. (Selective termination became a reality in the United Kingdom with the Abortion Act 1967, which stated that termination of pregnancy is permitted when there is a 'substantial risk that if the child were born it would suffer from such physical or mental abnormality as to be seriously handicapped'.) The product of the conception is sent to pathology for diagnostic confirmation.

Prenatal screening of all pregnancies for NTD has been in operation in many areas since the discovery of serum marker for affected pregnancies (Brock, Bolton and Monaghan, 1973).

Because of its unique ethical implications the implementation of screening on a mass scale requires careful evaluation both a priori and as a means of assessing its impact. Over the past few decades various criteria for evaluating screening have been proposed.

#### Screening:

The success of any screening depends on many well recognised criteria such as characteristics of the disease, test and

screening system that combine to make screening desirable.

A number of criteria for screening are required to be satisfied prior to the introduction of any screening programme (Wilson and Jungner, 1968; Cochrane and Holland, 1971; Holtzman, 1981).

#### Criteria for Screening (Holtzman, 1981)

Disease Characteristics	Test Characteristics	Screening System Characteristics
<ul style="list-style-type: none"> <li>- Occurs frequently</li> <li>- Causes severe functional impairment</li> <li>- Untreatable or treatment effective only when begun before the age when clinical diagnosis is usually made</li> <li>- Associated with a quantitative or qualitative alteration of a substance that permits affected individuals to be distinguished</li> </ul>	<ul style="list-style-type: none"> <li>- Reliable</li> <li>- Valid</li> <li>- Adapted to mass screening</li> </ul>	<ul style="list-style-type: none"> <li>- Mechanism for determining effectiveness under field conditions</li> <li>- Specimens analyzed reliably and promptly</li> <li>- Results reported promptly</li> <li>- Adequate follow-up and management</li> <li>- Physician and parent knowledge of screening</li> <li>- positive benefit-cost ratio</li> </ul>

Screening techniques should be introduced not only because they are available but because they solve a serious medical problem.

#### Characteristics of the disease:

Neural tube defects including anencephaly and spina bifida are among the most common congenital anomalies.



Open lesions associated with a poorer prognosis for survival and with much greater incidence of severe disability include mental retardation, paralysis and orthopedic and urological complications. As treatment of spina bifida is ineffective in restoring normality, and there is no evidence at the present time to suggest that fetal malformation such as anencephaly and spina bifida can be prevented, selective abortion of affected fetuses can allow families the option of trying again for a healthy child.

Maternal serum Alphafetoprotein (Ms AFP) is known to be of fetal origin and it is an indirect marker of neural tube defect. In the case of neural tube defects, AFP provides a non-specific quantitative difference so absolute separation of the affected from the non-affected is not possible. The aim of antenatal screening for neural tube defects by Ms AFP is to identify women with a high risk of having an affected infant to justify carrying out special diagnostic procedures such as detailed ultrasound, amniocentesis for amniotic fluid Alphafetoprotein (Am AFP) and Acetylcholinesterase (AchE) determination.

Women who have previously had an infant with neural tube defect have a high risk of having another - they are undergoing amniocentesis on account of their history alone.

Characteristics of the screening test:

The screening test must be reliable, easily performed reproducible and precise.

Ms AFP as a screening tool is most often measured by Immunoradiometric assay. The techniques are identical to those used in many other routine laboratory studies. Although the test is available through a number of clinical laboratories there is as yet no uniform standard and results from one laboratory cannot be compared directly with those from another. Laboratories must establish their own normative data at each gestational age.

The reliability of Ms AFP measurement as an effective screening tool and the suitable gestational age at which it should be performed was investigated by the nineteen-centre collaborative study (Report of UK Collaborative Study, 1977).

In the west of Scotland a centralised laboratory in the Duncan Guthrie Institute of Medical Genetics for maternal serum screening programme can most reliably screen large populations. In order to improve precision, reliability and accuracy of maternal serum screening programmes and to allow the study of the clinical significance of low levels of Ms AFP and small changes of levels, immunoradiometric assay has been introduced. A large number of specimens can be processed so any deviations from the expected distribution of results can rapidly be identified.

The validity of a test depends on its sensitivity and specificity, predictive value and ease of performance.

Determination of the sensitivity and specificity of a test requires that a diagnosis of disease be established or ruled out for every person tested. Sensitivity and specificity of Ms AFP for the detection of anencephaly and spina bifida have been calculated by the United Kingdom Collaborative Study (Report of the United Kingdom Collaborative Study, 1977). The use of multiples of the normal median (MOM) allows pooling of data from different centres. At 2.5 MOM 88% of anencephaly and 79% of spina bifida cases will be detected (Report of the UK Collaborative Study 1977). The probability that a pregnancy with a positive result involves an affected fetus is dependent on the prevalence of the condition, the detection rate and the false positive rate.

The AFP test is stable both for short-term shipment at room temperature and after several cycles of freezing and thawing. The assay allows many specimens to be processed and the test itself is not expensive. Because of these characteristics the test can be adapted for mass screening. A more detailed discussion of AFP and its use in screening is presented later (Alpha-fetoprotein, pp77)

#### Characteristics of screening system:

The use of a screening test during pregnancy places strict time limits on the entire sequence if the information is to be acted

on within legal constraints on pregnancy termination. In the West of Scotland screening programme specimens obtained by the obstetrician or the general practitioner are processed reliably and promptly by their laboratory and results are reported promptly; follow-up testing counselling and management are carried out if needed.

The prospective parents should be given adequate information about screening for neural tube defects, the procedure before prenatal diagnosis and the meaning of inaccurate diagnosis (false positive and false negative), the mechanism of diagnostic intervention and the risk involved, what type of information the procedures can and cannot provide, and the need to consider the possibility of terminating the pregnancy.

Support after the birth of a child or termination of the pregnancy is required - families will also need recurrence risk counselling at an appropriate time.

#### Economic aspects:

The financial cost of population screening depends on the prevalence of neural tube defects in the area, the lower the prevalence the greater the cost. Ms AFP screening for neural tube defect should be cost-effective, and should have sufficient resources to ensure adequate diagnostic and follow-up facilities. The cost-effectiveness of antenatal screening for NTD decreases as the birth prevalence declines (Pharoah and Alberman, 1987).

In summary, successful Ms AFP screening programmes need a high-quality laboratory analysis, rapid and skilled communication between laboratory and physician, adequate resources for follow-up testing, adequate counselling and epidemiological surveillance.

#### Antenatal screening for Neural Tube Defects:

Antenatal screening provides early information concerning the clinical state of the fetus and recognition of congenital malformations in utero. Over 95% of all children with neural tube defects are born to couples with no previous family history. It is only by screening the pregnant population that most pregnancies at risk can be identified. Antenatal screening may be the basis for many important decisions regarding the future of the mother and child and enables the physician to consider selective termination.

#### Alpha-fetoprotein (AFP):

AFP was first identified in the serum of early human fetuses (Bergstrand and Czar, 1956). Embryonic and fetal blood contain a high concentration of AFP. It is a glycoprotein with a molecular weight of 69000 daltons.

During fetal development, AFP is synthesised by the yolk-sac at the end of the first trimester; the yolk-sac atrophies so synthesis shifts to the liver (Gitlin, 1975). It is believed that the two sources produce different molecular forms of AFP, though whether these have any significance for antenatal

diagnosis is unknown. The biological function of AFP is unknown although it has been suggested that it may have an immunoregulatory role protecting the fetus against maternal immunologic attack (Burton, 1988). It is present in fetal serum from about six weeks of gestation; it peaks at the end of the first trimester (10-13 weeks) (Conner and Ferguson-Smith, 1987) but falls rapidly in the second trimester. At birth the AFP level falls but basal levels of up to 25 micrograms per litre persist into adult life (Conner and Ferguson-Smith, 1987).

That Am AFP is elevated when a fetus has an open neural tube defect was first reported by Brock (Brock and Scrimgeour, 1972; Brock and Sutcliff, 1972). Leakage of AFP into amniotic fluid occurs by transudation when the fetus has an open neural tube defect. Later an association between maternal serum AFP and open neural tube defects was also found (Brock, Bolton and Monaghan, 1973).

Fetal serum AFP levels are not increased in the case of open neural tube defects (Seller, Creasy and Alberman, 1974) but the concentration in the amniotic fluid is raised on account of leakage of fetal AFP through the open lesion. This leads to an increased transfer across amniotic fluid membranes producing the raised maternal serum level of AFP which forms the basis of the antenatal screening test. Consequently closed lesions would not be expected to be associated with raised maternal serum or amniotic fluid AFP levels (Laurence et al, 1973). There is some

degree of overlap in AFP concentration between normal pregnancies and those with neural tube defects. Ms AFP measurement is therefore more useful as a screening tool rather than as a diagnostic test.

To improve the precision and accuracy of AFP assay and to produce one method suitable for maternal serum and amniotic fluid testing, Immuno Radio Metric assay (IRMA) has been developed.

Normally Am AFP concentration is largely maintained by fetal urination peaks in early pregnancy and decreases steadily thereafter by about 13% a week (Wald and Cuckle, 1980). MsAFP is normally detected in increased quantities in the serum of pregnant women from approximately 12-14 weeks of gestation (Brock, Bolton and Monaghan, 1973) and increases steadily throughout pregnancy (by about 19% a week) during the second trimester (Wald and Cuckle, 1980), peaks around 32 weeks of gestation before falling towards term (Connor and Ferguson-Smith, 1987). Because there is a concentration gradient from fetal serum to amniotic fluid to maternal serum, contamination of either amniotic fluid or maternal serum with even a small quantity of fetal blood can produce AFP levels above normal.

To take account of the methodological differences found between laboratories the AFP result is expressed in multiples of each

laboratory's own median level in unaffected pregnancies for relevant gestational age. (Report of the UK Collaborative Study, 1971)

#### Maternal Serum AFP

There is an overlap in distribution between affected and unaffected pregnancies. In screening routine pregnancies, a cut-off defining normal results must be selected so that an acceptable rate of detection can be achieved while limiting the percentage of normal pregnancies subjected to further testing.

The best time for screening was found to be between 16-18 completed weeks of gestation (Report of UK Collaborative Study, 1977) at which the detection rate for anencephaly and spina bifida is high and adequate time is available to allow for follow-up testing and the eventual possibility of pregnancy termination.

Ferguson-Smith (1983) suggested offering screening only to women between 16-20 weeks of gestation since prenatal diagnosis beyond 20 weeks of gestation increased the distress for the mother.

The efficiency of Ms AFP screening in selecting pregnant women who are at increased risk for neural tube defects, for whom more definitive procedures of ultrasound and amniocentesis are needed, is documented in the Report of United Kingdom Collaborative Study (1977). The number of unaffected pregnancies with AFP levels above 2.5 (MOM) at 16-18 weeks of gestation can be reduced by



about a third if women with border-line AFP levels are retested (Report of UK Collaborative Study, 1977) although this would not greatly change the detection rate of affected pregnancies. Retesting only women with results just above the cut-off value and using a lower cut-off value for the second test is probably the most efficient way of reducing the false positive rate and necessitates the retesting of only about 2% of screened women (Fourth Report of the UK Collaborative Study on AFP, 1982). Maternal serum AFP screening is a powerful and effective screening tool and can be successfully integrated in routine obstetric practice (Macri and Weiss, 1982; Haddow et al, 1983).

Maternal weight needs to be taken into consideration when interpreting Ms AFP results. Lighter women have on average high Ms AFP levels presumably as a result of greater concentration of AFP in their relatively smaller blood volume (Haddow et al, 1981; Wald et al, 1981). Adjusting Ms AFP values according to maternal weight among those with border-line positive results might therefore reduce the number of women having a diagnostic amniocentesis.

The most common benign explanation for Ms AFP elevation is underestimated gestation. In about 15%-20% of pregnant women found to have elevated Ms AFP by routine screening at 18-20 weeks of gestation, the cause is underestimated gestation (Ferguson-Smith, 1983).

The other common cause of Ms AFP elevation is multiple pregnancy. Twins, on average, produce twice as much AFP as a single fetus both in the first and second half of pregnancy (Wald et al, 1975) but this does not exclude the possibility of neural tube defects in one or both.

In some instances the barrier between fetal and maternal circulations is altered by abnormalities in the placenta which permits direct transport from the fetal to the maternal circulation and leads to an elevation of Ms AFP. If this is associated with vaginal bleeding the diagnosis is threatened abortion. Ms AFP returns to normal a week later (Ferguson-Smith, 1983). Sometimes there are no overt symptoms of threatened abortion other than fetomaternal haemorrhage which leads to high Ms AFP. This may be the only evidence of concealed threatened abortion (Ferguson-Smith, 1983). Other causes of high Ms AFP are haemangioma of the placenta or the cord, tumour attached to the placenta or the cord, cardiac monsters (consisting of amorphous mass of fetal tissue resulting from previous intrauterine death of monozygous twin whose development has been partially maintained by the circulation of its living co-twin) (Ferguson-Smith, 1983).

High Ms AFP value is found to be more commonly associated with male fetuses but there is no explanation for this (Wald and Cuckle, 1984).

Hereditary persistence of AFP may be the explanation in pregnant women who have high levels of Ms AFP throughout pregnancy with normal Am AFP (Ferguson-Smith, 1983). Amniocentesis can also cause feto-maternal haemorrhage and elevate Ms AFP levels. For this reason post-amniocentesis determinations are avoided (Chard et al, 1976). The use of Ms AFP as an indicator of fetal well-being was suggested by Seppala and Ruoslahti (1973). Though pregnant women with high Ms AFP but normal Am AFP can be reassured that there is no evidence of neural tube defects, they constitute a high risk group for sub-optimal outcome of pregnancy such as spontaneous abortion, stillbirth, low birth weight (about 15% identified in this way) and neonatal death (Wald et al, 1977; Macri and Weiss, 1982; Brock et al, 1977).

#### Amniotic Fluid AFP

There is an overlap in values of amniotic fluid AFP between affected and unaffected pregnancies (Second Report of UK Collaborative Study, 1979). The values for anencephaly pregnancies are well separated from the distribution of unaffected pregnancies, while those for spina bifida show a small degree of overlap which was least at 16-18 weeks of gestation. This is consequently the best time to do Am AFP testing (Second Report of UK Collaborative Study, 1979).

As with Ms AFP, multiples of the median (MOM) are used to reduce the systematic differences in Am AFP measurement observed between laboratories but to obtain the same false positive rate at each gestational period it was necessary to increase the cut-off

levels with advancing gestational age as follows: 2.5 (MOM) at 13-15 weeks of gestation; 3.0 (MOM) at 16-18 weeks of gestation; 3.5 (MOM) at 19-21 weeks of gestation and 4.0 (MOM) at 22-24 weeks of gestation (Second Report of UK Collaborative Study, 1979). Using these cut-off levels the detection rate for anencephaly was 98.2% and for spina bifida 97.6%. The practical false positive rate (the number of viable pregnancies without abnormality terminated) in all samples was 0.48% and 2.7% in clear (non-blood stained) samples (Second Report of UK Collaborative Study, 1979). Fetal blood contamination of amniotic fluid AFP is a recognised cause of false positives (Doran et al, 1977). To exclude this possibility most laboratories routinely perform either a kleihaver test or haemoglobin electrophoresis on blood stained amniotic fluid samples to distinguish fetal from maternal blood contamination. It is preferable not to delay Am AFP determination beyond 18 weeks of gestation (Second Report of UK Collaborative Study, 1979).

If the Am AFP result is borderline or a blood stained specimen, it is worth obtaining a fresh amniotic fluid sample and performing a repeat AFP test. This will only have a marginal effect on the detection rate but will reduce the practical false positive rate by more than a half (Second Report of UK Collaborative Study, 1979).

The risk of having a fetus with neural tube defects in test

positives is important information for planning a screening programme and can be estimated accurately from the UK Collaborative Study data (1977; fourth report 1982) (Appendix 1).

A nomogram has been produced for estimating the individual risk of having a fetus with open spina bifida by using information from both maternal serum and amniotic fluid AFP levels when the amniotic fluid level is borderline (Wald and Cuckle, 1984) (Appendix 2).

High Ms AFP and Am AFP levels are associated with the presence of fetal open neural tube defects, but this is not specific. Other malformations of ventral wall defects such as exomphalos (abdominal viscera herniate into the umbilical cord) in the absence of neural tube defects have been associated with raised Ms AFP and Am AFP (Seppala et al, 1976; Wald et al, 1980).

Both gastroschisis (a defect in the abdominal wall lateral to the umbilicus) and body stalk abnormality (in which umbilical vessels are short so that the fetus is closely attached to the chorionic plate) are associated with high Ms AFP and Am AFP (Ferguson-Smith, 1983).

Meckels syndrome (a combination of encephalocele, polydactyly and polycystic kidneys) is an autosomal recessive disorder associated with high Ms AFP and Am AFP. Congenital nephrosis inherited as an autosomal recessive disorder in which the fetal kidneys may

excrete large quantities of AFP into the amniotic fluid. Confirmation of the diagnosis requires electron microscopy of the fetal kidney (Seppala et al, 1976; Kjessler et al, 1975).

Other abnormalities associated with high Am AFP are: polycystic kidney (Chemke et al, 1977); renal agenesis (Balfour and Laurence, 1980) which causes a failure of urinary and AFP excretion into amniotic fluid but this condition is associated with oligohydraminos in which there is high concentration of AFP in amniotic fluid (Stirrat et al, 1981).

Bladder neck obstruction (Vinson et al, 1977) and congenital absence of the urethra (Nevin et al, 1978) are both associated with high AFP in amniotic fluid due to oligohydraminos. Fetal teratomata are usually non-malignant and are associated with elevated Ms AFP and Am AFP. Some are amenable to surgery, for example when the tumour is large and pedunculated and visible on ultrasound screening (Ferguson-Smith, 1983). Intra-uterine death leads to raised Ms AFP and Am AFP due to fetal autolysis (Seppala and Rouslahti, 1972). About 12% of miscarriages are associated with a positive Am AFP result (Second Report of UK Collaborative Study, 1979). Esophageal atresia is associated with raised Am AFP in the third trimester of pregnancy (Seppala, 1973). In duodenal atresia Am AFP is high in the second trimester of pregnancy (Weinberg et al, 1975) due to reduced AFP digestion in the gut consequent on fetal swallowing. Fetuses with skin defects such as in nuchal bleb and pilonidal sinus (Bieber and

Petres, 1978; Jandial, Tham and Gibson, 1976) have raised Am AFP levels, probably due to leakage of AFP through the skin defect.

Turner's syndrome is associated with high Am AFP, the cause is thought to be leakage through the wall of cystic hygroma, or sampling of cystic fluid (Hunter et al, 1976).

Both normal Am AFP (Ishiguro and Nishimura, 1973) and abnormal levels (Seppala and Unnerus, 1974) have been reported in the presence of hydrocephaly in either the second or third trimester of pregnancy. In normal twin pregnancy Am AFP is not elevated (Second Report of UK Collaborative Study, 1979). If both of the fetuses are affected a high Am AFP is found. If one is affected, the Am AFP is high in one of the sacs. But problems arise if AFP from the affected sac diffuses through the membrane to the unaffected one leading to a high Am AFP in both sacs (Wald and Cuckle, 1984).

In order to avoid performing amniocentesis on a large number of unaffected pregnancies with elevated Ms AFP levels, a repeat maternal serum sample and ultrasound examination should be performed.

In an attempt to evaluate the performance of the screening programme, a large prospective study based in Glasgow has been reported (Ferguson-Smith, et al, 1978). It comprised two phases and in the first the 99th percentile (3.5 MOM) was used as a cut-

off point. The sensitivity for anencephaly was 88% and for spina bifida 71%. In the second phase the 97th percentile (2.8 MOM) was used as a cut-off point. The sensitivity for anencephaly was 100% and for spina bifida 81%. About 0.63% of pregnancies proceeded to amniocentesis, 46.4% of amniocentesis showed raised Am AFP, due to fetal abnormality. Fetal loss by abortion or perinatal death after amniocentesis occurred in 0.03% of pregnancies screened.

Wald et al (1979) measured the acceptability of the screening programme among patients who knew that they had a positive screening test. It was found that about 93% expressed a wish to be tested again in any future pregnancy.

#### Dangers of Amniocentesis

Mid-trimester amniocentesis has become common procedure in prenatal care and several studies have been conducted to assess the risks involved. In the United Kingdom (Report of the MRC, 1978), Canadian Medical Research Council, (1977) and the NICHD study by the United States Department of Health Education and Welfare (Lowe et al, 1978). It is difficult to compare these studies because of the different categories used by each but all showed a high risk of spontaneous abortion following amniocentesis. In the United Kingdom (Report of MRC 1978) a 1-1.5% spontaneous abortion risk after amniocentesis was found, while in South Carolina the abortion rate was about 1% (Young et al, 1983). A study in Canada (Simpson et al, 1976) observed a reduction in the number of spontaneous abortions in the



amniocentesis group. The abortion rate after amniocentesis in San Francisco was 1.5% (Golbus et al, 1979). In Belfast, at the regional referral clinic for genetic amniocentesis, spontaneous abortion rate was 2.2% (Ritchie and Thompson, 1982). This was reduced to 0.7% by excluding those that occurred more than two weeks after the amniocentesis and which were thought not to be due to the procedure. In the Queen Mother's hospital in Glasgow spontaneous abortion rates after amniocentesis were 1.4% reducing to 0.2% if those that occurred more than two weeks after amniocentesis were excluded (McNay and Whitfield, 1984). In an uncontrolled study of women undergoing amniocentesis for chromosomal abnormalities, spontaneous abortion resulting from the procedure was increased by 0.3%-0.7% (Philip and Bang, 1978).

The risk of fetal death or abortion is about 0.5% within three weeks after mid-trimester amniocentesis if only experienced obstetricians using modern techniques are involved (Leschort, Verjaal and Treffers, 1985). This is similar to the finding of Porreco et al (1982) who estimate the risk of procedure related fetal deaths in the range of 0.6%-0.9%.

Patients who have amniocentesis may have a higher than average risk of miscarriage and other abnormal outcomes not only from amniocentesis but also because of the factors which dictated the need for amniocentesis. Amniocentesis performed for elevated Ms AFP appears associated with greater fetal loss than when performed for other indications (Bennett, 1978).

Increased perinatal mortality rates have been reported in women who have had amniocentesis for elevated Ms AFP (Wald et al, 1977; Brock et al, 1979). Increased perinatal mortality rates have also been observed when Ms AFP has been elevated but amnioentesis has not been carried out (Read et al, 1980).

Sant-Cassia, Macpherson and Tyack (1984), in a controlled prospective study, found no significant increase in fetal loss, perinatal mortality or vaginal bleeding among women undergoing amniocentesis.

Bleeding from the fetal circulation as a result of placental puncture is now nearly always avoidable with ultrasound guidance (McNay and Whitfield, 1984), although some reported no significant difference in the frequency of complication whether an ultrasound scan is performed or not either before or at the time of amniocentesis (Sant-Cassia, Macpherson and Tyack, 1984).

In the West of Scotland during 1978-80 in 14 centres pregnancies in which high Ms AFP was not the indication for amniocentesis had an excess rate from abortions and perinatal deaths of 0.7% compared with a control group. While pregnancies in which amniocentesis was performed because of high maternal serum AFP had a wastage rate of 7.2% (comprising an abortion rate of 4.4% and a perinatal mortality rate of 2.8%) (Ferguson-Smith, 1983).

In the United Kingdom (Report of MRC study, 1978) premature labour did not occur more often in women who had undergone mid-trimester amniocentesis than in their controls. However there was an increase in deaths from respiratory distress syndrome in infants whose mothers had had amniocentesis compared with the controls. This could be due to altered amniotic fluid volume after amniocentesis or subsequent to chronic amniotic fluid leakage interfering with normal lung development (Hislop and Fairweather, 1982). There also appears to be increased frequency of antepartum haemorrhage due to placental abruption in the United Kingdom (Report of MRC 1978) following amniocentesis.

An increased number of orthopaedic postural malformations, such as talipes, dislocated hip (Report of MRC, 1978) have been reported. This is similar to the finding of Sant-Cassia, Macpherson and Tyack, (1984). This could be due to compression of the fetus in utero due to loss of amniotic fluid. Others have found no significant association between mid-trimester amniocentesis and congenital talipes or hip malformation (Wald et al, 1983). In a controlled study on women aged 35-40 years who were at risk of fetal chromosomal abnormality, amniocentesis was found not to influence infant mental and motor development, temperament, physical growth or risk of orthopaedic abnormalities (Finegan et al, 1985).

Fetal trauma is thought to be caused on occasions by mid-trimester amniocentesis. Minor skin trauma such as skin scars or

dimpling have been identified (Finegan et al, 1985). Major trauma include neonatal small bowel obstruction in association with an epigastric abdominal wall defect with no satisfactory embryological explanation (Swift, Driscoll and Vowles, 1979); ilial atresia, ileo cutaneous fistula (Rickwood, 1977) and gangrene of a fetal limb (Lamb, 1975) have also been described. But the use of ultrasound greatly reduces the risk of needle injury during amniocentesis (Jeanty et al, 1983).

Amniocentesis may also have a psychological effect on parents. It was found that more maternal stress was engendered when the indication was elevated Ms AFP than when amniocentesis was carried out for other reasons (Farrant, 1980). This stress can be alleviated by supportive counselling given prior to venepuncture and sustained until after the result of amniotic fluid analysis is known (Earle, 1981).

In the west of Scotland by repeating any high Ms AFP estimation and using 2.8 MOM (97th percentile) in both samples as the cut off point, the amniocentesis rate was kept below 0.7% of screened pregnancies (Ferguson-Smith et al, 1978).

#### Acetylcholine esterase

The most reliable test for the prenatal diagnosis of neural tube defects is amniotic fluid AFP assay. Its false positive rate remains low (Report of UK Collaborative Study, 1979), the mixture of fetal blood with amniotic fluid and other less well defined causes not infrequently prevents the accurate interpretation of

elevated amniotic fluid AFP concentration. This problem, as well as the non-specificity of the assay (Milunsky and Alpert, 1974), have spurred the search for more specific indicators of neural tissue exposure in utero. Acetylcholine esterase (AChE) for example has been proposed as a promising complementary test to AFP (Smith et al, 1979). AChE is released from the tissue of the brain and spinal cord and has an important role in neurotransmission; the source may become diminished as the nervous system matures, since the immature nerve terminals are expected to release more AChE than adult tissue (Chubb et al, 1979). It is likely that a fetal lesion in which cerebrospinal fluid is exposed to amniotic fluid will be associated with high amniotic fluid AChE (Smith et al, 1979). Red blood cells and muscle are enriched in AChE (Brock, 1983). AChE gains access to the fetal serum in the absence of a blood brain barrier (Silver, 1974) and also gains access to amniotic fluid from exposed nerve plexuses in the case of omphalocele or transudation of fetal plasma through the skin following fetal death (Buamah, Evans and Milford-Ward, 1980).

Raised amniotic fluid AChE levels are closely associated with anencephaly and open spina bifida. It is a useful marker in the diagnosis of neural tube defects in pregnancies with high amniotic fluid AFP results (Smith et al, 1979). Positive AChE results are observed in pregnancies associated with Turner's syndrome (Chubb et al, 1979) and Gastroschisis (Milunsky and Sapirstein, 1982); positive results are also observed in fetuses

with Trisomy 21, hyperplasia of the heart and lungs and fetal teratoma (Report of the Collaborative Acetylcholinesterase Study, 1981).

Amniotic fluid samples in the second trimester contain appreciable amounts of non-specific pseudo cholinesterase and those fetuses with neural tube defects usually have AchE together with an increased amount of non-specific pseudocholinesterase activity (Smith et al, 1979).

AchE can be distinguished from non-specific pseudocholinesterase by the qualitative method using polyacrylamide gel electrophoresis (Smith et al, 1979). In those with neural tube defects AchE appears as a fast-migrating band which can be suppressed by inhibitors.

Polyacrylamide gel electrophoresis appears 100% sensitive and specific as a test to discriminate between pregnancies with and without neural tube defects. Only 2/3 of abdominal wall defects were correctly predicted (Toftagen-Lansen, Wandrup and Norgaard-Pedersen, 1984).

False positive AchE results arise when amniotic fluid samples are contaminated with fetal blood (Report of Collaborative Study on Acetylcholinesterase, 1981) giving rise to a misleading band of AchE. The degree of blood contamination has to be greater than that giving rise to a spurious AFP result (Barlow et al, 1982).

Mishandling of amniotic fluid in which AchE has been stripped from red cells may lead to false positive results (Brock, 1983).

By using the AchE test when a high amniotic fluid AFP is found the amniotic fluid false positive can be reduced by 94% (Report of Collaborative Study on Acetylcholinesterase 1981). AchE is characterised by a low number of false positives. Its high specificity is explicable by its derivation from the nervous system while AFP originates from other fetal tissue (Elejalde, Peak and Elejalde, 1986).

Thus AchE is more sensitive and more specific for neural tube defects than is Am AFP (Smith et al, 1979). The great accuracy and reliability of the AchE result has reduced anxiety significantly and probably helped avert abortion (Milunsky and Sapirstein, 1982). Although AchE cannot distinguish fetal anterior abdominal wall defects from neural tube defects (Wald et al, 1980), AchE/total cholinesterase activity ratio is low in abdominal wall defects and high in open neural tube defects (Dale, 1980).

It was found that AchE polyacrylamide gel electrophoresis is more sensitive than ultrasound scanning in the detection of open neural tube defects (Toftager-Larsen and Norgaan-Pedersen, 1988). Although the AchE test is found to be a reliable and accurate test, it is no substitute for the AFP test (Read et al, 1982).

In summary, the development of antenatal screening (secondary prevention) for NTD by measurement of maternal serum AFP at 16-20 weeks gestation represents a major scientific advance which will help to reduce the birth prevalence of NTD as a major public health problem. Maternal serum AFP is not specific for NTD there are other conditions also associated with high Ms AFP but the use of amniocentesis for amniotic fluid AFP and AchE as diagnostic tests solve this problem.

The objective of antenatal screening is termination of the affected fetuses which may help to relieve some of the burden on family and society. These screening tests have usually been found to be valid, reliable and acceptable by the pregnant population.



### Ultrasound in Antenatal Screening for Neural Tube Defects

Ultrasound is a non-invasive technique which allows visualisation of the fetus in utero. Improvements in ultrasound technology have resulted in high resolution pictures.

Two main types of ultrasound are in common use. Continuous ultrasound using the Doppler principle which is used to detect moving structures such as the fetal heart and blood flow. And pulsed ultrasound which is used to outline structures within the uterus. The high resolution pictures which can now be obtained with both static and real time pulsed ultrasound, enables the ultrasonographer to identify intrafetal structures in the second trimester of pregnancy.

Ultrasound is regarded as an integral part of antenatal care and is used to screen all pregnancies, not only those at risk (Campbell and Little, 1980).

The real time scanners give a promising future - they are easy to operate, inexpensive, portable, clinically reliable and should be preferred as an initial test because it is without risk and produces no side effects (Kurjak et al, 1980). It was found that the real time is the method of choice for detection of anomalies (Campbell and Pearce, 1983). High operator expertise is required to avoid errors with ultrasound (Smith, Chudleigh and Campbell, 1984).

All users consider ultrasound safe when used at the intensities currently employed (below 20 mw/cm<sup>2</sup>) (Gough, 1984; Stark et al, 1984). There is no evidence that ultrasound has adverse effects on the human fetus; there has been no evidence that children exposed to ultrasound during pregnancy have an increased incidence of cancer (Kinner-Wilson and Waterhouse, 1984; Cartwright et al, 1984). The risk and efficacy of imaging ultrasound cannot be assessed until a large adequately designed randomised controlled trial is carried out (Mole, 1986).

The average time taken per real time scanning is six minutes (Anderson, Phillips and Midwinter, 1982). The shorter time taken by the scan allows a greater number of patients to be scanned.

The diagnosis of NTD has been enhanced by recent ultrasonic improvement which enables detailed evaluation of intracranial structure.

Diagnosis of anencephaly must be made through the long axis of the fetus when the normally ovoid and regular outline of the fetal head is replaced by an irregular mass of the fetal skull and facial bones. Sometimes there is a knot of echoes at the cephalic pole representing the base of the skull and orbits. The visualisation can be made as early as 12 weeks gestation, but to avoid mistake a definitive judgement should be delayed to 14-20 weeks gestation; the diagnosis should be confirmed by one or two scans or an elevated Am AFP (Campbell, 1977) but, due to the flexion,

the fetal head is often in a different linear plane to that of the body and early engagement of the fetal head can sometimes give a false impression of anencephaly (Campbell, 1977). Experienced investigators, however, rarely have trouble in making the diagnosis (Kurjak et al, 1980). The diagnosis facilitated by real time examination should not be missed with good equipment and experienced technicians. The fetal head occasionally is too deep within the maternal pelvis, in which case allowing the maternal bladder to fill will improve the view and ultrasound is the ideal method for detecting this condition (Campbell and Pearce, 1983).

The first anencephaly terminated on the basis of an ultrasound diagnosis was in 1972 (Campbell et al, 1972). Anencephaly is associated with spina bifida in approximately 50% of cases (Campbell and Pearce, 1983). Sonography has been shown to be 100% sensitive in identifying cases of anencephaly (Hashimoto et al, 1985; Roberts et al, 1983; Campbell, 1977).

Fetal spine visualisation has been improved by the introduction of real time techniques (Kurjak et al, 1980). The ability to demonstrate spina bifida on ultrasound examination is directly proportional to the resolution of the equipment used and the size of the defect (Petres and Redwine, 1982).

Scans performed in longitudinal axis of the fetal body (figure 1), the double or (tramline) outline of the fetal spine will be

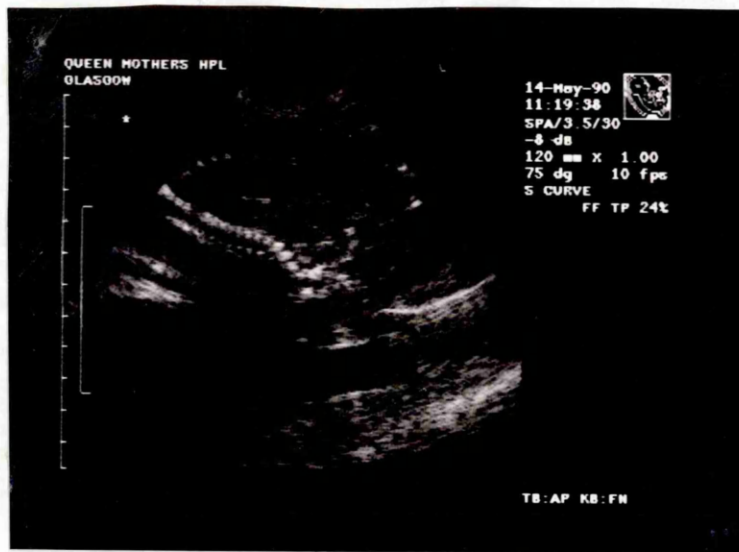


Figure 1. Longitudinal section of fetal spine showing discontinuity at the "tramline", with "Lumbar Spina bifida".

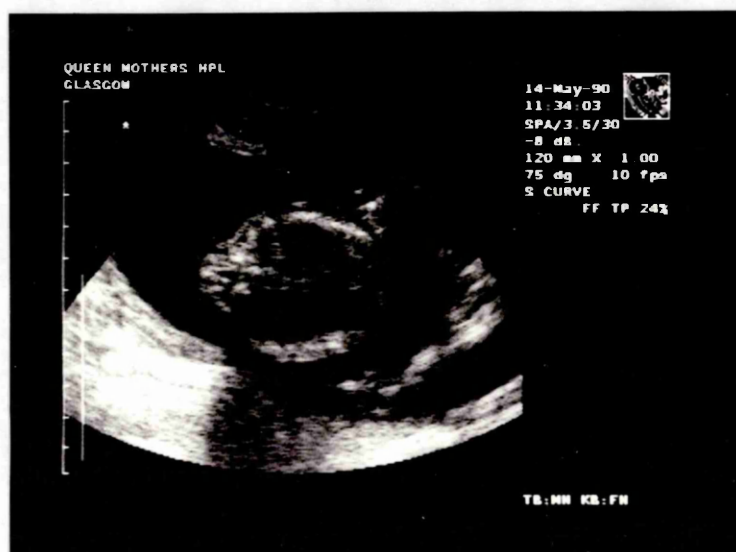


Figure 2. Transverse section of the fetal spine showing "Lumbar Spina bifida".

identified and shown to be caused by echoes from the wall of the spinal canal, is best detected between 16-20 weeks gestation (Campbell, 1977; Kurjak et al, 1980) because the spinal curvature is not marked and the full length of the spine can usually be displayed on a single longitudinal scan at this stage (Campbell, 1977).

The transverse scanning of the fetal spinal canal is needed from the cervical spine to the sacrum, the normal spine with intact neural arch appears as a closed circle while in the case of an incomplete neural arch it appears as a saucer or V-shaped or U-shaped deformity (Campbell, 1977; Campbell and Pearce, 1983). In practice, both the longitudinal and transverse scan is used; the real time scanner allows the site and the extent of the lesion to be predicted with a high degree of accuracy (Campbell and Pearce, 1983). Defects involving more than three vertebral segments can easily be diagnosed; if only one or two segments are involved the diagnosis is more difficult (Harrison, Golbus and Filly, 1984). These abnormal bone features should be used to make the diagnosis when the sac cannot be visualised. If a sac can be demonstrated (Figure 2), and the anomaly easily recognised as cystic extension of the dorsal aspect of the spine, even the neural element into the sac can be demonstrated by ultrasonography (Vintzileos et al, 1987). This will allow for differentiation between a meningocele and meningomyelocele (Campbell and Pearce, 1983). Open spina bifida may be easily diagnosed if the fetal position is appropriate; excessive fetal movement and kyphosis

may make precise transverse examination of the spine difficult (Lindfors et al, 1987).

Associated sonographic findings may also facilitate discovery of open spina bifida. The cranial and cerebellar signs were seen retrospectively in 70 fetuses with open spina bifida diagnosed by ultrasound at 16-23 weeks gestation (Nicolaidis et al, 1986), such as microcephaly, ventriculomegaly scalloping of the frontal bones (Lemon sign) and anterior curvature of the cerebellar hemispheres (Banana sign) or apparently absent cerebellum (Figure 3).

Campbell et al (1987) carried out a prospective study in pregnancies at high risk of fetal open spina bifida; they recognised the same markers as Nicolaidis et al (1986) had found. In both studies the B.P.D. and head circumference were reduced, while Wald et al (1980) also observed that and suggested that this was due to intrauterine growth retardation.

These ultrasound markers should alert the sonographer to the possibility of spina bifida and encourage a detailed examination of the fetal spine (Nicolaidis et al, 1986; Campbell et al, 1987); they are helpful in identifying fetuses with spina bifida.

The sensitivity and specificity of these markers was measured by Campbell et al (1987). The presence of a Banana sign or absent

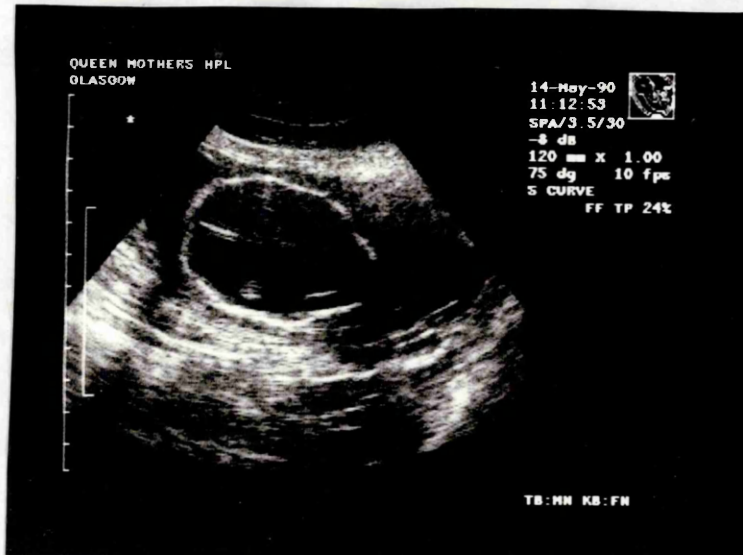


Figure 3. Suboccipital bregmatic view of fetal head showing the "Lemon sign".

Source: Dr. McNay; Queen Mothers Hospital

cerebellum gave a sensitivity of 96%; the specificity, predictive value of a positive and negative test, were all 100%. While the Lemon sign gave a sensitivity of 100%, specificity of 99%, the predictive value of a positive and negative test were 84% and 100% respectively.

In addition, observation of purposeful movement of the lower extremities may be helpful in counselling the patient regarding prognosis (Roberts et al, 1983). About 15% of spinal lesions that are skin covered are not amenable to diagnosis by AFP (Laurence, 1974). Ultrasound is the only examination suitable for their detection (Kurjak et al, 1980).

Second trimester ultrasonography can be extremely useful in determining the cause of an elevated maternal serum AFP. While AFP cannot define or indeed describe the particular abnormality, ultrasound has the ability to do so and may give qualitative information to the doctor or patient which will enable them to decide whether to continue with the pregnancy or opt for termination (Campbell et al, 1975).

Ultrasound can complement AFP estimation in accurate assessment of fetal maturity and determine gestational age which is calculated by measurement of the BPD in women attending antenatal care. Women who were sure of the dates of their last menstrual period (81%) were found to have appropriate BPD measurement; in 3% the pregnancy was more than two weeks further



advanced and in 14% was more than two weeks less than calculated (Bennett et al, 1982). Gough (1984) found about 20.2% of pregnancies appear to be below the cut-off after gestational age is readjusted. Women tend to over-estimate the duration of pregnancy while ultrasound dating will tend to reduce the number of abnormal AFP predictions in the amniotic fluid and increase the number in the maternal serum (Campbell et al, 1975). Other causes of high Ms AFP which can be readily diagnosed by sonography were multiple pregnancy and fetal demise (Campbell et al, 1975; Gough, 1984).

There are other potentially correctible defects which have high Ms AFP and can be imaged sonographically - anterior abdominal wall defects and urinary tract obstruction. Often amniocentesis can be avoided if a satisfactory explanation for elevated Ms AFP can be determined by ultrasound (Lindfors et al, 1987). If a satisfactory explanation for elevated Ms AFP level cannot be determined by ultrasound, amniocentesis for amniotic fluid AFP and AchE determination should always be carried out (Lindfors et al, 1987). No false negative result for open spina bifida with elevated Am AFP level and positive AchE was found (Maslak, 1985).

False positives have been reported in the presence of fetal blood but these are usually distinguishable from the true positive results by examination of the fluid for blood and by the distinctiveness of the AchE band on electrophoresis (Crandall and Matsumalo, 1986) although the diagnosis requires confirmation by

high resolution diagnostic ultrasound before termination of pregnancy could be recommended. Fetuses with normal AchE but raised Am AFP are likely to have anterior abdominal wall defects or kidney defects, some of which are surgically correctible (Buamah, Evans and Milfordward, 1980). The termination of fetuses with correctible defects should not be dismissed as an unimportant side effect of maternal serum AFP (Harris and Read, 1981).

Experienced ultrasound operators should be able to confirm normality with a high degree of confidence (Campbell and Pearce, 1983). Failure to identify a lesion related to its size and location with the majority of failures occurring with small defects in either the higher cervical or low sacral regions (Chamberlain, 1985). It was found that the false negative diagnosis rate by ultrasound was about 0.1% (Sabbagha, Tamura and Dalcompo, 1981) but Harris and Read (1981) found about 5%-10% of spina bifida are missed by ultrasound. They suggest that maternal obesity may be one reason for poor scans.

The accuracy of ultrasound depends greatly on operator experience together with the improvement in instrumentation (Campbell et al, 1975; Smith, Chudleigh and Campbell, 1984). The use of real time ultrasound for the identification of spinal defects appears to be very good (Campbell and Pearce, 1983). In some institutions this modality has now totally replaced the role of Am AFP assay (Chamberlain, 1985).

Ultrasound screening of all pregnant women can be a reliable and acceptable technique in the diagnosis of anencephaly and spina bifida and with experienced operators is probably superior to any other method (Christie, 1984). Detection rates of 73% were achieved in a small population in a period of eight years (1975-1983). In the same population during 1982 the detection rate was 100% due to improvements in equipment and technique (Christie, 1984).

Hobines et al (1979) concluded that in contrast to anencephaly, spina bifida is difficult to diagnose with ultrasound and requires significant operator experience.

The detection rate for open spina bifida was found to be 79%, suggesting that the fetal position made spinal visualisation more difficult (Robinson et al, 1980). A two-stage study was carried out in 1977-83 in high risk mothers; it was found that the sensitivity for anencephaly was 100% during both stages, while for open spina bifida sensitivity improved from 33% to 80%, specificity improved from 96% to 99%, the false positive rate fell from 57% to 9% and the false negative rate fell from 1% to 0.3%. It was concluded that improvements in operator experience led to improvement in the detection rate from stage one to stage two (Roberts et al, 1983).

The use of ultrasound as a screening technique during pregnancies

was increased gradually. In France in 1976 only 11% of pregnant women received screening by ultrasound; by 1981 it had increased dramatically to 82% (Poisson-Salomon et al, 1987).

When antenatal diagnosis of certain fetal abnormalities is made the parent should receive appropriate genetic and perinatal counselling based on antenatal findings and the management should take their wishes into consideration; the parents should be offered the option of termination (Vintzileos et al, 1987).

In summary, ultrasound is a non-invasive method of visualising the fetus in utero. It may become routine for all pregnancies. Ultrasound acts as an adjunct to AFP screening, though it may be used independently in the future as an alternative to AFP estimation in maternal serum and amniotic fluid for the detection of Anencephaly and Spina bifida. This would require the development of considerable skills and experience for their accurate interpretation.

Criteria for Evaluation:

In order to evaluate a screening programme various interdependent factors which can effect its success require exploration: (Wilson and Junger 1968; Hotlzman 1981). These may be summarised as follows:

A. Definition of the problem:

1. What abnormality of medical significance is to be detected?
2. What prevention or therapy is to be offered?
3. Which group is to be screened?

B. Review of position before screening:

1. Evidence concerning the epidemiology. The Natural history and medical significance of the abnormality.

C. Review of evidence concerning the screening procedure:

1. Effectiveness of proposed treatment and its acceptability.
2. Effectiveness of proposed diagnostic methods (Validity).
3. Acceptability of screening test.
4. Available resources.

The present study has been designed to address these issues which have been already discussed in some detail in the introduction, section one.

SECTION II - OVERVIEW OF LITERATURE  
AND RATIONALE OF THE STUDY

SECTION II: OVERVIEW OF LITERATURE AND RATIONALE OF THE STUDY

Open neural tube defects (Anencephaly and Spina bifida) are the commonest malformations in the European Community. The population of the West of Scotland suffer one of the highest prevalence rates of congenital neural defects in the world.

The chief consequence of Anencephaly is either stillbirth or neonatal death, while Spina bifida is often associated with a high early infant mortality rate and physical and mental disability in the survivors.

Genetic factors appear to play a minor role in the aetiology of the defects: about 95% of all children with NTD are born to couples with no relevant family history. To reduce birth prevalence is by secondary prevention, whereby diagnosis of these malformations is made in early pregnancy while therapeutic abortion is still possible. These methods should be both cost-effective and acceptable to pregnant women.

Screening for NTD became a practical proposition when it was discovered that an increase in alpha-fetoprotein in the blood and amniotic fluid of the affected fetus was accompanied by increased maternal serum alphafeto-protein. This phenomenon, along with the use of ultrasound, has been exploited to enable neural tube defects to be either detected or suspected at a relatively early gestational age (16-20 weeks). The detection and termination of

affected pregnancies by antenatal screening may therefore be offered to the entire pregnant population and has been done so in the West of Scotland for several years.

In order to clarify the issue, an epidemiological approach is necessary. The essence of any epidemiological investigation lies in its population-based methodology, in contrast to most clinical studies which often define subjects in terms of groups of patients or comparisons with other patient categories. Antenatal screening is a good example of this conceptual divide: a clinically orientated judgement of performance will tend to evaluate success in terms of the sensitivity and specificity of the test, while a public health view requires an extension of these data to embrace the impact of the screening procedure on the frequency of affected births in the population at risk rather than merely amongst those screened. These are not mutually exclusive approaches, but they do represent different research philosophies and hence methodologies. An epidemiological evaluation of screening should incorporate several elements into its frame of reference:

The epidemiological characteristics (including any secular changes in prevalence) of the conditions being screened, or understanding of the natural history of the condition (and consequently of the outcome of non-intervention).

An assessment of the effectiveness of the screening in changing the outcome (both for the individuals and especially for the population as a whole).



An assessment of the efficiency of screening (since this will influence its ultimate effectiveness), including the proportions screened, detected and terminated, and an appraisal of the practical implications of the findings for service providers.

The present study was designed to evaluate antenatal screening for NTD in epidemiological public health terms, along the lines of the conceptual framework described above.

Glasgow is ideal for an epidemiological evaluation of antenatal screening programmes because it is a high risk geographical area with a population based register of congenital malformations and it has been served by an antenatal screening programme for NTD since 1975.

**SECTION III - OVERALL AIM AND OBJECTIVES**

### SECTION III: OVERALL AIM AND OBJECTIVES

#### OVERALL AIM

To evaluate the programme of antenatal screening for Neural tube defects (Anencephaly and Spina bifida) in Greater Glasgow for the years 1976-1986.

#### OBJECTIVES OF THE STUDY

In order to evaluate antenatal screening for the detection of NTD (Anencephaly and spina bifida), the following questions required to be answered:

- 1 - What is the epidemiology and the natural history of the condition?
  - What is the prevalence of Anencephaly and spina bifida in the study population?
  - Are there any significant secular trends, and what are their implications for screening?
  - What is the natural history of Anencephaly and spina bifida and how is it affected by screening?
  
- 2 - What is the effectiveness of screening?
  - What is the impact of screening on the birth prevalence of NTD?
  - Has birth and pregnancy prevalence diverged over time?

3 - What is the efficiency of screening?

- How successfully is screening delivered to the target population?
- What are the technical and organisational obstacles to efficiency?
- What is the sensitivity and specificity of the screening test?

4 - What are the conclusions of the study?

- How effective and efficient is screening for NTD as a public health measure?
- What are the key factors influencing the impact of screening?

5 - What are the policy implications?

- What do the findings mean for screening policy in the West of Scotland, and generally?
- How can screening be improved in terms of its effectiveness and efficiency?
- What is the future of antenatal screening for NTDs?
- What future research is required?

**SECTION IV: MATERIAL AND METHODS**

SECTION IV: MATERIAL AND METHODS4.1 Study Population:-

The Greater Glasgow Health Board area was created after the reorganisation of the NHS in 1974. Five main maternal hospitals serve pregnant women (Figure 4). Its total population is currently less than one million and is about one fifth of that for Scotland. There has been a continuous decline in the estimated size of the GGHB population from 1976-1986 (Table 1). The annual number of total births has fluctuated around 13,000 while the annual outward migration has decreased from about 2% of the total population in the 1970's to 1% or less in the 1980's.

The social class distribution in the GGHB area compared with that of Scotland and England (Table 2) indicates that social classes I and II are under-represented in Glasgow compared to Scotland and England, while the population of social classes IV and V are higher in Glasgow than in Scotland and England.

There has been a consistent marked decline in stillbirth, perinatal, neonatal and infant mortality rates (Table 3). In 1986 the stillbirth rate for GGHB was the same as that for Scotland, while the neonatal and infant mortality rates were less than that for Scotland. Neonatal mortality in Scotland was similar to that in England, 5.2 per 1000 live births during 1986; while infant mortality in Scotland was lower than that in England during the

**Maternity Hospitals in Glasgow:**

- Stobhill Hospital
- Queen Mothers Hospital
- Royal Maternity Hospital
- Southern General Hospital
- Rutherglen Maternity Hospital

**Hospitals closed:**

- Eastern District Hospital (Duke Street)
- Robroyston Hospital
- Redlands Hospital

**Other Glasgow Hospitals:**

- Royal Samaritan Hospital (associated with Rutherglen - terminations)
- St. Frances Maternity Hospital (Catholic hospital)

**Hospitals not in the GGHB area but with maternal address in Glasgow:**

- Paisley Maternity Hospital
- Vale of Levan Maternity Hospital
- Bellshill Maternity Hospital

Figure 4. Hospitals contributing data to the study.

same year, 8.8 and 9.5 per 1000 live births respectively (Pharoah and Alberman 1988). In the 1970's Glasgow had higher stillbirth, perinatal, neonatal and infant mortality rates than Scotland (Registrar General Scotland 1970). This may be partly due to advances in neonatal and obstetric care and to the higher proportion of mothers attending early for antenatal care and screening.



#### 4.2 Glasgow Register of Congenital Malformations:-

The Glasgow Register of Congenital Malformations was established in 1972 by the Corporation of Glasgow health department. After the reorganisation of the NHS in 1974 the responsibility for the Register was assumed by the Greater Glasgow Health Board. It is population-based in that it relates to the population resident within the boundaries of the Greater Glasgow Health Board area.

Glasgow was selected as one of the centres to participate in the multi-national EUROCAT (European Registration of Congenital Anomalies and Twins) project of the European Community in 1979 (Weatherall, De Wals and Lechat, 1984).

#### 4.3 Sources of Ascertainment:-

Multiple sources of information were employed in order to achieve maximum levels of ascertainment and to ensure that as few cases as possible were missed. No formal time limit exists for registration of newly diagnosed cases. Whatever the source of ascertainment, all diagnostic information was validated by direct scrutiny of clinical or pathological records.

The ascertainment was both active and passive (Figure 5). Active ascertainment involves the careful scrutiny of data which are held centrally or in clinical departments. Passive ascertainment is a process of communication of details of malformations from the notifying agency directly to the Register.

Different sources of information have been used over the years; the number and nature of these sources changed either because one or more of the sources ceased or because more rewarding sources became available (Hamilton et al, 1985).

The principal active sources of data were:

##### Hospital Records:-

Maternal and paediatric case notes at the various maternity hospitals located throughout the Greater Glasgow Health Board area are scrutinised by the clerical staff of the Information Services Unit. The main areas of interest in these case notes are the routine hospital discharge forms. A summary document is completed for every woman discharged from the

Active Sources	Passive Sources
Hospital records Scanning of routine hospital discharge forms (SMR1, SMR2, SMR11) Post-mortem reports Perinatal meetings Department of medical genetics	Paediatric discharge letters Health visitor notification Stillbirth and death registers

Figure 5. Sources of ascertainment, Glasgow Register of Congenital Malformations

*Source:* Stone and Hamilton (1987)

hospital after childbirth and for every child discharged after delivery.

Form SMR2 - Maternal Discharge Record:

This covers details recorded concerning the mother and can be used as a check on data already in the reports, e.g. post code, gestation, mother's date of birth, date of l.m.p., previous pregnancies, occupation of the mother (not always available), occupation of the father (not always available). (Appendix 3)

Form SMR11 - Neonatal Discharge Record:

This contains details concerning the baby and lists malformations if any. One of three copies is retained by the maternity units which permitted Register staff to examine batches of the forms periodically. The main shortcoming of this source was its incomplete coverage. (Appendix 4)

Form SMR1 - Hospital Discharge Record:-

A child hospitalised after the neonatal period has a hospital summary form (SMR1) completed on discharge. These forms have diagnostic information including the presence of any congenital anomaly. It comes in a computer printout of all hospital discharges in Scotland from the Information Statistics Division, Common Services Agency, Edinburgh. (Appendix 5)

Post Mortem Reports:-

A report of all post mortems performed on fetuses terminated with

congenital malformations is sent to the Department of Medical Genetics from the pathology department in Yorkhill. The clerical staff at the Registry examine them during their visits to the Medical Genetics Department.

Department of Medical Genetics:-

A computer printout of all terminations known to have been performed subsequent to prenatal diagnosis of a congenital anomaly, is examined regularly by Registry staff. (This is discussed in more detail later, 4.4.)

Perinatal Meetings:-

The Registry staff attend many of these meetings which are held in maternity units in order to obtain further information about known cases. Occasionally a new case of congenital anomaly is identified in this way.

The principal passive sources of data were:-

Paediatric discharge letters:-

When a child with congenital abnormality is discharged from the hospital a copy of the letter from the paediatrician to the family doctor is sent to the Registry. If the information contained in the letter is not complete the hospital case record is examined.

Health Visitor notification:-

Every child resident within the Greater Glasgow Health Board area

has a health visitor and child health record. This record is structured for developmental screening and immunisation consent. There are four tear-out pages in the record (Appendix 6), the immunisation consent form and three developmental screening returns for use at 8-10, 16-20 and 42-48 months of age. On each of the four returns a question is specifically asked about the presence of any congenital malformation. The health visitor notifies the child health department about the congenital malformations and the Registry staff have direct access to this information.

Stillbirth and Death Registers:-

The Registrar General for Scotland in Edinburgh provides a computer printout for these events and they are used to identify cases of congenital malformation in which the appropriate causes of death are coded (Appendix 7).

#### 4.4 Department of Medical Genetics

In the West of Scotland Ms AFP has been used as a screening test for neural tube defects since 1974. The test is voluntary and its purpose is to identify a group of women in which AFP levels were above the normal range since the option of termination may arise from abnormal test results.

Blood samples were drawn by the general practitioner or the obstetrician at 16-20 weeks of gestation during the antenatal care. All the samples are sent to the Duncan Guthrie Institute of Medical Genetics laboratory for testing. The screening programme not only depends on assay precision but also on the precision with which the period of gestation is determined in every pregnancy tested.

Once the patient's Ms AFP level is determined it is compared with normal values established within the laboratory for each week of gestation. An intervention point has to be chosen which is a reasonable compromise between affected and unaffected pregnancies. At the start of the West of Scotland programme a high cut-off level was used - the 99th centile (3.0 MOM) - to keep the number of false positives to a minimum. In 1979 the cut-off level was reduced to the 97th centile (2.5 MOM). In 1983 only the design of the form was changed; from 1985 to the present the 95th centile (2.0 MOM) has been used as an intervention level (Appendix 8). It takes about 4-7 days (from the date the sample is taken) for the result to be ready. The reports are typed with

the aid of a mini-computer which simplifies filing and helps in the maintenance of adequate quality control.

Those with normal Ms AFP levels have no further action taken (Figure 6) and a written report is sent to the referring obstetrician. Those with Ms AFP above the intervention point are reported by telephone to the referring obstetrician, antenatal clinic sister or the unit secretary for immediate examination of the antenatal clinic notes with recall of the patient for ultrasonography.

Ultrasound examination is an integral part of the screening programme; in some clinics ultrasound was used at the booking visit to check the patient's dates. This is called a routine scanning.

One of the following causes for elevation of Ms AFP may be found, such as wrong date, twin pregnancy, fetal demise, abortion or an abnormality.

If no cause is found a second blood sample is taken and sent to the laboratory. It usually takes about 2-3 days for the result to be ready from the date the sample is taken from the patient. If the result is normal, a written report is sent to the referring obstetrician and if the ultrasound is normal no further action is taken.



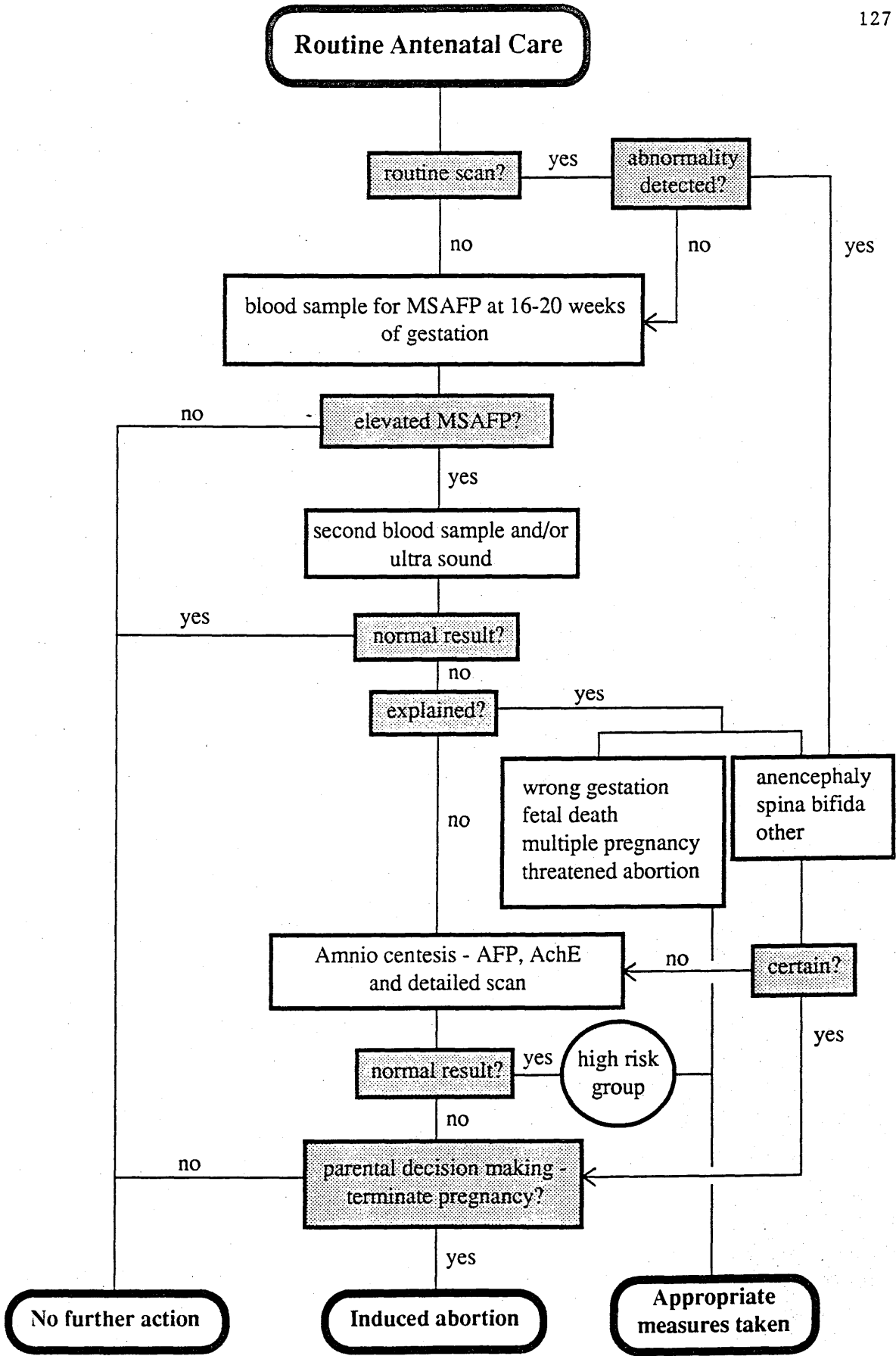


Figure 6. Flow chart for follow up of antenatal screening programme in Greater Glasgow Health Board Area

If the result is high (above the intervention point), this is reported by telephone. The obstetrician is informed and asked to consider a detailed ultrasound (diagnostic) and amniocentesis. It takes about 2-3 days from the time the sample is taken to get Am AFP and polyacrylamide gel for AchE electrophoresis (usage started in 1981) to ensure that false negative Am AFP results will become even rarer.

Those with normal Am AFP and AchE are considered to be high risk obstetric patients and they need a good follow-up. Those with a result of Am AFP above the intervention point and a second AchE band are offered termination of pregnancy by the obstetricians after counselling.

Mothers who have an increasing risk due to an affected previous birth and maternal age more than 35 and who have requested prenatal diagnosis are offered amniocentesis and detailed ultrasound.

An increasing number of anencephalic cases have been detected by routine ultrasound examination without requiring an Ms AFP test.

All amniotic fluid samples are examined for fetal blood contamination.

Information is obtained by the Medical Genetic Department about

the result of those with levels above the intervention point from several sources.

Postcards:-

The Medical Genetic Department keep postcards in each hospital in the labour room so that those terminated or born with an abnormality are reported on these cards and sent back to them.

Pathology Department:-

The product of termination is usually sent to pathology. After examination a copy of the result is sent to the Medical Genetics Department.

Labour Room:-

Staff from the Medical Genetics Department regularly check the labour room record to see if any congenital abnormality is recorded.

Surgical Ward:-

Some of the staff from the Medical Genetics Department check the surgical ward record in the Royal Hospital for Sick Children. In this way most of the missed cases and those not tested are identified.

In recent years a cross-check of known cases has been conducted with the Register of Congenital Malformation. All the cases with neural tube defects in the whole of the west of Scotland known to

the Department of Medical Genetics are recorded on cards structured alphabetically by surname of person, address, date of birth, report about the result of the test including detection and diagnosis, missed or not tested, abnormality present, result of pathology if termination carried out.

Those who are tested by AFP and missed are reported in a separate book called 'the missed book' with the reason of missing them.

A detailed analysis of each step in the screening process Fig.26 was confined to a single year (1986) because it was only for this year that comprehensive data were available.

#### 4.5 Numerator and Denominator Data:

The study was carried out in Glasgow for the period 1976-1986. The Glasgow Register of Congenital Malformations and the Duncan Institute of Medical Genetics, Yorkhill, are the key points for collection of data on anencephaly and spina bifida births (live and still), both multiple and singleton births are included, therapeutic termination and antenatal screening. Spina bifida occulta is not included.

The Register, involved in EUROCAT, has adopted the five-digit British Paediatric Association code, based on the latest revision of the International Classification of Diseases which was used for diagnostic coding (World Health Organisation, 1977).

If a combination of defects was present, like anencephaly and spina bifida, anencephaly was always regarded as the principal malformation.

Although the study is a retrospective one, all the data and information were collected prospectively (on the expected date of delivery for those terminated).

Because Glasgow is one of the members of EUROCAT a special form called the EUROCAT Report on Congenital Malformations (Appendix 9) started to be used in 1980. One form is filed for each registered defect, such as anencephaly and spina bifida births (live and still) and therapeutic termination with relevant

material in date of birth order. Therapeutic terminations were filed separately on date of termination. For each defect, whether birth or termination, information is recorded about the child, the mother and, to a limited extent, the father.

For NTD births (live and still) for the years 1976-1979 there was information missing, usually on maternal age, previous pregnancies, occupation of the father and antenatal screening. Some were sought from hospital case records with the assistance of the Medical Records Office (but some of them were not recorded on the case notes).

For therapeutic terminations for the years 1976-1979 the only information available was on maternal age, address and the cause for therapeutic termination. All the rest of the information required was sought from the hospital case record with the assistance of Medical Records Office. All the detailed information about the antenatal screening for neural tube defects was sought from the Department of Medical Genetics, Yorkhill, on both alpha-feto protein and ultrasound screening.

If a patient had high Ms AFP then an ultrasound scan and amniocentesis was carried out. If the fetus turns out to have a NTD then the case was referred to be detected by Ms AFP and diagnosed by ultrasound or Am AFP and AchE. If the patient had a chance to have a routine scan at booking and before the test of Ms AFP and an abnormality was observed, it will be said that it

was detected by ultrasound.

Because the total number of pregnant women 1976-1986 in GGHB area was unknown, the number of pregnant women in GGHB area screened was also unknown. (In the west of Scotland programme the number of patients referred from General Practitioners or from the hospital to get AFP screening tests were recorded but not by area of resident.) Those screened by GGHB hospital and General Practitioner were used as an estimate number of those screened for the GGHB area for those expected to be born in 1982-1986 were available.

Information on maternal age, parity and social class to enable a comparison of the screened and not screened pregnancies was not available.

Information about the date of birth and date of death for those who died were sought from the GGHB Register of Congenital Malformations. For those surviving there was no information about the degree of disability they have.

For calculating the pregnancy prevalence for Anencephaly and Spina bifida the denominator consisted of the number of total births (live and still) during the period but did not include abortions (spontaneous or induced). This does not undermine the value of the prevalence later as the number of induced abortions for fetal malformations is very low compared with the total

numbers of births. Data on spontaneous abortions are not available from any source.

#### Methodological Note

Although the complete study period is 1976-1986 the results and tables occasionally deviate from this period for the following reasons:

1. In order to demonstrate the secular trend in the prevalence, it is necessary to look at an earlier period, so the years 1964-1986 are presented.
2. In order to estimate the proportion of all pregnant women who were screened in the years 1982-86 were employed because data for earlier years were not available; even for 1982-86 information on the maternal age parity and social class for screened and not screened was not available.
3. Data on age parity and social class were available for affected pregnancies for the years 1979-86. They were not available for the period 1976-78.
4. The number of normal fetuses aborted during 1976-1981 was not known and so assessment of the specificity of screening was confined to the period 1982-86.
5. In order to describe each step in the screening process, the single year 1986 was employed for detailed study because it was only for this year that all data necessary for this analysis were available.



**SECTION V: METHODS OF ANALYSIS**

## SECTION V METHODS OF ANALYSIS

### 5.1 - Data processing

The Register collected information on both affected births and therapeutic termination. Figures 7 and 8 illustrate the many steps involved in the transmission of data along the pathways from sources to analysis.

Following the birth of an affected child, an initial diagnosis was made which was either suspected or definitive, followed by a prolonged clerical process involved in identifying defects from sources which had to be scrutinised by Registry staff. Because some data were incomplete or unsatisfactory, verification was required. This was followed by completion of a registration form (Eurocat) related to diagnostic classification. If more than one defect was listed in order of severity, then the form was filed in date of birth order.

Updating of the file is carried out in the event of death, which is ascertained from the death register, by recording the date, place and cause of death.

Missing data on maternal age, parity and social class were sought from hospital case records with the assistance of the medical records officer.

Data from the registration forms were transferred to coding forms

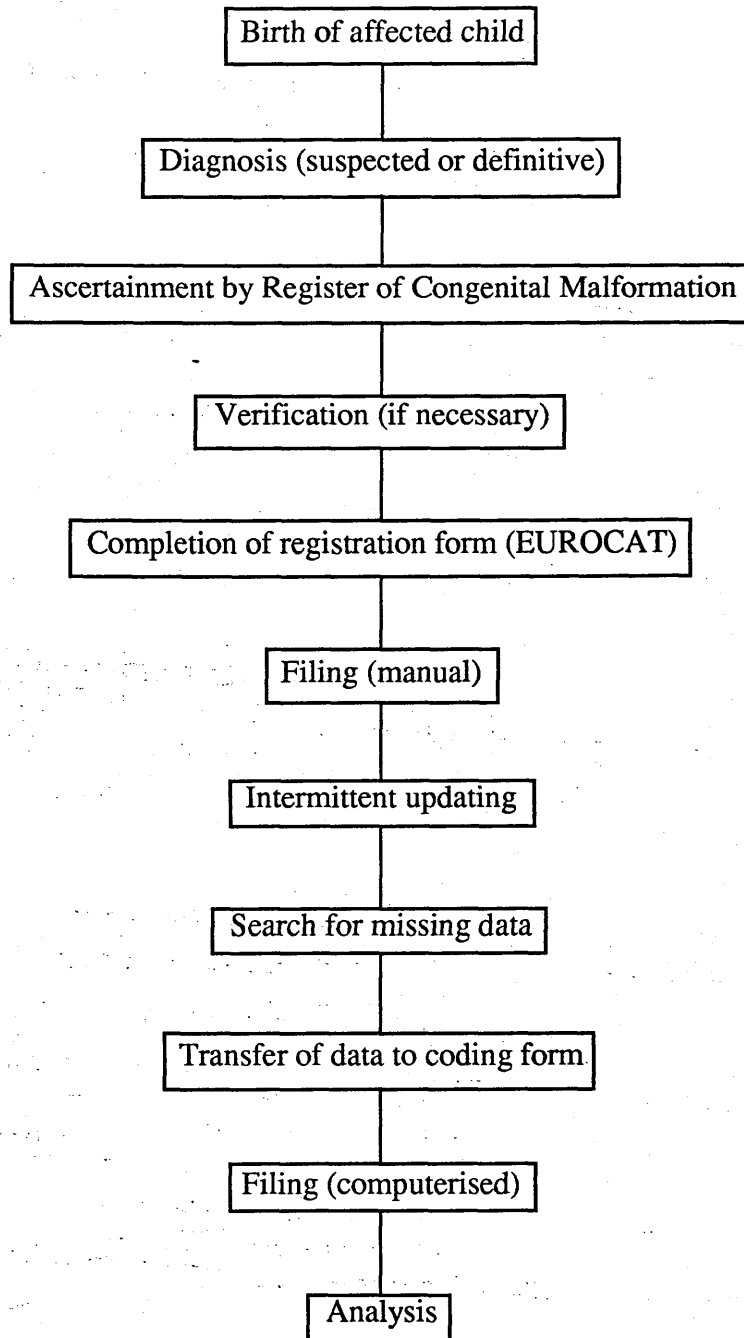


Figure 7. Flow chart of data on Anencephaly and Spina bifida births.

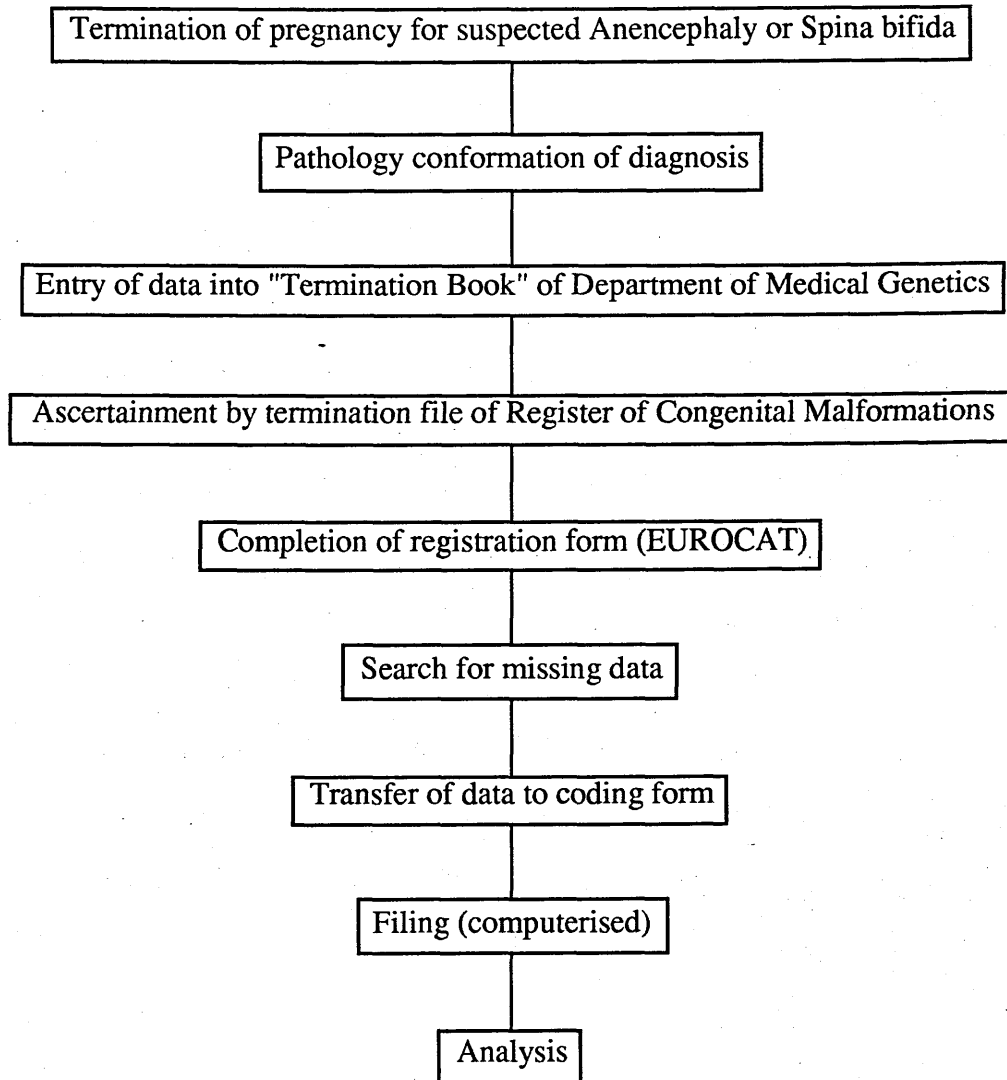


Figure 8. Flow chart of data on Anencephaly and Spina bifida terminations.

The coded data was then entered on a computer file and a series of computer print-outs generated for analysis.

After termination of pregnancy for suspected anencephaly or spina bifida all aborted specimens were examined pathologically and the Department of Medical Genetics received written details about the aborted fetuses which were entered into their termination book. Access to this book was granted to Registry staff who entered the case details into a termination file of the Glasgow Register of Congenital Malformations. The registration forms (Eurocat forms) were completed, then a search for missing data such as maternal age, parity and social class was carried out by the Registry staff with the assistance of hospital medical record officers. Thereafter analyses were carried out.

The data concerning this study were transferred to a microcomputer and standard statistical packages SPSSX were used on the Glasgow University mainframe.

The graphics were produced by Harvard Graphics on IBM PS/2.

The numbers are presented in percentages or rates per 1000. To obtain an estimate of the prevalence the numerators and the denominators were transformed into annual rates per 1000 total births (live and still).

The data are presented in tables, diagrams, and graphs. A variety of statistical tests were used to assess trends and associations between variables. These included standard chi-squares, Z-test-scores, poisson and logistic regression analyses.

The data were analysed in order to generate tabulation as follows:

- Epidemiology and natural history (see 5.2)
- Effectiveness of antenatal screening (see 5.3)
- Efficiency of delivery screening service (see 5.4)
- Efficiency of screening procedure (see 5.5)

## 5.2 Epidemiology and the natural history

- Prevalence rate of NTD. (Anencephaly, Spina Bifida and both together) per 1000 total births in Glasgow population for the years 1976-1986.
- Glasgow, the period 1976-1986 being disaggregated into two periods, 1976-1981 and 1982-1986, the rates being calculated and examined for evidence of secular trends
- Glasgow, the period 1979-1986 being treated as a single unit for comparison with an earlier period
- The outcome of anencephalic pregnancies from conception to birth, birth to survival (all died), the percentages compared between the two time periods (1976-1981 and 1982-1986)
- The outcome of spina bifida pregnancies from conception to birth and following the survival to more than one year. From birth and following the survival to more than one year. Comparison between the two time periods (1976-1981 and 1982-1986).
- Perinatal, neonatal and infant mortality for anencephaly, spina bifida and compare the two time periods (1976-1981 and 1982-1986).

### 5.3 Effectiveness of Antenatal Screening

- Anencephaly and spina bifida. Pregnancy prevalence and birth prevalence per 1000 total births and percentages of pregnancies terminated in Glasgow 1976-1986 for evidence of the effectiveness of antenatal screening for neural tube defects
  
- The period 1976-1986 being disaggregated into two periods (1976-1981 and 1982-1986) and the percentages of termination and birth for anencephaly and spina bifida were compared
  
- The proportions screened, detected and those terminated when detected for anencephaly and spina bifida, which give an insight into the effectiveness of antenatal screening, Glasgow 1976-1986, were examined for evidence of a trend.



#### 5.4 Efficiency of delivery of screening service

- Pregnancies screened as a proportion of total births Glasgow 1982-1986 and pregnancies screened as a proportion of total pregnancies Glasgow 1982-1986. To show the difference when total birth is used and total pregnancy. They also can be used as an estimate of the acceptability of antenatal screening for NTD.
  
- A comparison of the proportions of NTD pregnancies, screened and not screened, in terms of maternal age, parity and social class for the screened and not screened and the outcome of pregnancy.

### 5.5 Efficiency of the technique

- The method which is used for the identification of those at a high risk of neural tube defects and the method of diagnosis were analysed for anencephaly, spina bifida and neural tube defects. For those terminated to identify which method was more frequently used.
- The sensitivity for anencephaly, spina bifida and ASB to identify the detection rate for NTD in Glasgow using the combined approach during the periods 1976-1982 and 1982-1986.
- The proportion of those detected and terminated as a consequence of antenatal screening for anencephaly, spina bifida and NTD. Glasgow (1976-1981 and 1982-1986) for measurement of the efficacy of the techniques.
- The specificity for Anencephaly and Spina bifida antenatal screening in Glasgow for the years 1982-1986 only.
- A detailed description of the process of screening during the single year 1986 to elucidate the proportion with high MsAFP in the first blood sample, second blood sample, and the proportion offered amniocentesis.

**SECTION VI: RESULTS**

SECTION VI: RESULTS6.1 THE EPIDEMIOLOGY AND NATURAL HISTORY

During the study period 1976-1986 there were 142,565 total births to Glasgow residents. The following are the numbers (and prevalence rates) of anencephaly and spina bifida births both live and still, (i.e. fetuses born at 28 weeks or more gestation):

Anencephaly	61 (0.43	per 1000 total birth)
Spina bifida	180 (1.26	" " " " )
Anencephaly and spina bifida	241 (1.69	" " " " )

The time trend in prevalence of ASB were examined in terms of both annual and secular trends.

The annual changes in prevalence within the study period (1976-1986) are shown in Tables 4, 5, 6. There was a marked decline in birth prevalence of anencephaly, particularly in 1982 and 1985. There was a decline in birth prevalence of spina bifida, with the lowest during 1983. Trends in birth prevalence were modelled using poisson regression models (Figures 9, 10).

Lines for the trend were fitted to the rates for anencephaly and spina bifida birth prevalence over the study period 1976-1986. There was a significant decline in birth prevalence for both anencephaly ( $X^2 = 44.42$  (1dF)  $p < 0.0005$ ) and spina bifida ( $X^2 = 20.9$  (1dF)  $p < 0.0005$ ).

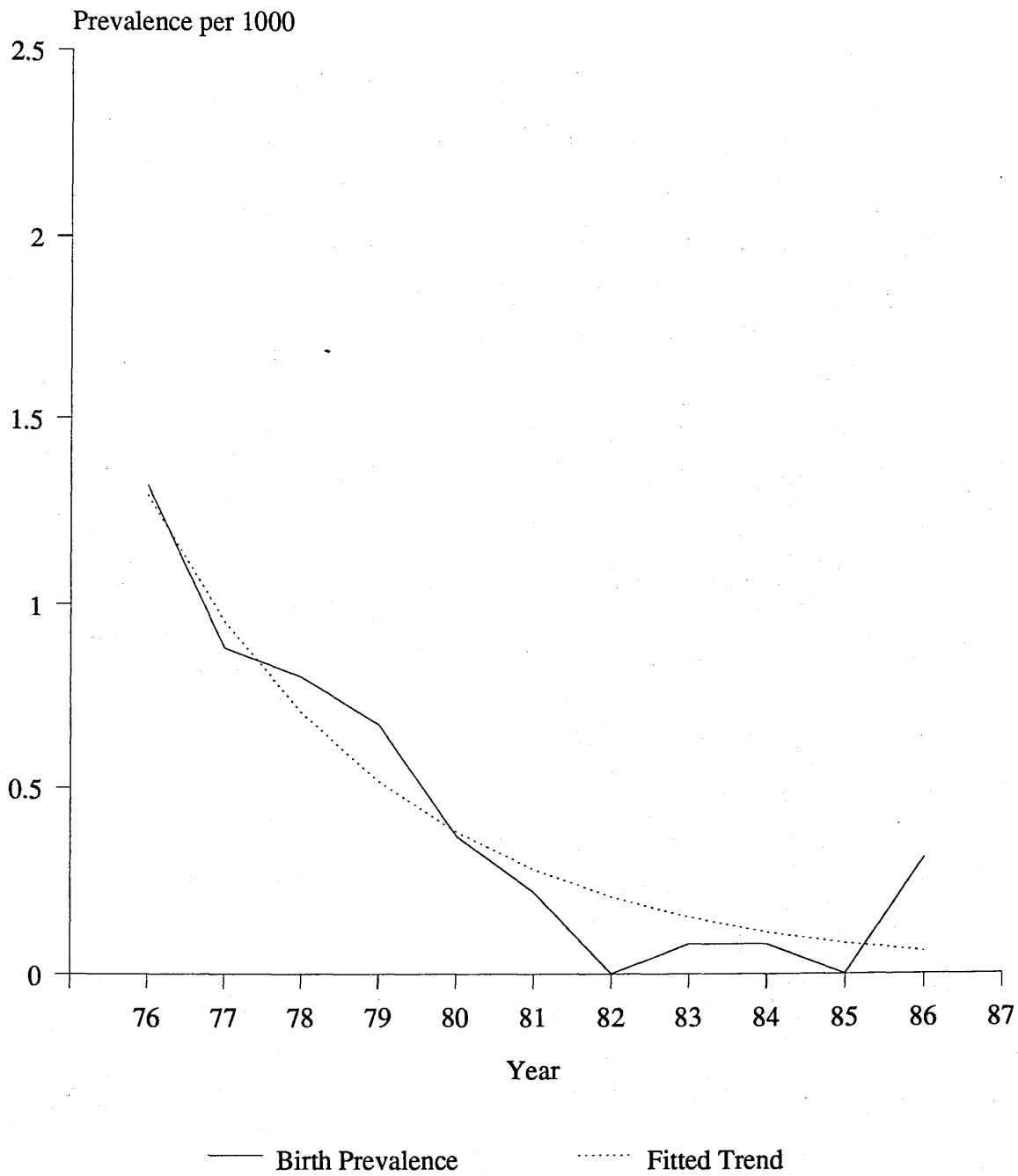


Figure 9. Birth prevalence of anencephaly :  
Glasgow 1976-86.

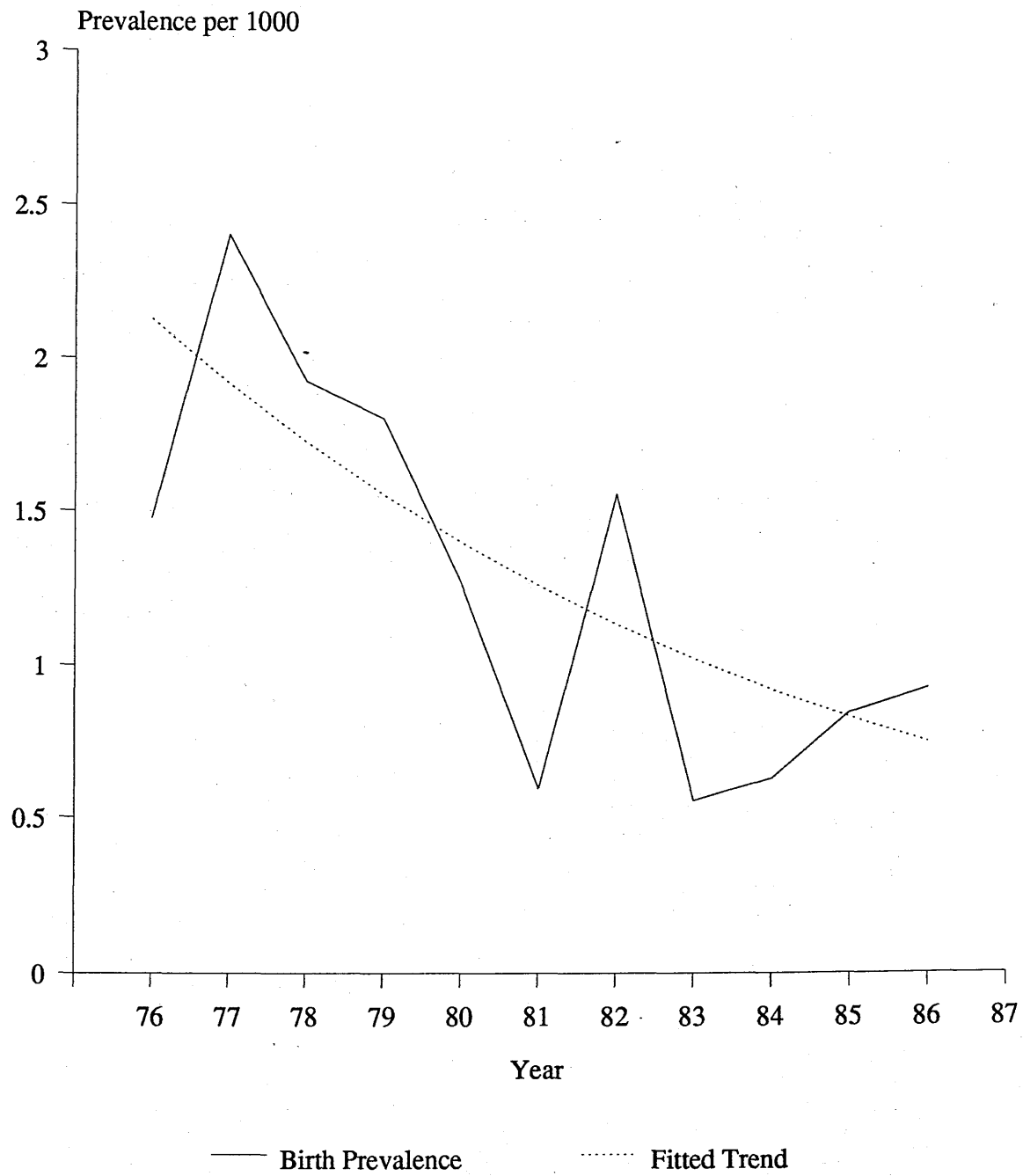


Figure 10. Birth prevalence of spina bifida :  
Glasgow 1976-86.

The rates of birth prevalence of anencephaly and spina bifida were divided into two periods 1976-1981 and 1982-1986 (Table 7). There was a marked and significant decline in birth prevalence for anencephaly ( $\chi^2 = 30.8$  (1dF)  $p < 0.05$ ) and spina bifida ( $\chi^2 = 12.2$  (1dF)  $p < 0.05$ ) during 1982-1986 compared to 1976-1981 time period

There was also a significant decline in pregnancy prevalence for anencephaly, spina bifida and ASB (Table 8).

Evidence of secular trend (Table 9, 10; Figure 11, 12) was sought by comparing the prevalence found in the present study period (1979-1986) with that reported in an earlier Glasgow study by Wilson (1970) and Stone (1981); these too drew upon multiple sources of ascertainment.

There was a significant decline in anencephaly birth prevalence in 1972-1978 compared to 1964-1968 ( $\chi^2 = 21.2$  (1dF)  $p < 0.001$ ) and in 1979-1986 compared to 1972-1978 ( $\chi^2 = 129.7$  (1dF)  $p < 0.001$ ). For spina bifida birth prevalence during 1972-1978 compared to 1964-1968 ( $\chi^2 = 0.06$  (1dF)  $p > 0.05$ ) did not decline significantly. When 1979-1986 was compared to 1972-1978 there was a significant decline ( $\chi^2 = 71.0$  (1dF)  $< 0.001$ ).

In the case of pregnancy prevalence (birth and termination) the picture was different. There was a non-significant decline in both anencephaly and spina bifida pregnancy prevalence during 1972-1978 compared to 1964-1968 ( $\chi^2 = 2.56$  (1dF)  $p > 0.05$  and  $\chi^2 = 0.03$  (1dF)  $p > 0.05$ ) respectively, while 1979-1986 compared to 1972-1978 for both anencephaly and spina bifida shows a

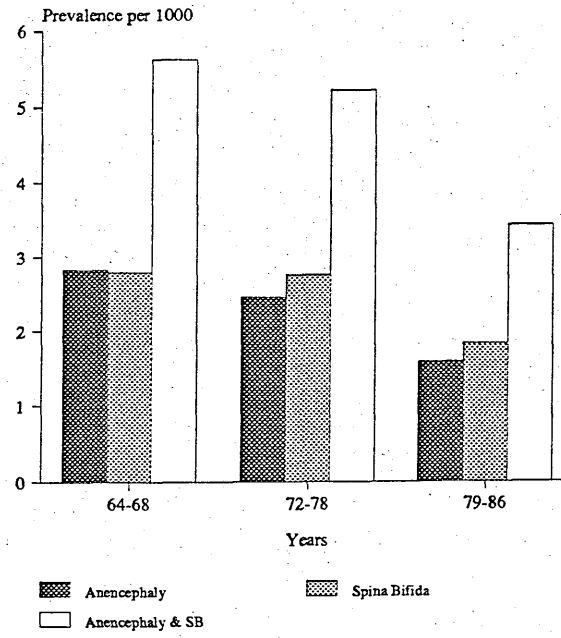


Figure 11. Trend in anencephaly and spina bifida pregnancies : Glasgow 1964-68; 1972-78; 1979-86.

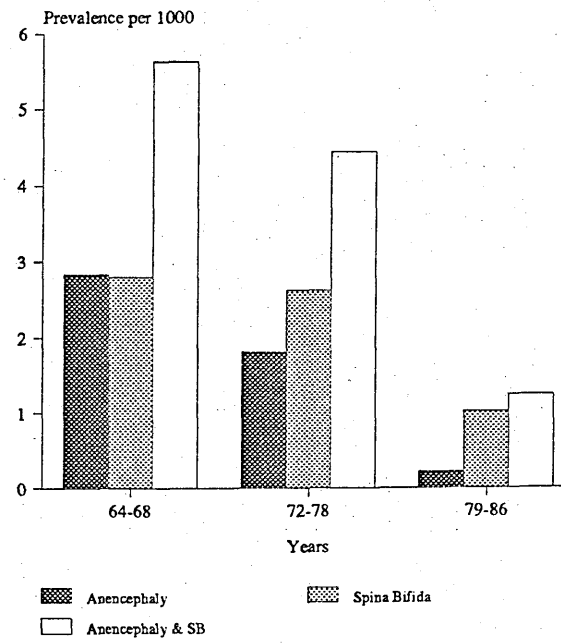


Figure 12. Trend in anencephaly and spina bifida births : Glasgow 1964-68; 1972-78; 1979-86.



significant decline for anencephaly ( $X^2 = 18.3$  (1dF)  $p < 0.05$ ) and spina bifida ( $X^2 = 18.7$  (1dF)  $p < 0.05$ ).

Figure 13 shows anencephaly and spina bifida pregnancies from 1964-1986; for the years 1969-1971 data were not available.

Of 91 anencephaly pregnancies during 1982-1986 - 93% were induced abortions (Figure 14, Table 11). This was a statistically significant difference from the 65% in 1976-1981 ( $X^2 = 24.6$  (1dF)  $p < 0.001$ ). Still-births comprised about 1.10% which is a significantly lower proportion ( $X^2 = 28.5$  (1dF)  $p < 0.001$ ) than that (28%) during 1976-1981. But there were no significant differences in the number of live births during the two time periods ( $X^2 = 0.06$  (1dF)  $p > 0.05$ ). All died during the first week of life. Frequency of death during 1982-1986 was not significantly different from 1976-1981 ( $X^2 = 0.06$  (1dF)  $p > 0.05$ ).

In the case of spina bifida pregnancies (Figure 14, Table 12) there were 107 total spina bifida births during 1982-1986 of which induced abortions accounted for about 44% ( $X^2 = 8.4$  (1dF)  $p < 0.01$ ) and stillbirths about 6% ( $X^2 = 3.9$  (1dF)  $p < 0.05$ ). From 1976-1981 induced abortions accounted for 27%, stillbirths 13%. (These differences are statistically significant.)

If we follow the survival of spina bifida fetuses starting from pregnancy (Table 13) 32.7% survived more than one year during 1982-1986 compared to 34% during 1976-1981, but this difference

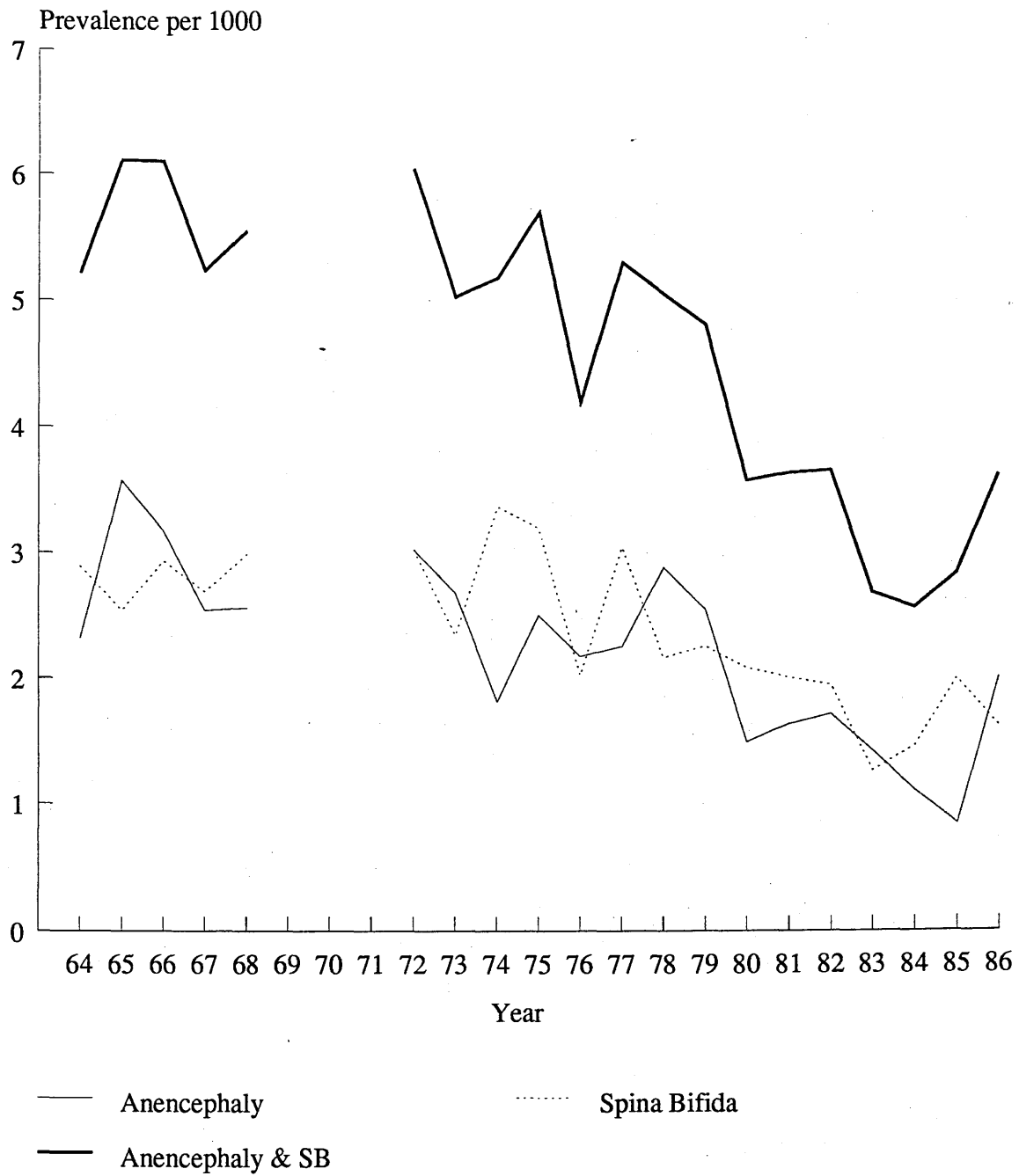


Figure 13. Anencephaly and spina bifida pregnancies :  
 Glasgow 1964-86.

Anencephaly Pregnancies

Spina Bifida Pregnancies

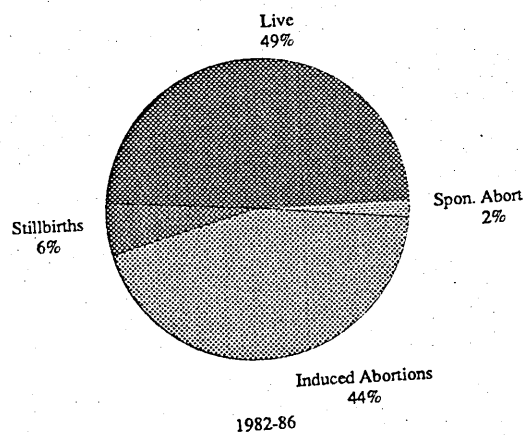
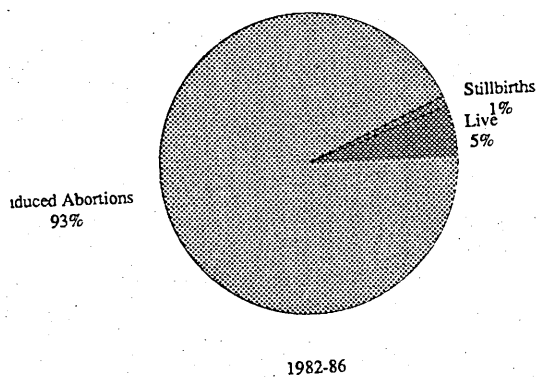
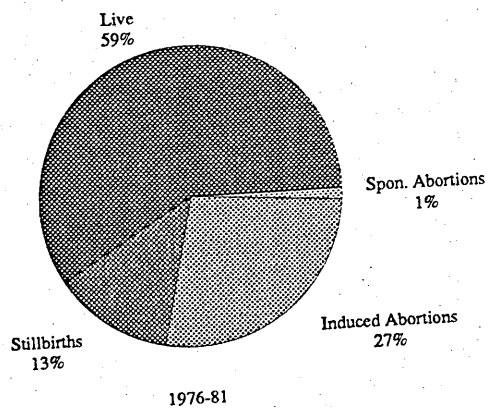
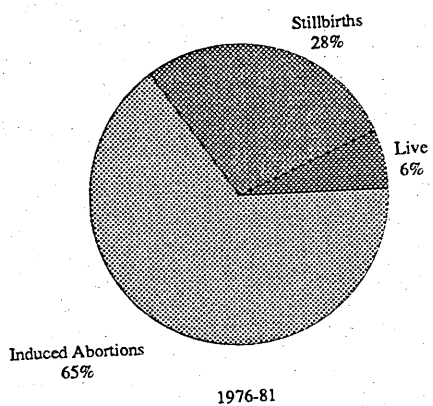


Figure 14. Outcomes for anencephaly and spina bifida pregnancies in Glasgow : 1976-81 and 1982-86.

is not statistically significant ( $\chi^2 = 0.06$  (1dF)  $p > 0.05$ ).

But if we follow the survival from birth (Table 14) to those surviving more than one year, about 60.4% survived more than one year among 1982-1986 births in comparison with 47.5% during 1976-1981. This is a non-significant difference ( $\chi^2 = 2.6$  (1dF)  $p > 0.05$ ).

Table 15, 16, show the perinatal, neonatal and infant mortality for anencephaly and spina bifida respectively. All anencephaly babies died during the perinatal period.

For spina bifida the perinatal, neonatal and infant mortality was lower during 1982-1986 in comparison with 1976-1981, but the differences are not significant ( $\chi^2 = 3.5$  (1dF)  $p > 0.05$ ) ( $\chi^2 = 0.84$  (1dF)  $p > 0.05$ ) and ( $\chi^2 = 1.25$  (1dF)  $p > 0.05$ ) respectively.

## 6.2 THE EFFECTIVENESS OF ANTENATAL SCREENING

The differences between pregnancy prevalence and birth prevalence is one means of estimating the effectiveness of antenatal screening.

The effectiveness of antenatal screening is affected by three factors: the proportions of affected pregnancies screened, the proportion of affected pregnancies detected (sensitivity) and the proportion of affected pregnancies terminated when detected.

The annual trends in pregnancy prevalence, birth prevalence and percentage terminated for anencephaly and spina bifida are shown in Table 17 and 18. The total number of anencephaly pregnancies was 250 during 1976-1986 and the pregnancy prevalence (birth + termination) was 1.75 per 1000 total births; 75.6% of these pregnancies were terminated during the same period. The total number of spina bifida pregnancies was 277 giving a pregnancy prevalence of 1.94 per 1000 total births; only 35.02% of pregnancies terminated during this period.

The trend in birth and pregnancy prevalence were analysed using poisson regression models. In the case of anencephaly (Figure 15) the regression slopes for both birth and pregnancy prevalence were found to be significant over the period 1976-1986 ( $X = 44.42$  (1dF)  $p < 0.0005$ ), ( $X^2 = 8.68$  (1dF)  $p < 0.005$ ) respectively (Appendix 10 (i)).

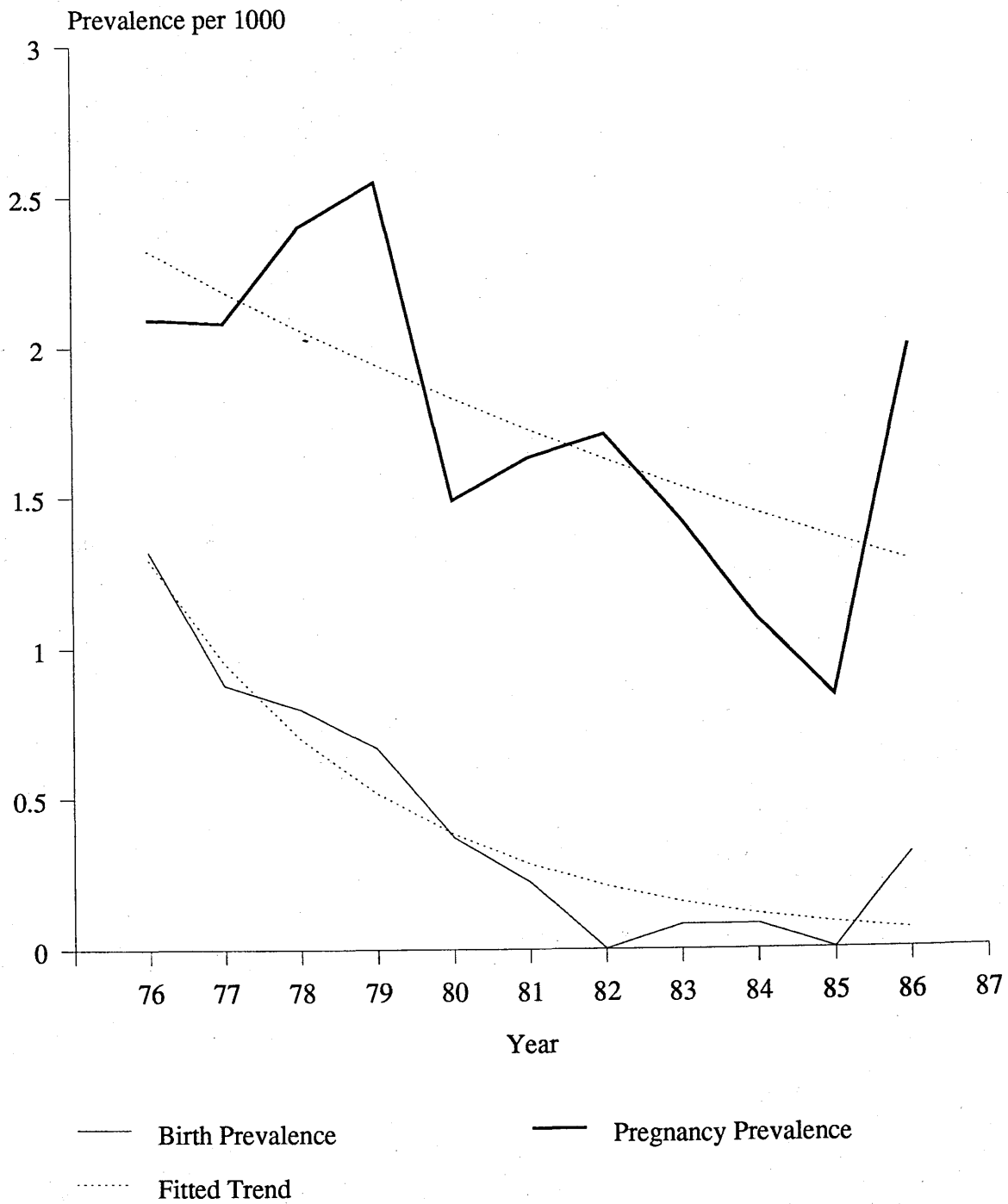


Figure 15. Pregnancy and birth prevalence of anencephaly with fitted trends : Glasgow 1976-86

In the case of spina bifida pregnancy prevalence (Figure 16) there was no significant trend in the regression slope during 1976-1986 ( $X^2 = 3.78$  (1dF)  $p > 0.05$ ) while in the case of birth prevalence there was a significant trend during 1976-1986 ( $X^2 = 20.9$  (1dF)  $p < 0.0005$ ) (Appendix 10 (i)).

There was a significantly lower births for anencephaly during 1982-1986 compared to 1976-1981 (Table 19) ( $X^2 = 24.6$  (1dF)  $p < 0.005$ ) with a high percentage terminated. In the case of spina bifida (Table 20) there was also a significantly lower birth with a higher percentage terminated during 1982-1986 compared with 1976-1981 ( $X^2 = 8.9$  (1dF)  $p < 0.005$ ). A high proportion (97.8%) of anencephaly pregnancies were screened during 1982-1986. This was significantly different from 1976-1981 ( $X^2 = 25.0$  (1dF)  $p < 0.0005$ ). (Table 21).

The proportion of spina bifida pregnancies screened during 1982-1986 was 75.7% compared with 61.8% during 1976-1981. This is also a significant difference ( $X^2 = 5.8$  (1dF)  $p < 0.025$ ). (Table 22).

The proportion of anencephaly and spina bifida pregnancies terminated is an outcome of the proportion screened, the proportion detected when screened (sensitivity) and the proportion terminated when screened and detected. Changes in proportion terminated, (an estimate of the effectiveness of screening), could be due to changes in one or any combination of

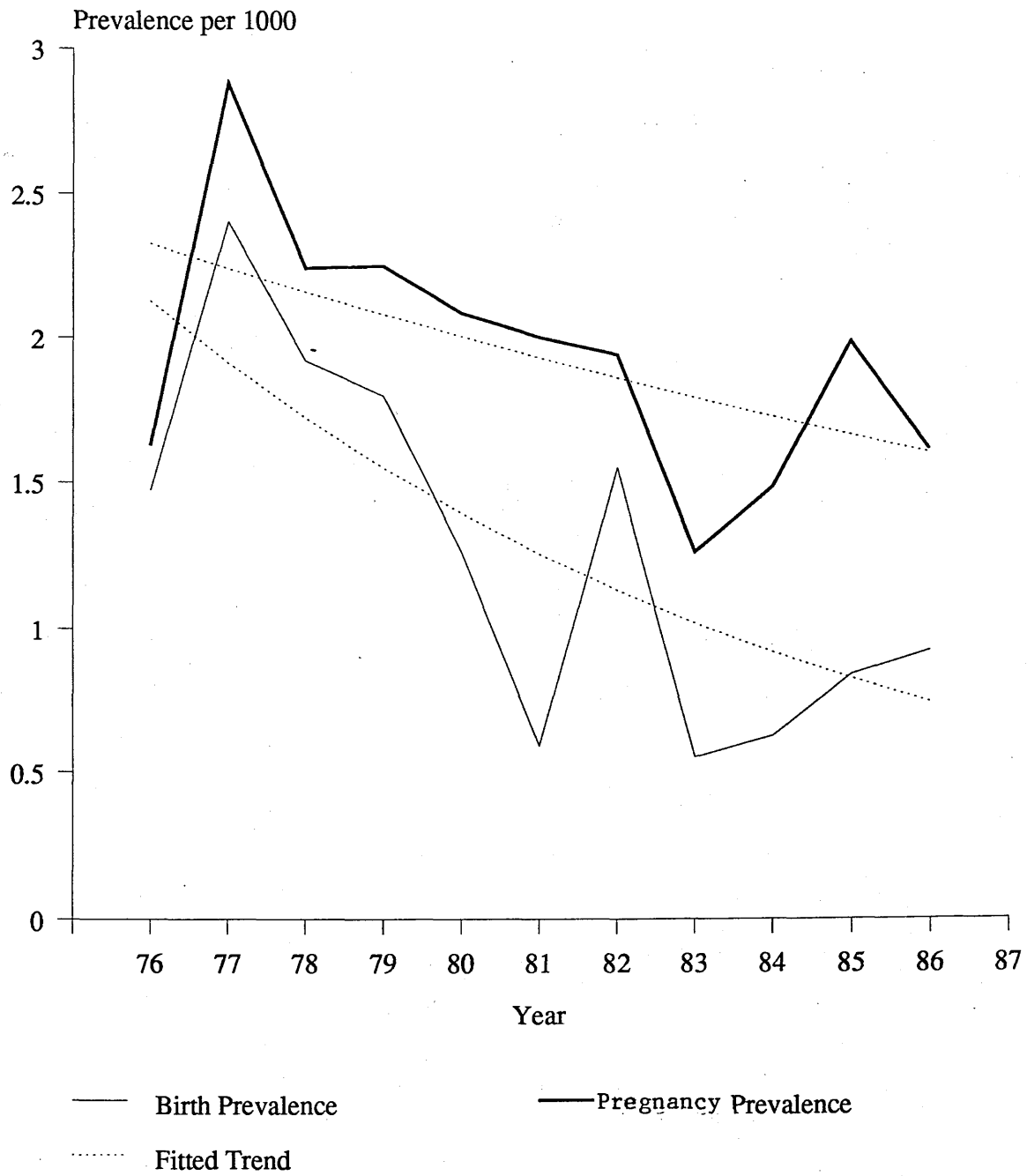


Figure 16. Pregnancy and birth prevalence of spina bifida with fitted trends : Glasgow 1976-86.



these three factors. Trends over time were modelled individually for these three factors using logistic regression. The details of the significance and fit of the regression curves are given in Appendix 10 (ii).

Factors Contributing to the Effectiveness of Antenatal Screening for Anencephaly:

The proportion of anencephaly pregnancies screened was below 50% in 1976, increased rapidly to 100% in 1982 until 1985, and in 1986 dropped to 92.3% (Table 23, Figure 17, 18). There was a significant trend in the proportion of affected pregnancies screened (Z score = 8.5  $p < 0.0001$ ).

The proportion of anencephaly pregnancies detected when screened (sensitivity) was 91.6 in 1976 and increased to 100% in 1986 (Table 23, Figure 17, 19). There was a significant upward trend in the proportion detected when screened ( $X^2 = 6.6$  (1dF)  $p < 0.025$ ).

The proportion terminated when screened and detected fluctuated between 90% and 100% during 1976-1986 (Table 23, Figure 17, 20).

Factors Contributing to the Effectiveness of Antenatal Screening for Spina Bifida

The proportion of spina bifida screened in 1976 was also below 50% and then started to increase gradually to more than 84% in 1985 and declined in 1986 to 71.4% (Table 24, Figure 21, 22).

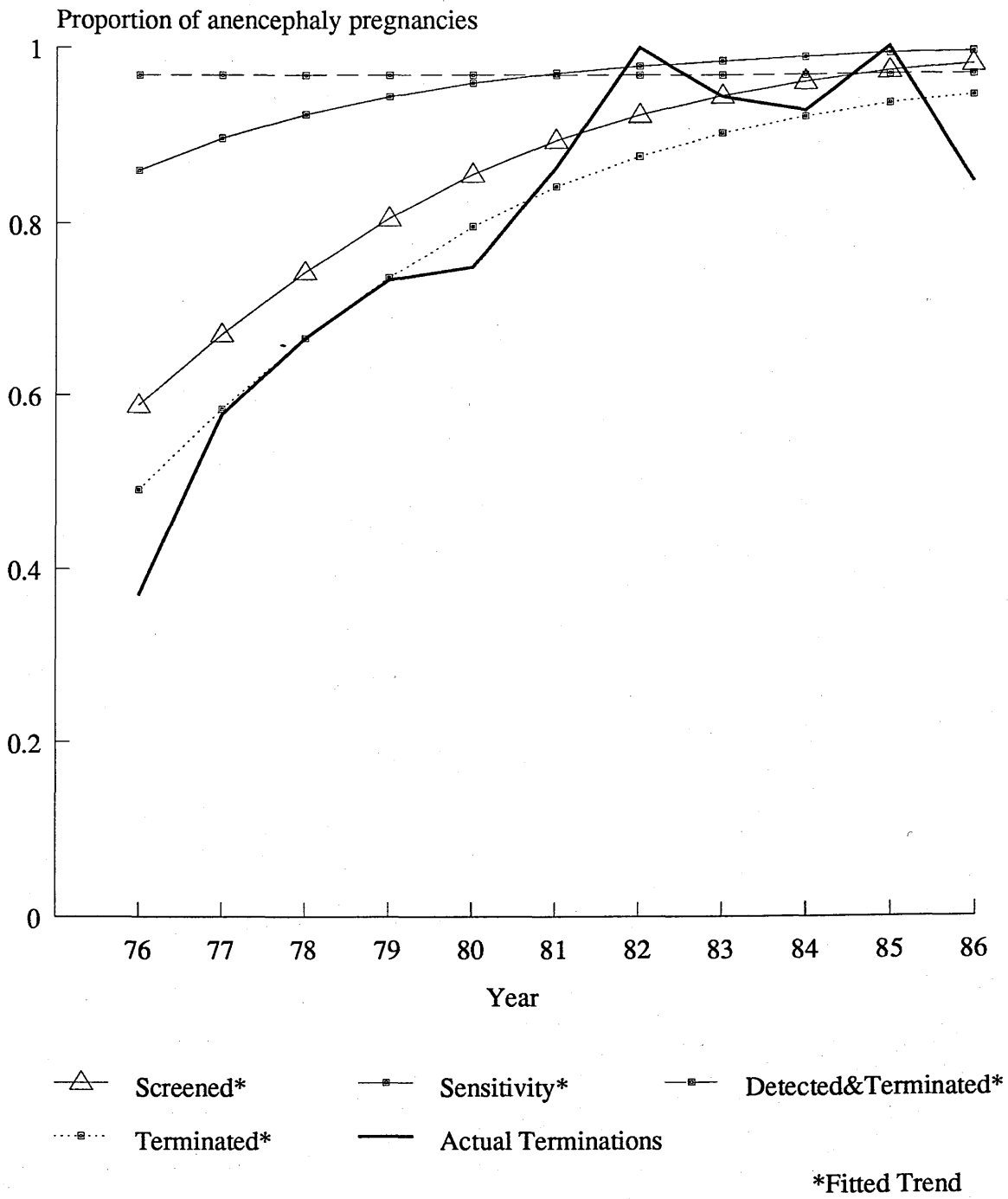


Figure 17. Screening and outcomes of screening for anencephaly : Glasgow 1976-86.

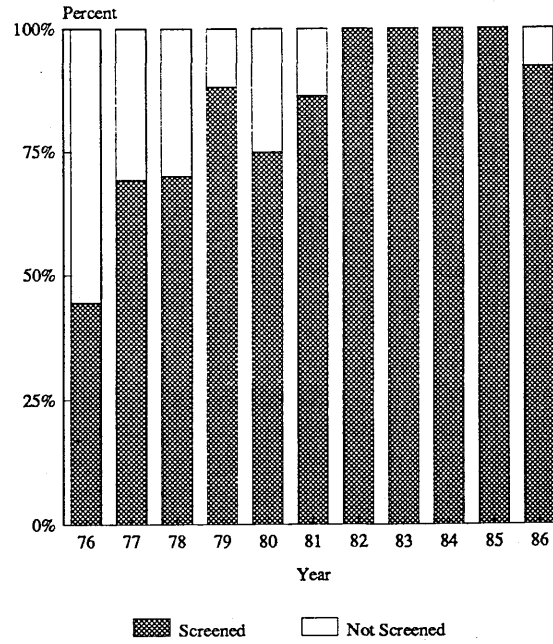


Figure 18. Anencephaly screening : proportion (%) screened in each year 1976-86.

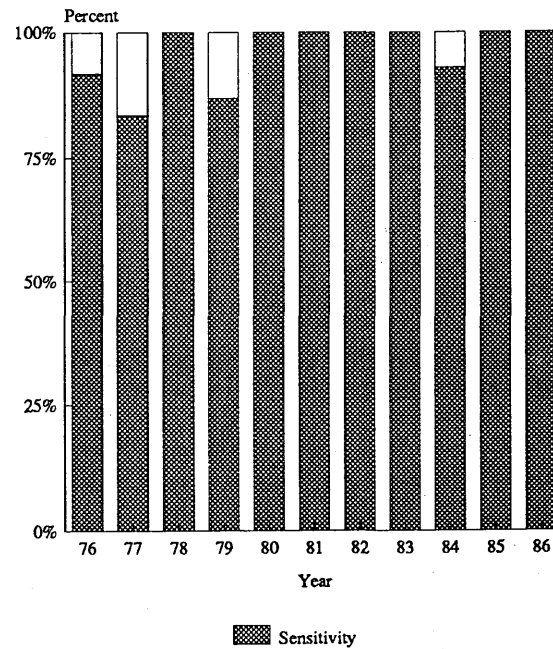


Figure 19. Anencephaly detected : sensitivity of screening (%) for each year 1976-86.

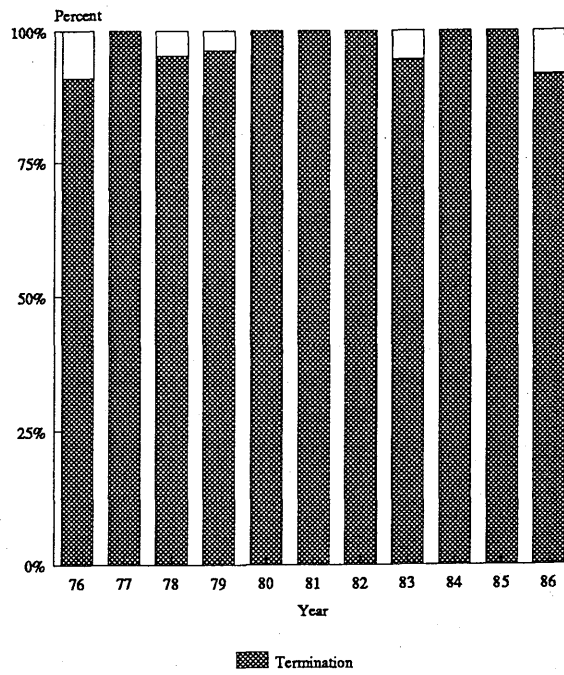


Figure 20. Anencephaly terminated : terminated when detected (%) for each year 1976-86.

There was a significant trend in the proportion screened (Z score = 6.45  $p < 0.05$ ).

The proportion of spina bifida pregnancies detected when screened also increased gradually over the period 1976-1986 (Table 24, Figure 21, 23). There was a significant upward trend in the proportion detected when screened (Z score = 4.16  $p < 0.05$ ).

The proportion terminated when screened and detected (Table 24, Figure 21, 24) also shows a significant upward trend over the period (Z score = 6.03  $p < 0.05$ ).

The trends in proportion screened, proportion detected, proportion terminated when detected, enable the trend in termination to be modelled. The expected proportions for these variables are multiplied together to produce the expected proportion terminated (Figure 17, 21). The fit of the expected number terminated is assessed by Pearson's goodness of fit Chi-Square statistic (Appendix 10 (ii)).

The results may be summarised as indicating a more consistent improvement over time in the effectiveness of screening for anencephaly than for spina bifida.

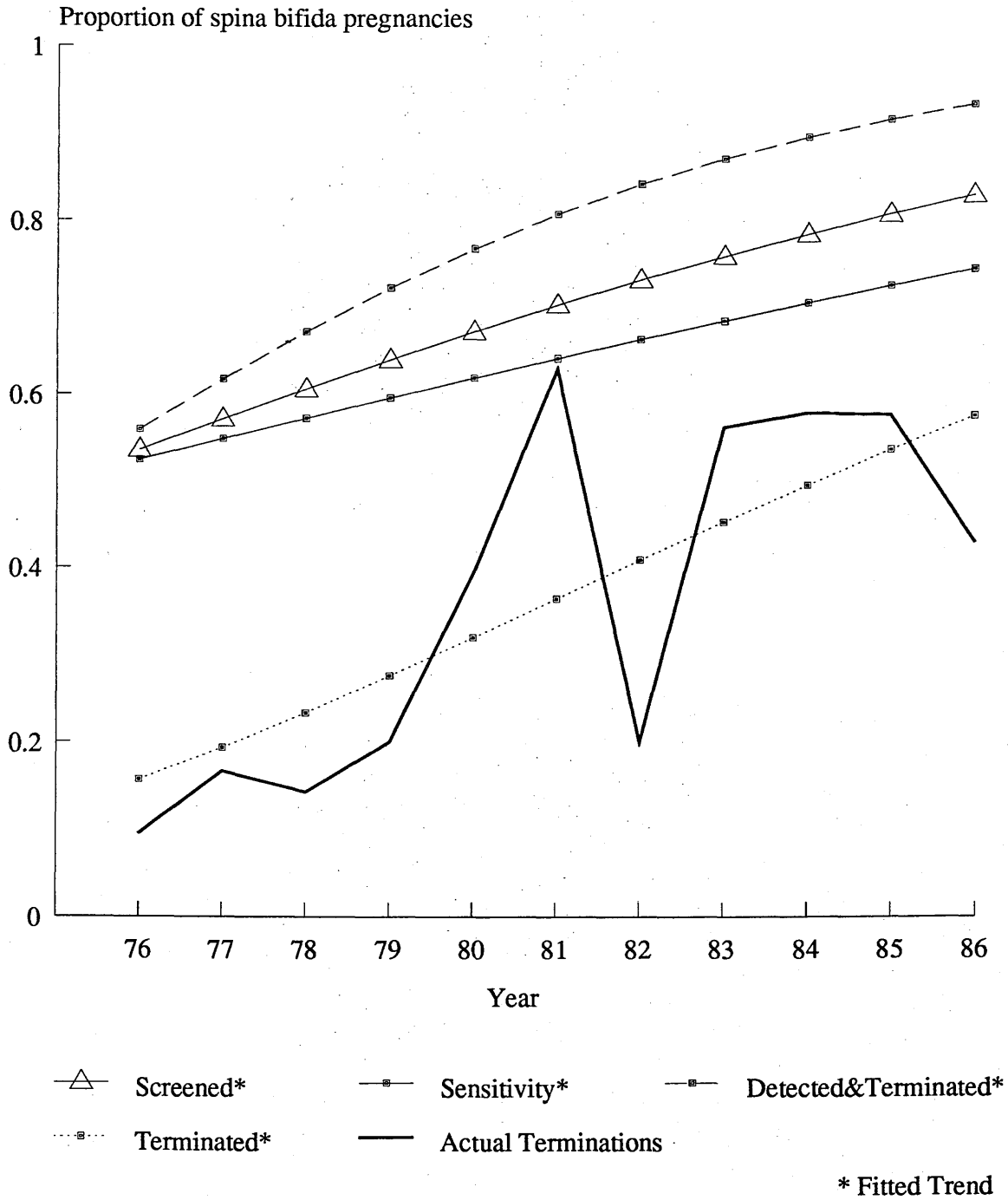


Figure 21. Screening and outcomes of screening for spina bifida : Glasgow 1976-86.

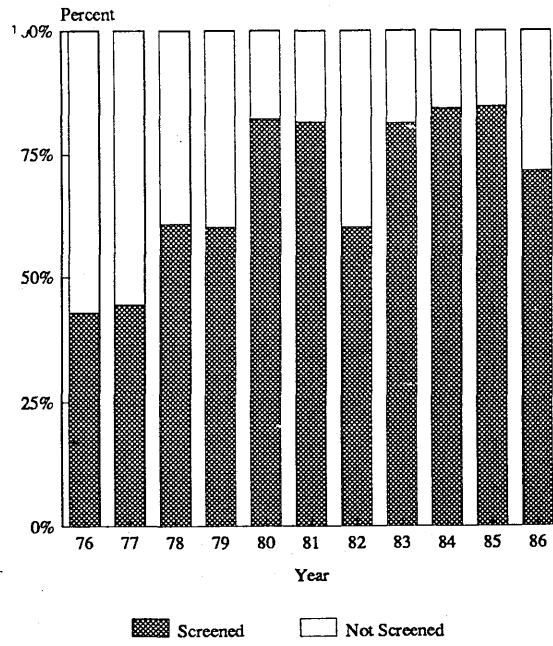


Figure 22. Spina bifida screening : proportion (%) screened in each year 1976-86.

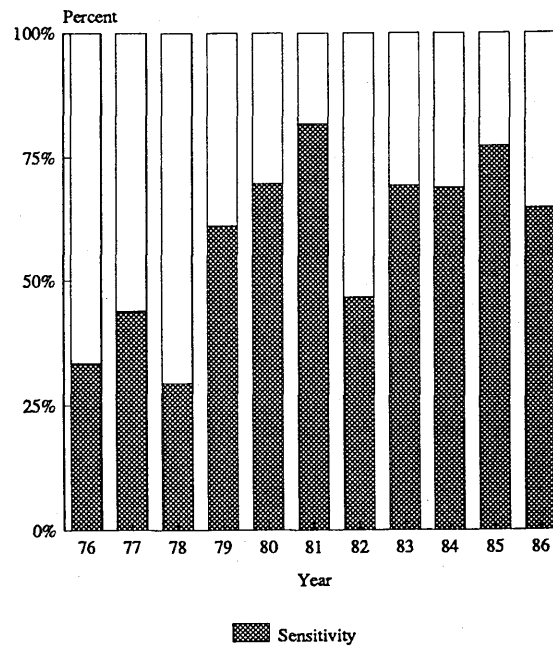


Figure 23. Spina bifida detected : sensitivity of screening (%) for each year 1976-86.

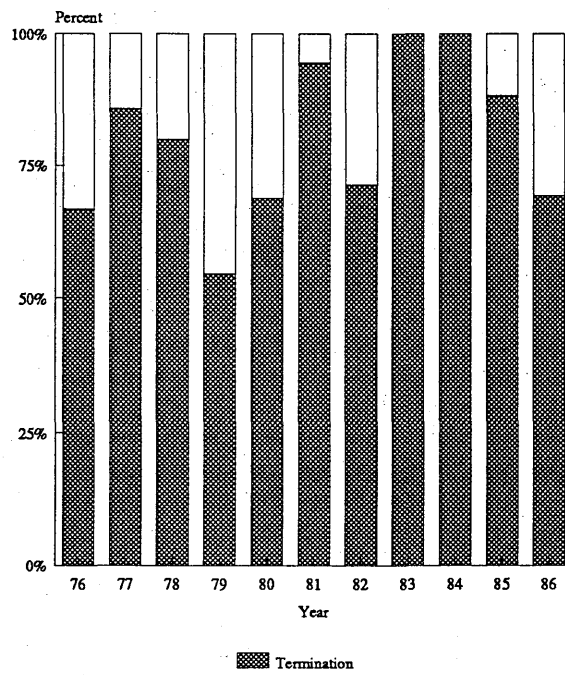


Figure 24. Spina bifida terminated : terminated when detected (%) for each year 1976-86.



### 6.3 EFFICIENCY OF SCREENING SERVICE

The acceptability of antenatal screening for neural tube defect was assessed indirectly by examining the proportions of pregnancies screened in the GGHB area, whether in hospitals or by general practitioners. 84.5% of total pregnancies were screened during 1982-1986.

There were 117,193 pregnancies in Glasgow during 1979-1986 with 359 ASB pregnancies; of these 297 ASB pregnancies were screened and 227 detected and terminated; 21 were detected and born and about 49 missed (Figure 25).

Only 62 ASB pregnancies (17%) were not screened; 24 declined screening; 28 booked too late and 10 were put under other reasons, which included those with no antenatal care or only minimal antenatal care, no record of antenatal screening on their case note, or concealed pregnancy.

Figure 25,a summarises the outcome of anencephaly pregnancies 1979-1986. 91.6% were screened, and of them 86.23% were detected and terminated. 2.39% were detected and born and only 2.99% missed by the screening technique. Only 8.38% were not screened, while 4.19% declined and 2.39% booked too late.

Figure 25,b summarises the outcome of spina bifida pregnancies during 1979-1986. 75% were screened but only 43.23% were detected and terminated. 23% were not detected. 25% were not

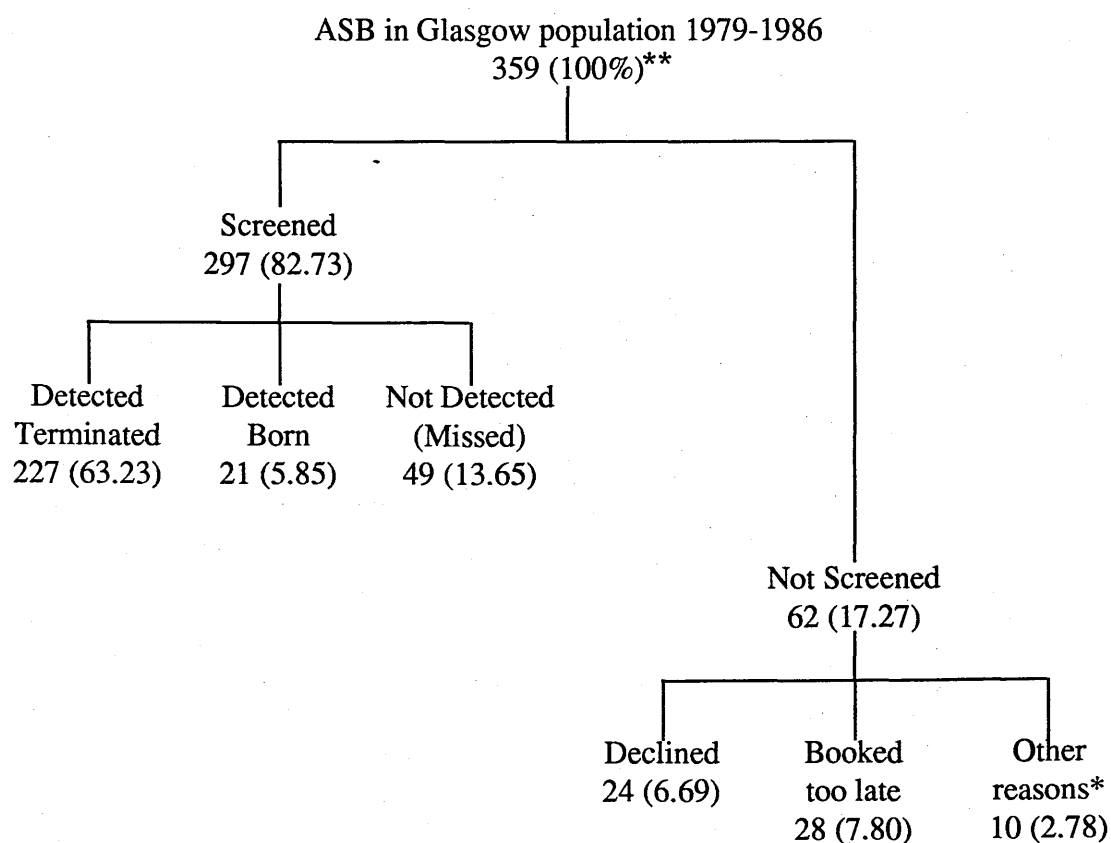


Figure 25. Outcomes of screened and not screened pregnancies with ASB.  
Glasgow 1979-1986.

\* no antenatal screening or minimal antenatal care  
no record of antenatal screening on the case note  
concealed pregnancy

\*\* numbers in brackets represent a percentage

screened. Of these 8.85% declined and 2.5% booked too late.

This contrasting pattern confirms the view that the screening process tends to favour the detection of anencephaly rather than spina bifida.

The frequencies of the variables of maternal age, parity and social class were compared in the screened and not screened ASB pregnancies 1979-1986. There were significant differences in the proportions of affected pregnancies screened and not screened in different age groups. The age-group least screened were those aged under 20, 34.2% were not screened ( $X^2 = 16.22$  (4dF)  $p < 0.01$ ) (Table 27).

There was a variation in different parity groups in the proportions of affected pregnancies screened and not screened, but this is not statistically significant ( $X^2 = 9.5$  (4dF)  $p > 0.05$ ) (Table 28).

There was a high proportion of these NTD pregnancies not screened in lower social classes: about 23.2% in social class IV and 25.78% in social class V (Table 29) compared with 6.3% and 13.6% in social classes I and II respectively. There is a trend in social class (not screened) with a significant increase in proportions not screened in lower social classes.

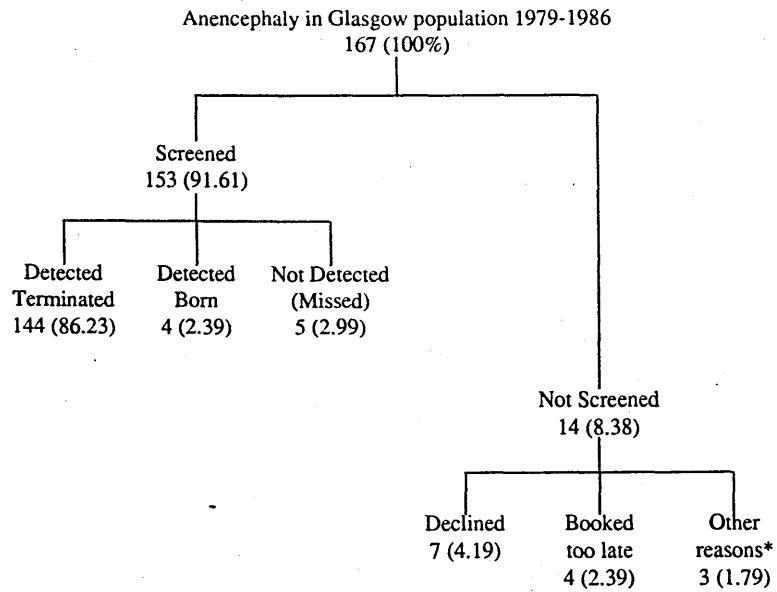


Figure 25a. Outcomes of screened and not screened pregnancies with Anencephaly. Glasgow 1979-1986.

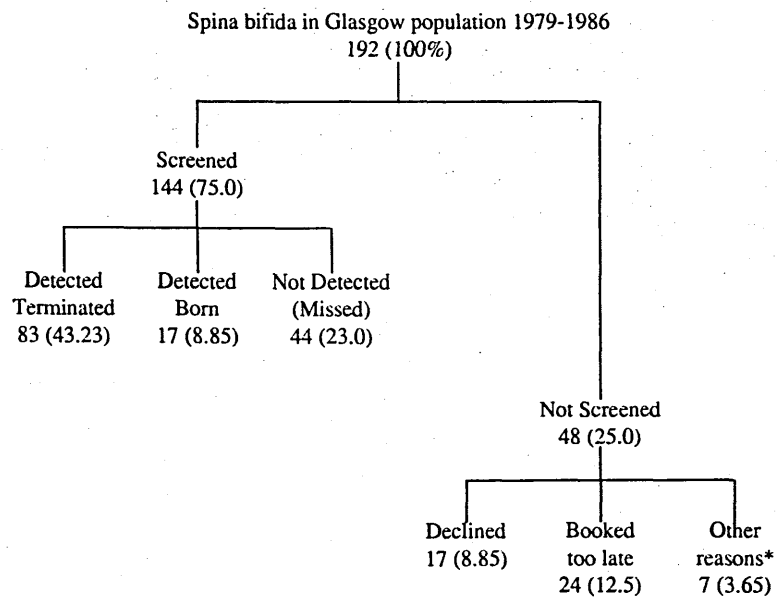


Figure 25b. Outcomes of screened and not screened pregnancies with Spina bifida. Glasgow 1979-1986.

\* no antenatal screening or minimal antenatal care  
no record of antenatal screening on the case note  
concealed pregnancy

#### 6.4 EFFICIENCY OF THE SCREENING PROCEDURE

Table 30 shows the proportions of those terminated upon detection and then diagnosed by specific methods. (Ms AFP/ultra - means detected by maternal serum AFP and diagnosed by ultrasound.) 67.06% of anencephaly cases were detected and diagnosed by ultrasound during 1982-1986; this is highly significant ( $\chi^2 = 42.6$  (1dF)  $p < 0.001$ ) when compared with 1981-1982, while in the case of spina bifida the use of ultrasound for detection and diagnosis of spina bifida accounted for only 8.2% which is not significant ( $\chi^2 = 2.2$  (1dF)  $p > 0.1$ ).

A high proportion, 48.98%, of spina bifida pregnancies were detected by Ms AFP and diagnosed by AmAFP compared with only 3.53% of anencephaly during the same period 1982-1986. Those spina bifida pregnancies detected by MsAFP and diagnosed by ultrasound and AmAFP was 26.53% during 1982-1986 compared with 26.09% during 1976-1981; despite a growing use of ultrasound as a diagnostic procedure, AFP remained an important case finding method.

In the case of anencephaly, 4.71% detected by MsAFP and diagnosed by Uls and AmAFP during 1982-1986 compared with 45.19% during 1976-1986.

The sensitivity for anencephaly in Glasgow during 1982-1986 was 96.7% (Table 31) compared to 93.9% during 1976-1986.

The sensitivity for spina bifida was 67.9% during 1982-1986 compared to 58.1% during 1976-1981.

For ASB the sensitivity was 83.14% (Table 31).

(Table 32) The proportion of anencephalic pregnancies detected and terminated as a consequence of antenatal screening techniques during 1982-1986 for anencephaly was 93.4%. This was significantly higher than the 65.4% in that category in 1976-1981 ( $X^2 = 24.18$  (1dF)  $p < 0.001$ ). For spina bifida the proportions were 45.8% which is also significant in comparison with only 27% during 1976-1981 ( $X^2 = 9.8$  (1dF)  $p < 0.005$ ). For both together it was 67.68% which is highly significant ( $X^2 = 23.7$  (1dF)  $p < 0.001$ ).

The specificity of the screening process for anencephaly (Table 33) and spina bifida (Table 34) was 100% during 1982-1986. There were no false-positive terminations for either anencephaly and spina bifida.

The specificity refers to the performance of the screening programme in the total pregnant population, in contrast with the performance of the laboratory assay or other individual elements within the screening process.

However the detailed analysis of screening process shown in Figures 26,27 enable the reader to examine the sensitivity and specificity of the individual screening steps.

Analysis of the various steps involved in MsAFP and ultrasound screening in Glasgow is presented for 1986 in Figure 26. The salient points are as follow:

The proportion of women offered antenatal screening for ASB represented 77.4% of all pregnancies.

709 (6.2% of women initially tested) had MsAFP levels above the intervention level which is 95th centile 2.0 (MOM).

In 251 (35.4%) of those (with high first blood sample) the result was explained by the use of ultrasound. 152 pregnant women with high first blood sample had normal results on repeat testing.

Four pregnancies with Spina bifida were missed by the initial MsAFP testing despite screening.

281 pregnant women had two elevated MsAFP results follow-up procedures involved first detailed ultrasound scanning in which one Anencephalic and five Spina bifida were diagnosed resulting in a total of 24 cases of ASB diagnosed by ultrasound.

Four pregnancies with sequential MsAFP above the intervention point refused amniocentesis and did not accept abortion, two of them led to anencephaly births and two to Spina bifida.

195 of 202 women offered amniocentesis had normal results. Seven Spina bifida pregnancies were diagnosed, resulting in a total of





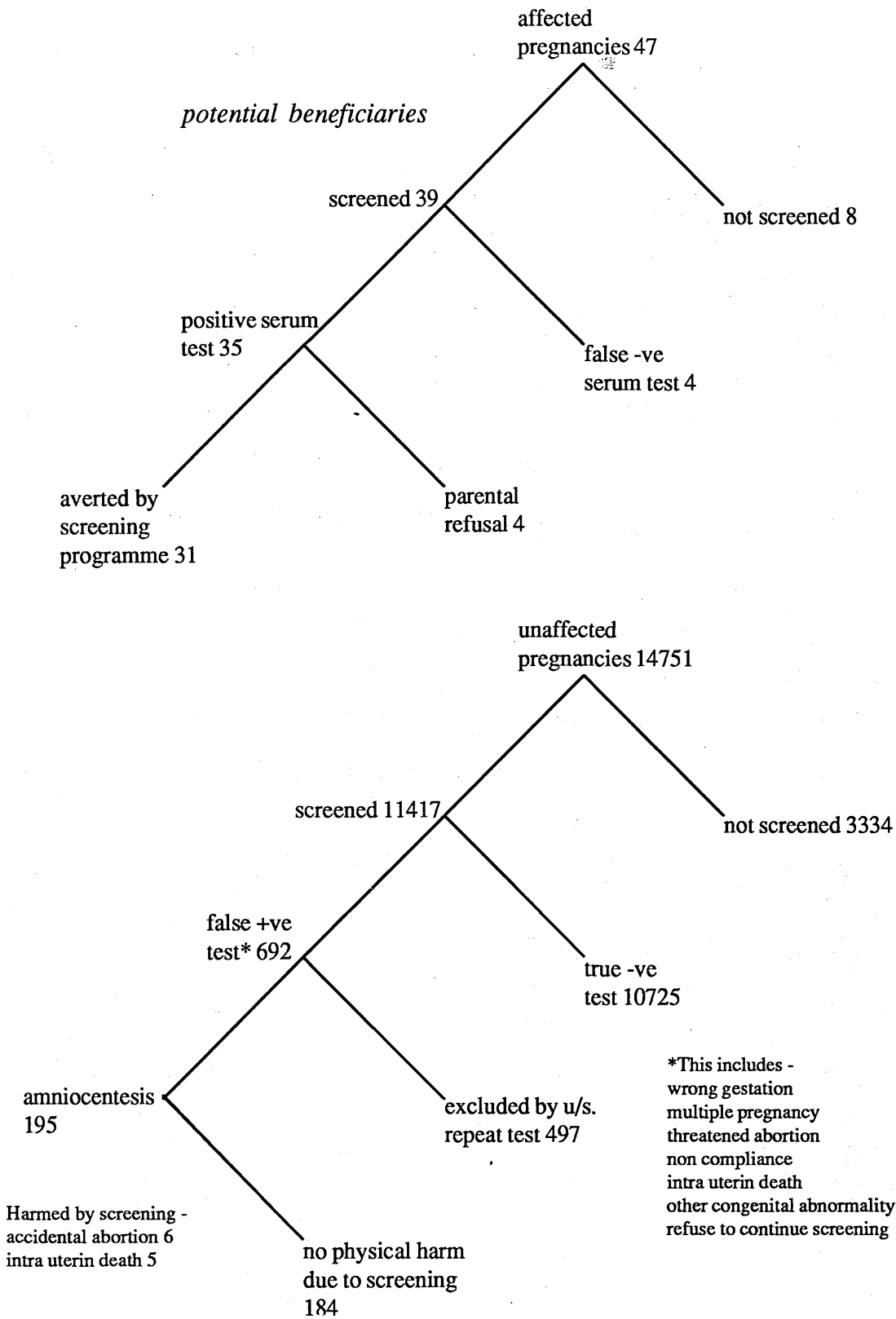


Figure 27. Extent of benefit of screening for ASB and physical harm from screening to unaffected pregnancies. 1986.

Adapted from Chamberlain, J. 1978.

SUMMARY OF THE RESULTS

1 - What is the epidemiology and the natural history of the conditions?

- What is the prevalence of anencephaly and spina bifida in the study of the population?

The birth prevalence during 1976-1986 for anencephaly was 0.43 per 1000 total births. The birth prevalence for spina bifida was 1.26 per 1000 total births during the same period.

There was a marked decline in birth prevalence for anencephaly and spina bifida which was statistically significant (Table 4,5; Figure 9,10).

- Are there any significant secular trends, and what are their implications for screening?

There was a downward secular trend in both birth and pregnancy prevalence of anencephaly and spina bifida (Table 9,10; Figure 11,12).

- What is the natural history of anencephaly and spina bifida and how is it affected by screening?

For anencephaly a high proportion (93%) of fetuses were terminated during 1982-1986, while a low proportion (1.1%) were

stillbirths over the same period (Table 11). The perinatal and neonatal mortality was 100% (Table 15).

For spina bifida during 1982-1986 was under 50% affected fetuses terminated, while a low proportion (5.6%) were still births in comparison with 12.9% for 1976-1981 (Table 12).

The proportion of affected pregnancies surviving more than one year after birth was higher during 1976-1981 than 1982-1986 but this is not significant (Table 13).

If we follow the survival from birth, a higher proportion survive more than one year in 1982-1986 compared to 1976-1981. This is not a significant difference either (Table 14).

Perinatal, neonatal and infant mortality during 1976-1981 was lower than during 1981-1986, but this is not significant (Table 16).

2 - What is the effectiveness of screening?

- What is the impact of screening on the birth prevalence?

Have birth and pregnancy prevalence diverged over time?

The difference between the pregnancy prevalence and birth prevalence (which is equal to the proportion terminated) represents the impact of antenatal screening.

75.6% of anencephaly were terminated during 1976-1986, but only 35.02% of spina bifida terminated during the same period. There was a significant downward trend in both birth and pregnancy prevalence during 1976-1986 in anencephaly, but a significant trend found for spina bifida birth only. (Table 17,18; Figure 15,16).

There were significant increasing trends in affected pregnancies with regard to the proportion screened, proportion detected and proportion terminated when detected during 1976-1986 for both anencephaly and spina bifida (Table 23, 24; Figure 17,21).

3 - What is the efficiency of screening?

- How successfully was screening delivered to the target population?

84.5% of all pregnancies were screened during 1982-1986 when total birth was used as the denominator, a figure which dropped to 75% when total pregnancies (live + still + termination) are used as the denominator during the same period (1982-1986)

- What are the technical and organisational obstacles to efficiency?

For the period 1979-1986, 82.75% of ASB pregnancies were screened. Of these, 63% were detected and terminated, 5.85% detected and born and 13.65% were missed by the technique. 17.27% of ASB were not screened (Figure 25).

91% of anencephaly were screened and only 8.38% were not screened.

In the case of spina bifida, 75% were screened and 25% were not screened (Figure 25 a, b).

A high proportion (76.1%) of anencephaly was detected and diagnosed by ultrasound during 1982-1986 in comparison with only 8.2% of spina bifida during the same period (Table 30).

- What is the sensitivity and specificity of screening?

The sensitivity for anencephaly was 97.6% while the specificity was 100% during 1982-1986 (Table 31,33).

For spina bifida the sensitivity was 67.9% with a specificity of 100% during 1982-1986 (Table 31, 34).

While the sensitivity and specificity of the assay can be calculated from figure 27.

**Table 1. Annual Changes in Births, Deaths, and Migration (1971-1986)  
Greater Glasgow Health Board**

Year	Estimated Home Population	Changes Affecting Population					
		Population Change	Births	Deaths	Natural Increase	Net Migration	Other Changes
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	-14.9	12.8	14.8	-1.9	-13.2	+0.2
1979	1,022.1	-11.0	13.3	14.0	-0.7	-10.2	-0.1
1980	1,012.0	-10.2	13.4	13.7	-0.3	-13.9	+4.0
1981	1,007.3	-11.0	12.9	14.2	-1.2	-9.8	0.0
1982	996.3	-11.2	12.8	13.5	-0.7	-10.5	0.0
1983	985.1	-6.1	12.4	13.4	-0.9	-5.1	0.0
1984	979.1	-10.3	12.9	13.1	-0.2	-10.1	0.0
1985	968.8	-9.0	13.1	13.4	-0.3	-8.6	0.0
1986	959.8	-8.6	12.9	12.7	0.2	-8.8	0.0

Source: Annual Reports of the Registrar General for Scotland. (1981, 1987)  
Edinburgh.

**Table 2. Percentage Distribution of the Populations of Greater  
Glasgow Health Board,  
Scotland and England by the Registrar General's Social Classes (1981)**

Social Class	G.G.H.B.	Scotland	England
I	5.8	5.6	6.0
II	20.0	22.4	25.9
III N	13.7	12.9	14.1
III M	34.2	34.4	32.5
IV	17.5	18.1	16.3
V	8.8	6.7	5.2

Sources:

Census 1981 Scotland Report for Strathclyde Region  
vol. 2 table 49.

Census 1981 National Report for Great Britain  
vol. 2 table 49.

**Table 3. Infant, Neonatal, Perinatal Mortality and Still Births  
Greater Glasgow Health Board Area and Scotland (1981-1986)**

Years	Scotland				G.G.H.B.			
	Infant* Mortality	Neonatal* Mortality	Perinatal** Mortality	Still** Births	Infant* Mortality	Neonatal* Mortality	Perinatal** Mortality	Still** Births
1976	15	10	18	10	17	11	20	10
1977	16	11	18	9	18	12	20	9
1978	13	9	15	18	14	8	16	10
1979	13	9	14	7	13	9	13	6
1980	12	8	13	7	13	9	14	7
1981	11	7	12	6	12	7	12	7
1982	11	7	12	6	11	6	11	6
1983	10	6	11	6	9	5	9	5
1984	10	6	11	6	9	5	10	6
1985	9	5	10	5	9	5	10	7
1986	9	5	10	6	8	4	9	6

Source: Annual Report of the General Registrar for Scotland (1981-1986).

\* Per 1000 live births.

\*\* Per 1000 total births.



**Table 4. Birth Prevalence of Anencephaly in Glasgow 1976-1986**

Year	Total Births (Live + still)	Anencephaly Births	Anencephaly Birth Prevalence*	95% C.I.**
1976	12889	17	1.32	0.77 - 2.11
1977	12487	11	0.88	0.44 - 1.58
1978	12491	10	0.80	0.38 - 1.47
1979	13339	9	0.67	0.31 - 1.28
1980	13438	5	0.37	0.12 - 0.87
1981	13491	3	0.22	0.05 - 0.65
1982	12884	0	0.00	0.00 - 0.29
1983	12661	1	0.08	0.00 - 0.44
1984	12783	1	0.08	0.00 - 0.44
1985	13089	0	0.00	0.00 - 0.28
1986	13013	4	0.31	0.08 - 0.79
<b>Total</b>	<b>142565</b>	<b>61</b>	<b>0.43</b>	<b>0.33 - 0.55</b>

\* Prevalence is expressed as rate per 1000 total births.

\*\* Confidence interval.

Table 5. Birth Prevalence of Spina Bifida in Glasgow 1976-1986

Year	Total Births (Live + still)	Spina Bifida Births	Spina Bifida Birth Prevalence*	95% C.I.**
1976	12889	19	1.47	0.82 - 2.30
1977	12487	30	2.40	1.62 - 3.43
1978	12491	24	1.92	1.23 - 2.86
1979	13339	24	1.80	1.15 - 2.68
1980	13438	17	1.27	0.74 - 2.03
1981	13491	8	0.59	0.26 - 1.17
1982	12884	20	1.55	0.95 - 2.40
1983	12661	7	0.55	0.22 - 1.14
1984	12783	8	0.63	0.27 - 1.23
1985	13089	11	0.84	0.45 - 1.63
1986	13013	12	0.92	0.48 - 1.61
Total	142565	180	1.26	1.09 - 1.46

\* Prevalence is expressed as rate per 1000 total births.

\*\* Confidence interval.

**Table 6. Birth Prevalence of Anencephaly and Spina Bifida Combined  
in Glasgow 1976-1986**

Year	Total Births (Live + still)	A.S.B. Births	A.S.B. Birth Prevalence*	95% C.I.**
1976	12889	36	2.79	2.03 - 3.85
1977	12487	41	3.28	2.43 - 4.44
1978	12491	34	2.72	1.96 - 3.79
1979	13339	33	2.47	1.77 - 3.46
1980	13438	22	1.64	1.03 - 2.48
1981	13491	11	0.81	0.41 - 1.46
1982	12884	20	1.55	0.95 - 2.40
1983	12661	8	0.63	0.27 - 1.24
1984	12783	9	0.71	0.32 - 1.34
1985	13089	11	0.84	0.42 - 1.50
1986	13013	16	1.23	0.70 - 2.00
<b>Total</b>	<b>142565</b>	<b>241</b>	<b>1.69</b>	<b>1.49 - 1.92</b>

\* Prevalence is expressed as rate per 1000 total births.

\*\* Confidence interval.

**Table 7. Prevalence of Anencephaly and Spina Bifida Births:  
Glasgow, 1976-1981 and 1982-1986**

Year Grouping	Total Births (Live + Still)	Anencephaly Births		Spina Bifida Births		A.S.B. Births	
		No.	Rate	No.	Rate	No.	Rate
1976-1981	78135	55	0.70	122	1.56	177	2.26
1982-1986	64430	6	0.09	58	0.90	64	0.99
1976-1986	142565	61	0.43	180	1.26	241	1.69
		$\chi^2 = 30.8$ (1df)		$\chi^2 = 12.2$ (1df)		$\chi^2 = 33.9$ (1df)	
		P < 0.05		P < 0.05		P < 0.05	

**Table 8. Prevalence of Anencephaly and Spina Bifida Pregnancies:  
Glasgow, 1976-1981 and 1982-1986**

Year Grouping	Total Births (Live + Still)	Anencephaly Pregnancies		Spina Bifida Pregnancies		A.S.B. Pregnancies	
		No.	Rate	No.	Rate	No.	Rate
1976-1981	78135	159	2.03	170	2.18	329	4.21
1982-1986	64430	91	1.41	107	1.66	198	3.07
1976-1986	142565	250	1.75	277	1.94	527	3.69
		$\chi^2 = 7.82$ (1df)		$\chi^2 = 4.83$ (1df)		$\chi^2 = 12.4$ (1df)	
		P < 0.05		P < 0.05		P < 0.001	

**Table 9. Secular Change in Birth Prevalence of Anencephaly and Spina Bifida:  
Glasgow, 1964-1968; 1972-1978; 1979-1986**

Year Grouping	Total Births (Live + Still)	Anencephaly Births		Spina Bifida Births		A.S.B. Births	
		No.	Rate	No.	Rate	No.	Rate
1964-1968*	103,123	292	2.83	289	2.80	581	5.63
1972-1978**	92,325	168	1.82	242	2.62	410	4.44
1979-1986***	104,698	23	0.22	107	1.02	130	1.24

Anencephaly Births (1972-1978)/(1964-1968)  $\chi^2 = 21.2$  (1df)  $P < 0.001$   
 (1979-1986)/(1972-1978)  $\chi^2 = 129.7$  (1df)  $P < 0.001$

Spina Bifida Births (1972-1978)/(1964-1968)  $\chi^2 = 0.6$  (1df)  $P > 0.05$  (N.S.)  
 (1979-1986)/(1972-1978)  $\chi^2 = 71.0$  (1df)  $P < 0.001$

Anencephaly and Spina Bifida Births (1972-1978)/(1964-1968)  $\chi^2 = 13.7$  (1df)  $P < 0.001$   
 (1979-1986)/(1972-1978)  $\chi^2 = 183.7$  (1df)  $P < 0.001$

\* Wilson, T.S. (1970).

\*\* Stone, D.H. (1981).

\*\*\* Present study. (1979-1986) chosen so as not to overlap with Stone (1981).

**Table 10. Secular Change in Pregnancy Prevalence of Anencephaly and Spina Bifida:  
Glasgow, 1964-1968; 1972-1978; 1979-1986**

Year Grouping	Total Births (Live + Still)	Anencephaly pregnancies		Spina Bifida Pregnancies		A.S.B. Pregnancies	
		No.	Rate	No.	Rate	No.	Rate
1964-1968*	103,123	292	2.83	289	2.80	581	5.63
1972-1978**	92,325	227	2.46	255	2.76	482	5.22
1979-1986***	104,698	167	1.59	192	1.83	359	3.43

Anencephaly Pregn. (1972-1978)/(1964-1968)  $\chi^2 = 2.56$  (1df)  $P > 0.05$  (N.S.)  
 (1979-1986)/(1972-1978)  $\chi^2 = 18.3$  (1df)  $P < 0.05$

Spina Bifida Pregn. (1972-1978)/(1964-1968)  $\chi^2 = 0.03$  (1df)  $P > 0.05$  (N.S.)  
 (1979-1986)/(1972-1978)  $\chi^2 = 18.7$  (1df)  $P < 0.05$

Anencephaly and Spina Bifida Pregn. (1972-1978)/(1964-1968)  $\chi^2 = 1.54$  (1df)  $P < 0.05$  (N.S.)  
 (1979-1986)/(1972-1978)  $\chi^2 = 37.1$  (1df)  $P < 0.05$

\* Wilson, T.S. (1970).

\*\* Stone, D.H. (1981).

\*\*\* Present study. (1979-1986) chosen so as not to overlap with Stone (1981).

**Table 11. Outcome of Anencephaly Pregnancies  
Glasgow: 1976-1981 and 1982-1986**

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Induced	104	65.41	85	93.41
Abortions	$\chi^2 = 24.6$ (1df) $P < 0.001$			
Still	45	28.30	1	1.10
Births	$\chi^2 = 28.5$ (1df) $P < 0.001$			
1st Week	10	6.29	5	5.49
Death	$\chi^2 = 0.06$ (1df) $P > 0.05$			
Total	159		91	

There were no spontaneous abortions or death after 7 days in either periods.

**Table 12. Outcome of Spina Bifida Pregnancies \***  
**Glasgow: 1976-1981; 1982-1986**

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Spontaneous Abortions	2	1.18	2	1.87
Induced Abortions	46	27.06	47	43.92
	$\chi^2 = 8.4$ (1df) $P < 0.01$			
Still Births	22	12.94	6	5.61
Live Births	100	58.82	52	48.60
	$\chi^2 = 2.8$ (1df) $P > 0.05$			
Total Pregnancies	170	100	107	100

\* Proportions surviving to live birth (%)



**Table 13. Outcome of Spina Bifida Pregnancies \***  
**Glasgow: 1976-1981; 1982-1986**

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Spontaneous Abortions	2	1.18	2	1.87
Induced Abortions	46	27.06	47	43.92
	$\chi^2 = 8.4$ (1df) $P < 0.01$			
Still Births	22	12.94	6	5.61
	$\chi^2 = 3.9$ (1df) $P < 0.05$			
1st Week Death	15	8.82	4	3.74
	$\chi^2 = 2.7$ (1df) $P > 0.05$			
1st Month Death	13	7.65	7	6.54
1st Year Death	14	8.23	6	5.61
Survival > One Year	58	34.12	35	32.71
	$\chi^2 = 0.05$ (1df) $P > 0.06$			
Total Pregnancies	170	100	107	100

\* Proportions surviving to one year (%)

**Table 14. Outcome of Spina Bifida Births \***  
**Glasgow: 1976-1981; 1982-1986**

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Still Births	22	18.03	6	10.34
	$\chi^2 = 1.7$ (1df) $P > 0.05$			
1st Week Death	15	12.29	4	6.90
1st Month Death	13	10.66	7	12.07
1st Year Death	14	11.48	6	10.34
Survival	58	47.54	35	60.35
> One Year	$\chi^2 = 2.6$ (1df) $P > 0.05$			
Total births	122	100	58	100

\* Percentage distribution of deaths and survival

**Table 15. Births, Perinatal, Neonatal and Infant Mortality associated with Anencephaly: Glasgow, 1976-1981 and 1982-1986**

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Live Births	10		5	
Still Births-	45		1	
Perinatal Mortality* Still Births + 1st Week Death	55	100.0	6	100.0
Neonatal Mortality** Death 1-28 Days Old	10	100.0	5	100.0
Infant Mortality** Death < One Year Old	0	0	0	0

\* Proportions out of Live Births and Still Births.

\*\* Proportions out of Live Births.

**Table 16. Births, Perinatal, Neonatal and Infant Mortality associated with Spina Bifida: Glasgow, 1976-1981 and 1982-1986**

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Live Births	100		52	
Still Births	22		6	
Perinatal Mortality* Still Births + 1st Week Death	37	30.33	10	19.23
	$\chi^2 = 3.5$ (1df) $P > 0.05$			
Neonatal Mortality** Death 1-28 Days Old	28	28.00	11	21.15
	$\chi^2 = 0.84$ (1df) $P > 0.05$			
Infant Mortality** Death < 1 yr	42	42.00	17	32.69
	$\chi^2 = 1.25$ (1df) $P > 0.05$			

The data in the above table can also be presented as

Years Grouping	1976-1981		1982-1986	
	No.	%	No.	%
Live Births	100		52	
Still Births	22		6	
Perinatal Mortality*	37	30.33	10	19.23
Early Neonatal Mortality**	15	15.00	4	7.69
Late Neonatal Mortality**	13	13.00	7	13.46
Post Neonatal Mortality**	14	14.00	6	11.54

\* Proportions out of Live Births and Still Births.

\*\* Proportions out of Live Births.

**Table 17. Anencephaly: Annual Rates of Pregnancy and Birth Prevalence and percentage of affected pregnancies terminated: Glasgow 1976-1986**

Year	Total Births (Live + still)	Total Anencephaly	Anencephaly Births	Anencephaly Pregnancy Prevalence	Anencephaly Birth Prevalence	% Anencephaly Termination
1976	12889	27	17	2.09	1.32	37.04
1977	12487	26	11	2.08	0.88	57.69
1978	12491	30	10	2.40	0.80	66.67
1979	13339	34	9	2.55	0.67	73.53
1980	13438	20	5	1.49	0.37	75.00
1981	13491	22	3	1.63	0.22	86.36
1982	12884	22	0	1.71	0.00	100.00
1983	12661	18	1	1.42	0.08	94.44
1984	12783	14	1	1.10	0.08	92.86
1985	13089	11	0	0.84	0.00	100.00
1986	13013	26	4	2.00	0.31	84.62
<b>Total</b>	<b>142565</b>	<b>250</b>	<b>61</b>	<b>1.75</b>	<b>0.43</b>	<b>75.60</b>

(Prevalence is expressed as rate per 1000 total births.)

Trend in Pregnancy Prevalence  $\chi^2 = 8.68$  (1df)  $P < 0.005$

Trend in Birth Prevalence  $\chi^2 = 44.42$  (1df)  $P < 0.0005$

**Table 18. Spina Bifida Annual Rates of Pregnancy and Birth Prevalence and percentage of affected pregnancies terminated: Glasgow 1976-1986**

Year	Total Births (Live + still)	Total Spina Bifida	Spina Bifida Births	Spina Bifida Pregnancy Prevalence	Spina Bifida Birth Prevalence	% Spina Bifida Termination
1976	12889	21	19	1.63	1.47	9.52
1977	12487	36	30	2.88	2.40	16.67
1978	12491	28	24	2.24	1.92	14.29
1979	13339	30	24	2.25	1.80	20.00
1980	13438	28	17	2.08	1.27	39.29
1981	13491	27	8	2.00	0.59	70.37
1982	12884	25	20	1.94	1.55	20.00
1983	12661	16	7	1.26	0.55	56.25
1984	12783	19	8	1.49	0.63	57.89
1985	13089	26	11	1.99	0.84	57.69
1986	13013	21	12	1.61	0.92	42.86
<b>Total</b>	<b>142565</b>	<b>277</b>	<b>180</b>	<b>1.94</b>	<b>1.26</b>	<b>35.02</b>

(Prevalence is expressed as rate per 1000 total births.)

Trend in Pregnancy Prevalence  $\chi^2 = 3.78$  (1df)  $P > 0.05$   
Trend in Birth Prevalence  $\chi^2 = 20.9$  (1df)  $P < 0.0005$

**Table 19. Anencephaly: Terminations, Births and Pregnancies:  
Glasgow, 1976-1981; 1982-1986**

Years Grouping	Anencephaly Terminations		Anencephaly Births		Anencephaly Pregnancies	
	No.	%	No.	%	No.	%
1976-1981	104	65.4	55	34.6	159	100
1982-1986	85	93.4	6	6.6	91	100
1976-1986	189	75.6	61	24.4	250	100

$$\chi^2 = 24.6 \text{ (1df) } P < 0.0005$$

**Table 20. Spina Bifida: Terminations, Births and Pregnancies:  
Glasgow, 1976-1981; 1982-1986**

Years Grouping	Spina Bifida Terminations		Spina Bifida Births		Spina Bifida Pregnancies	
	No.	%	No.	%	No.	%
1976-1981	48	28.2	122	71.8	170	100
1982-1986	49	45.8	58	54.2	107	100
1976-1986	97	35.02	180	64.98	277	100

$$\chi^2 = 8.9 \text{ (1df) } P < 0.005$$

**Table 21. Anencephaly: Distribution of Pregnancies Screened and not Screened:  
Glasgow, 1976-1981; 1982-1986**

Years Grouping	Anencephaly				Total
	Screened		Not Screened		
	No.	%	No.	%	
1976-1981	115	72.33	44	27.67	159
1982-1986	89	97.80	2	2.20	91

$$\chi^2 = 25.0 \text{ (1df) } P < 0.0005$$

**Table 22. Spina Bifida: Distribution of Pregnancies Screened and not Screened:  
Glasgow, 1976-1981; 1982-1986**

Years Grouping	Spina Bifida				Total
	Screened		Not Screened		
	No.	%	No.	%	
1976-1981	105	61.76	65	38.24	170
1982-1986	81	75.70	26	24.30	107

$$\chi^2 = 5.8 \text{ (1df) } P < 0.025$$



**Table 23. Anencephaly: affected pregnancies screened;  
detected and detected and terminated:  
Glasgow, 1976-1986**

Year	Affected Pregnancies*		Affected Pregnancies**		Affected Pregnancies***	
	No	%	No	%	No	%
1976	12	44.4	11	91.6	10	90.9
1977	18	69.2	15	83.3	15	100.0
1978	21	70.0	21	100.0	20	95.2
1979	30	88.2	26	86.6	25	96.2
1980	15	75.0	15	100.0	15	100.0
1981	19	86.4	19	100.0	19	100.0
1982	22	100.0	22	100.0	22	100.0
1983	18	100.0	18	100.0	17	100.0
1984	14	100.0	13	92.9	13	100.0
1985	11	100.0	11	100.0	11	100.0
1986	24	92.3	24	100.0	22	91.6
Total	204	81.6	195	95.6	189	96.9
	Z-score = 8.5 P < 0.0001		$\chi^2 = 6.61$ (1df) P < 0.025		$\chi^2 = 0.042$ (1df) P > 0.8	

\* Proportion out of total Anencephaly pregnancies.

\*\* Proportion out of the total screened.

\*\*\* Proportion out of Anencephaly pregnancies screened and detected (sensitivity).

**Table 24. Spina Bifida: affected pregnancies screened;  
detected and detected and terminated:  
Glasgow, 1976-1986**

Year	Affected Pregnancies*		Affected Pregnancies**		Affected Pregnancies***	
	Screened		Detected (Sensitivity)		Detected and Terminated	
	No	%	No	%	No	%
1976	9	42.8	3	33.3	2	66.7
1977	16	44.4	7	43.8	6	85.7
1978	17	60.7	5	29.4	4	80.0
1979	18	60.0	11	61.1	6	54.6
1980	23	82.1	16	69.5	11	68.8
1981	22	81.5	18	81.8	17	94.4
1982	15	60.0	7	46.6	5	71.4
1983	13	81.3	9	69.2	9	100.0
1984	16	84.2	11	68.8	11	100.0
1985	22	84.6	17	77.3	15	88.2
1986	15	71.4	11	73.3	9	81.8
Total	186	67.1	115	61.8	95	82.6
	Z-score = 6.45 P < 0.05		Z-score = 4.16 P < 0.05		Z-score = 6.03 P < 0.05	

\* Proportion out of total Spina bifida pregnancies

\*\* Proportion out of the total screened.

\*\*\* Proportion out of Anencephaly pregnancies screened and detected (sensitivity).

**Table 25. Pregnancies Screened as Proportion of Total Pregnancies  
Glasgow (1982-1986)**

Expected Year of Confinement	Total Pregnancies* Live + still + Term.	Pregnancies Screened**	
		No.	%
1982	14521	10751	74.0
1983	14117	10633	75.3
1984	14418	10435	72.4
1985	14766	11171	75.7
1986	14798	11456	77.4
1982-1986	72620	54446	75.0

\* Total births (live + still) + total terminations for all causes.

\*\* Pregnancies screened in G.G.H.B. hospitals and G.P.

**Table 26. Pregnancies Screened as Proportion of Total Births  
Glasgow (1982-1986)**

Expected Year of Confinement	Total Births (Live + still)	Pregnancies Screened**	
		No.	%
1982	12884	10751	83.4
1983	12661	10633	84.0
1984	12783	10435	81.6
1985	13089	11171	85.3
1986	13013	11456	88.0
1982-1986	64430	54446	84.5

\*\* Pregnancies screened in G.G.H.B. hospitals and G.P.

**Table 27. A.S.B. Pregnancies: Age Distribution (%) of Screened and not Screened Groups Glasgow (1979-1986)**

Age Group	Screened		Not Screened	
	No.	%	No.	%
<20	25	65.8	13	34.2
20-24	99	82.5	21	17.5
25-29	105	91.3	10	8.7
30-34	42	75.0	14	25.0
35-39	20	87.0	3	13.0
40+	6	85.7	1	14.3

Ages over 35 combined,  $\chi^2 = 16.22$  (4dF)  $P < 0.01$

**Table 28. A.S.B. Pregnancies: Parity Distribution (%) of Screened and not Screened Groups Glasgow (1979-1986)**

Parity Group	Screened		Not Screened	
	No.	%	No.	%
0	132	82.5	28	17.5
1	99	88.4	13	11.6
2	40	76.9	12	23.1
3	9	81.8	2	18.2
4	7	70.0	3	30.0
5+	4	50.0	4	50.0
Not Known	6	100		

para 4 and 5 combined, and excluding "not known",  
 $\chi^2 = 9.5$  (4dF)  $P > 0.05$  (N.S.)

**Table 29. A.S.B. Pregnancies: Social Class Distribution of Screened and not Screened Groups: Glasgow, 1979-1986**

Social Class	Screened		Not Screened	
	No.	%	No.	%
I	15	93.8	1	6.3
II	38	86.4	6	13.6
III	141	84.9	25	15.1
IV	43	76.8	13	23.2
V	49	74.2	17	25.8
Not Known	11	100.0		

$\chi^2 = 6.07$  (1df)  $P < 0.025$   
 (Social class I and II combined, not known excluded)

**Table 30. Methods of detection or diagnosis of Anencephaly and Spina Bifida terminations:  
Glasgow, 1976-1981; 1982-1986**

Methods of Det/Diag	Anencephaly				Spina Bifida			
	1976-1981		1982-1986		1976-1981		1982-1986	
	No	%	No	%	No	%	No	%
MS.AFP/Ultra	10	9.62	21	24.70	2	4.35	5	10.20
MS.AFP/Amnio	17	16.35	3	3.53	27	58.69	24	48.98
Ultra/Ultra	21	20.19	57	67.06*	0	0.00	4	8.16
Ultra/Amnio	2	1.92	0	0.00	0	0.00	0	0.00
Amnio/Amnio	7	6.73	0	0.00	5	10.87	3	6.13
MS.AFP/Ultra/Amnio	47	45.19	4	4.71	12	26.09	13	26.53
Total	104	100.00	85	100.00	46	100.00	49	100.0

\* Anencephaly Ultra/Ultra  $\chi^2 = 42.4$  (1df)  $P < 0.001$

**Table 31. Sensitivity of Antenatal Screening for Anencephaly and Spina Bifida:  
Glasgow, 1976-1981; 1982-1986**

Years Grouping	Anencephaly		Spina Bifida		A.S.B.	
	1976-1981	1982-1986	1976-1981	1982-1986	1976-1981	1982-1986
No of True Positives	108	88	61	55	169	143
No of False Negatives	7	3	44	26	51	29
Sensitivity (%)	93.9	96.70	58.09	67.90	76.82	83.14

**Table 32. Efficacy of Antenatal Screening for Anencephaly and Spina Bifida:  
Glasgow, 1976-1981; 1982-1986**

Years Grouping	Anencephaly		Spina Bifida		A.S.B.	
	1976-1981	1982-1986	1976-1981	1982-1986	1976-1981	1982-1986
Total No of Pregnancies Affected	159	91	170	107	329	198
No of detected and Terminated	104	85	46	49	150	134
Efficacy of the Screening %	65.41	93.41	27.06	45.79	45.59	67.68

Anencephaly Efficacy of the Screening  $\chi^2 = 24.18$  (1df)  $P < 001$

Spina Bifida Efficacy of the Screening  $\chi^2 = 9.8$  (1df)  $P < 005$

A.S.B. Efficacy of the Screening  $\chi^2 = 23.7$  (1df)  $P < 001$

**Table 33. Specificity of Antenatal Screening for Anencephaly:  
Glasgow, 1982-1986**

Anencephaly	1982	1983	1984	1985	1986
No of True Negative	10729	10615	10421	11160	11430
No of False Positive	0	0	0	0	0
Specificity %	100.0	100.0	100.0	100.0	100.0

**Table 34. Specificity of Antenatal Screening for Spina Bifida:  
Glasgow, 1982-1986**

Spina Bifida	1982	1983	1984	1985	1986
No of True Negative	10736	10620	10419	11149	11441
No of False Positive	0	0	0	0	0
Specificity %	100.0	100.0	100.0	100.0	100.0



**SECTION VII: DISCUSSION**

## SECTION VII: DISCUSSION

### 7.1 Epidemiology and Natural History

It is generally agreed that a decline in the prevalence of neural tube defects has occurred in the British Isles as well as in some other parts of the world. In Northern Ireland, which is considered as one of the highest risk areas for neural tube defects, there was a decline in both birth prevalence and pregnancy prevalence over the period 1964-1979. Antenatal screening by the use of AFP is not routinely offered but mothers at risk have access to prenatal diagnosis. The decline is therefore unlikely to be due to prenatal diagnosis (Nevin, 1981).

In south-east Wales, which is also a high risk area, primary prevention has been attempted by genetic counselling and supplementation with folic acid since 1969. Antenatal screening using AFP has been carried out since 1973 and lately ultrasound scanning. During 1964-1987 both birth prevalence and pregnancy prevalence fell (Laurence, 1989).

In the Liverpool and Bootle area during 1961-1979 a progressive decline in both birth and pregnancy prevalence was noted by Owens et al (1981). Antenatal screening by AFP started in 1975 in that region.

A clear decline appeared to take place in continental Europe, including Italy, Belgium and France (Eurocat, 1986).

In the Netherlands during 1950-1980 there was a decline in anencephaly prevalence apart from some minor fluctuations. Antenatal screening was introduced in 1974 and more reliable ultrasound techniques have been available only in recent years (Romijn and Treffers, 1983).

The United States and Canada appear to have experienced a long-term epidemic of ASB. Prevalence apparently began to rise in Boston and Providence towards the end of the last century, reaching a peak in 1930-1934 and thereafter decreasing until the occurrence of another peak in 1950-1954, followed by a steady decline thereafter (Elwood and Elwood, 1980; MacMahon and Yen, 1971; Naggan, 1969). Naggan analysed the decline from 1930 to 1965 in Boston and found that it affected all ethnic groups (except Jews, whose rate was always low) and all occupational and parity groups (Naggan, 1969).

In British Columbia data indicate that 1950-1954 was an epidemic period, although the subsequent decline seems to have been less clear-cut as was the slight peak in the early 1960's (Elwood and Elwood, 1980).

In New York the prevalence of myelomeningocele decreased at a linear rate since 1930 so the decline started well before

screening was available (Stein et al, 1982).

Glasgow shares with Ireland, Wales and other Celtic areas of Britain a relatively high prevalence of neural tube defects. The programme of antenatal screening, based both on the measurement of Ms AFP and ultrasound for the whole of the west of Scotland (including Glasgow) has been operating since 1974. In Glasgow the annual birth prevalence of anencephaly (Table 4, Figure 9) declined from 1.32/1000 in 1976 to 0.31/1000 in 1986; there were no affected births during 1982 and 1985. There was a statistically significant decline in both anencephaly birth and pregnancy prevalence rates. There were two peaks in pregnancy prevalence, one in 1979 and the other in 1986 (Figure 15).

Although spina bifida birth prevalence declined from 1.47/1000 in 1976 to 0.92/1000 in 1986 (Table 5, Figure 10), which is a significant decline, there was a steady non-significant decline in spina bifida pregnancy prevalence during the study period (Figure 16).

The decline in anencephaly prevalence (birth and pregnancy) was more obvious than that for spina bifida. The same observation has been made in Dublin, Belfast, and Liverpool (Eurocat Working Group, 1987).

There was a significant decline in both birth and pregnancy prevalence for both anencephaly and spina bifida during 1982-1986

compared to 1976-1981 (Table 7, 8) which might indicate that antenatal screening programme was more effective during 1982-1986 for both anencephaly and spina bifida.

There were a number of peaks and troughs in pregnancy prevalence in Glasgow for both anencephaly and spina bifida; during 1964-1986 they are not consistent and diverging (Figure 13) which is different from what is found in Northern Ireland (Nevin, 1981) and Liverpool (Owens et al, 1981) where the peaks and troughs are more parallel. It is possible that in Glasgow the mechanism which caused the decline for one defect was not responsible for the same effect on the other defect.

By comparing the previous studies by Wilson (1970) and Stone (1981) with the present study (1979-1986, Table 9, 10) a statistically significant secular trend in both birth and pregnancy prevalence in Glasgow was evident.

It seems that the secular trend in prevalence was independent of intervention during pregnancy (Figure 11, 12). This presumably reflects a true decline. Similar observations have been made in Dublin, Belfast and Liverpool (Eurocat Working Group, 1987).

Prenatal diagnosis and termination of affected fetuses have played an increasingly large part in reducing the birth prevalence. Prenatal diagnosis is not, however, the sole explanation for the decline which began in most places before

prenatal diagnosis was available (Nevin, 1981; Owens et al, 1981; Laurence, 1989).

Other possible explanations for the decline include an increased public health awareness of neural tube defects resulting in better prenatal care; improved maternal life style; a changing maternal environment; and alteration in maternal diet and nutrition.

An increase in requests for genetic counselling, especially by families who had a child with ASB, may be causing a decline in familial recurrence of cases by avoidance of further pregnancies; this would have had little effect, however, on the overall prevalence of NTD, at least 90% of which are not familial recurrences.

Another factor which might be expected to lower the prevalence of ASB is the drop in the overall birth rate particularly in younger and older women. In Greater Glasgow the annual number of births in the early 1970's was more than 19000 and dropped to about 13000 in the 1980's (Annual Report of the Registrar General for Scotland, 1970-1986).

The total number of births to mothers in younger and older age groups fell proportionately more than did births to mothers in all age groups. Changes also occurred in social class ratio favouring social class one and two (Bradshaw, Weale, Weatherall,

1980). The lower social classes may be in a state of transition from relatively ineffective family planning to more effective contraception causing the rate of unplanned pregnancies to decline (Westaff, 1976), particularly at the extremes of maternal age. In contrast to NTD, however, the prevalence of other congenital anomalies including chromosomal defects has not decreased (Stone, 1989).

Several dietary factors have been implicated as a cause of neural tube defect including tea (Fedrick, 1974), blighted potatoes (Renwick, 1972) zinc and other minerals (Coffey, 1970). Evidence from two studies by Smithells et al (1980) and Laurence et al (1981) show reductions in neural tube defect prevalence in those given preconceptional vitamin treatment, particularly folic acid.

While the secular decline in ASB prevalence antedates the vitamin supplementation debate, the continuing decline in the early 1980's presumably coincides with the increased use of vitamins in pregnancy and could therefore represent a preventive effect. (However, the slight upward trend in prevalence in the mid-1980's in Glasgow tends to undermine this explanation.) But the recent results of the Medical Research Council on vitamin study (1991) suggest that preconceptional supplementation with folic acid may indeed prevent neural tube defects. There is also a view that the mother's diet during childhood may be as important as her preconceptional diet and the subsequent conception of an affected fetus (Emanuel and Sever, 1973; Baird, 1974). The steep decline in the 1970's and early 1980's (Figure 13) occurred about a generation after the prosperous 1950s and

early 1960's when most of these mothers were born and reared. Unemployment and poverty, which have been implicated as a risk factor in some studies, declined throughout the 1960's and 1970's in the United Kingdom but this trend may have been reversed in the 1980's (Morris, 1990).

The rise in ASB prevalence observed in the mid-1980's could be a manifestation of the increasing poverty and unemployment levels occurring at that time. This interpretation assumes the existence of an unspecified teratogen mediated through a component of social deprivation. Despite its lack of specificity, the socio-economic hypothesis is plausible given the repeated observation of a high risk of ASB in social classes IV and V (Elwood and Elwood, 1980).

Identification of the reasons for the secular decline would be valuable for etiological and preventive purposes. Recognising the scale of the decline even without knowing the reason is important for health services planning. But the decline should not lead to complacency given our ignorance about its causes. The rate which has been labile historically could presumably increase at any time (Elwood and Elwood, 1980).

Before screening started most anencephalic babies were stillborn, while those born alive died a few days after birth. Spina bifida is a more variable malformation, ranging widely in severity, leading either to stillbirth or livebirth. Larger



lesions are associated with a poorer survival, and these infants are often severely handicapped and require frequent surgical procedures and institutional care.

After screening started (Table 11, Figure 14) there was a statistically significant increase in the proportion of induced abortion during 1982-1986 for anencephaly, while the proportion of stillbirths significantly decreased during 1982-1986; the proportion of live births also declined but the reduction is not significant. It seems therefore that most of the anencephalic stillbirths became abortions. Those that were live births, all died during the first week.

For spina bifida two approaches to the natural history were employed - the first approach started from conception (Table 12, Figure 14); there was a significant increase in the proportion of induced abortion, with a significant decrease in the proportion of stillbirths during 1982-1986. The proportion of live births decreased by about 10% compared to 1976-1981. Following the infants beyond one year of age (Table 13), fewer survived during 1982-1986 than in the earlier period, but the difference is not significant.

The second approach adopts birth as the starting point (Table 14). The proportion of those surviving more than one year was higher during 1982-1986 than in the earlier period. Although this is not statistically significant, it lends some support to

the hypothesis that screening selects out the most lethal lesions (Bradshaw, Weal and Weatherall, 1980). This interpretation is reinforced by the observation that perinatal, neonatal and infant mortality all decreased during 1982-1986, in comparison with 1976-1981 (Table 16).

Anencephaly showed little variation since all such babies died during the first week of life; the perinatal, mortality and neonatal mortality rates were 100% (Table 15) for this defect.

## 7.2 Effectiveness of Antenatal Screening

The effectiveness of any programme is ideally measured by assessing its achievements in relation to its objectives. The epidemiological effectiveness of antenatal screening programme is judged by its ability to reduce the birth prevalence of neural tube defects in the population.

Arguably the most rigorously scientific way of obtaining evidence about the effectiveness of antenatal screening for neural tube defects is by assessing the alteration in the natural history through a randomised controlled trial. Because of the nature of the condition and its low prevalence, such a trial would require to be long term and would involve very large numbers; moreover there would be strong ethical objections. An alternative method of evaluation is through a retrospective review of the impact of antenatal screening. Selective screening of those pregnancies who have had previous children with neural tube defects or who have some family history could only reduce the prevalence by 10% (at most). To reduce the prevalence further the screening of all pregnancies is required and that is what was initiated in Glasgow and other cities in the United Kingdom in the 1970's. Antenatal screening for neural tube defects to residents of Greater Glasgow Health Board area avoided 286 (54.22%) of both anencephaly and spina bifida births out of a potential total of 527 births during the period 1976-1986.

This finding, however, requires to be placed in the context of the changing epidemiological patterns of ASB and in particular the long term secular decline in pregnancy prevalence.

There was a statistically significant decline in both pregnancy prevalence and birth prevalence of anencephaly over the study period (Table 17, Figure 15). 93.4% of anencephaly fetuses were "avoided" during 1982-1986 (Table 19). Antenatal screening has clearly been highly effective in preventing anencephaly mainly due to high sensitivity of maternal serum AFP (Ferguson-Smith, 1983) for this defect. Anencephaly can also be detected early by ultrasound examination (Roberts et al, 1983). There was a steady non-significant decline in spina bifida pregnancy prevalence (Table 18, Figure 16) during 1976-1986. 45.8% of spina bifida pregnancies were terminated (Table 20) during 1982-1986. The decline is however statistically significant in comparison with the earlier period (1976-1981). So analysis of the changes in pregnancy and birth prevalence of anencephaly and spina bifida is not only important for aetiological studies but also for evaluating the effectiveness of preventive programmes.

Antenatal screening has been responsible for part of the decline in the birth prevalence of anencephaly and spina bifida and undoubtedly has been instrumental in reducing the number of live births with spina bifida and the consequent burden of disability from this condition.

The effectiveness of antenatal screening for neural tube defects is influenced by these interacting factors:

1. the proportion of pregnancies with neural tube defects screened
2. the proportion of affected pregnancies detected, sensitivity of the screening procedures
3. the proportion of those terminated when detected

Each will be considered in turn.

Antenatal screening for neural tube defects is available to all mothers in GGHB area on an entirely voluntary basis - screening can be a long process with a complex series of decision-making starting from referral to the ultimate decision to terminate the pregnancy. There are many opportunities for clinical and administrative events to occur which might deter some pregnant women from attending or undergoing further tests.

1. The Proportion of Pregnancies Screened:

The proportions of anencephaly pregnancies and spina bifida pregnancies screened was less than 50% (Figure 18, 22) during 1976 but started to increase gradually to more than 97% of anencephaly pregnancies being screened (Table 21) during 1982-1986 and more than 75% of spina bifida pregnancies were screened (Table 22) during the same period. There was an increasing trend in the proportion screened for both anencephaly and spina bifida and this was found to be significant (Figures 17, 21; Tables 23, 24). The proportion of pregnant women opting

in and staying in the screening procedure could be increased by ensuring that all pregnant women attending antenatal clinics are screened by ultrasound and Ms AFP before 20 weeks gestation.

2. The Proportion of Pregnancies Screened and Detected:

Maternal serum AFP assay is more sensitive in detecting neural tube defects if measured between 16-20 weeks gestation. The interpretation of maternal serum AFP in terms of normality and abnormality is influenced by gestational age. Some obstetricians tend to overestimate gestational age, thus placing a slightly raised maternal serum AFP just below the cut-off point. Thus one element in the effectiveness of antenatal screening depends on the accuracy of assessing gestational age. The increased use of obstetric ultrasound in antenatal screening has improved the precision of gestational age dating.

The proportions of anencephaly fetuses detected by antenatal screening procedures i.e. sensitivity was 95.6% during 1976-1986 (Table 23, Figure 19). In the case of spina bifida the proportions detected by antenatal screening was 61.8% (Table 24, Figure 23). The more severe the neural tube defect the greater the likelihood of detection and so the procedure is highly sensitive for anencephaly. The sensitivity of Ms AFP depends on a cut-off point between positive and negative for the

laboratory concerned. Lowering the cut-off point would lead to more pregnancies with neural tube defects being detected and fewer cases missed but on the other hand would also lead to an increase in the number of false positive cases and hence an increase in the amniocentesis rate. But the skilled use of ultrasound in identifying false positives may help avoid unnecessary amniocentesis. The amniocentesis failure rate may also be reduced by simultaneous ultrasonography. Both amniocentesis false positive and false negative rates can be reduced by the use of amniotic-fluid acetylcholinesterase (Smith et al, 1979).

### 3. Proportion Screened, Detected and Terminated

In cases of anencephaly, more than 96% of those detected were terminated (Table 23, Figure 20) during 1976-1986 and more than 82% of those spina bifida detected were terminated during the same period. Some of the cases detected by antenatal screening procedures do not proceed to termination; 3.1% of anencephaly and about 17.4% of spina bifida. Aversion to abortion could be due to religious or social reasons. Some may fear that a normal pregnancy may be terminated, others may have declined for another reason.

The proportion of anencephaly pregnancies detected and proceeding to termination was much greater than that for spina bifida. This could be because anencephaly is detected early with confidence by ultrasound and also that the consequence for the child is well

known and the parents are therefore more likely to agree to termination. Spina bifida, on the other hand is detected later when the pregnancy is more advanced and there is uncertainty about the consequence of spina bifida and a lack of confidence regarding its diagnosis. The proportions of spina bifida pregnancies screened during 1982 was low. This may have been due to the National Health Service strike that year and it may be that a proportion of affected pregnancies were not satisfactorily screened.

For these reasons, antenatal screening made less impact in the case of spina bifida than is the case of anencephaly. From the public health perspective, if the health service personnel intend to improve the effectiveness of antenatal screening programmes further, especially for spina bifida, they might be able to tackle this problem by improving one or a combination of these three factors: the proportion with the defects screened; the proportion with the defects detected; and the proportion with the defects terminated when detected.

Running an antenatal screening programme for neural tube defects requires a considerable degree of organisation and the maintenance of good communication between the pregnant women and the obstetricians, the laboratory and obstetrician is essential. They may generate a considerable amount of anxiety among mothers whose maternal serum AFP value lies above the defined action



point (Fearn et al, 1982) and thus demand expert forms of counselling and reassurance.

There have been several criticisms of the role of antenatal screening for the detection of neural tube defects. In East Anglia the programme was discontinued in the belief that AFP had a poor predictive value in detecting spina bifida (Standing et al, 1981).

Owens et al (1981) pointed to the declining prevalence of neural tube defects in the United Kingdom and the promising result of preconceptional vitamin supplementation in primary prevention (Smithells et al, 1981a). Edwards (1982) argued that a further substantial reduction in prevalence would make screening uneconomic.

The prevalence of neural tube defects has declined in recent years, but it is not clear whether it is a temporary or permanent phenomenon. Rates of pregnancy prevalence have not declined to the level where the experiments in the 1970s of setting up screening programmes are no longer valid. In general, these programmes have also achieved public acceptance. If the wide-scale use of preconceptional folic acid supplementation also contributes to a further decline, it may be necessary to reconsider the situation.

### 7.3 Efficiency of Screening Service

Antenatal services in the United Kingdom can be general practitioner based, hospital/obstetric unit based or shared between both services. The patient initially attends her general practitioner for confirmation of pregnancy and is then referred to a booking clinic at a hospital, which is generally the time at which a complete history and examination are performed and a plan of care established.

Efficiency may be assessed in various ways but the response of pregnant women to the provision of antenatal care services is an important determinant of the outcome of screening services.

84.5% as a proportion of total births of pregnancies were screened in Glasgow during 1982-1986 (Table 26) but this figure drops to 75% when a denominator of total pregnancies (live and still and termination) is used (Table 25). This compared with 77.4% of pregnancies screened as a proportion of total births during 1982-1986 in the west of Scotland (Heather and Stevenson, personal communication). These represent estimated percentages of pregnant women who accept antenatal screening for neural tube defects and utilise the service.

Another way of measuring the acceptability indirectly is by the number of normal fetuses aborted. In Glasgow no normal fetus has been aborted due to antenatal screening for neural tube

defects since 1981, the time at which AchE started to be used as a diagnostic test.

The acceptability of antenatal screening for neural tube defects may be expressed in terms of "losses" and "gains". The unnecessary exposure of normal pregnancies to diagnostic tests and the termination of normal fetuses represent "losses". The "gains" are those pregnancies with ASB detected by antenatal screening techniques.

Some might argue that a severe disease like anencephaly associated with death at birth causes little burden either to the family or to society. But since antenatal screening and induced abortion reduce the average duration of pregnancy, this is a substantial benefit to the parents. They can plan a subsequent pregnancy earlier and avoid the emotional consequences of giving birth to a full-term baby which dies. On the other hand, if affected fetuses with spina bifida survive they require continued care and treatment, thereby inflicting a severe and expensive burden on surviving individuals, their families and society.

There were 359 ASB pregnancies in Glasgow during 1979-1986 (Figure 25); about 82.7% of those women were screened with an efficacy (the proportion of ASB detected and terminated out of the total ASB) of 63.2%. 13.6% of affected pregnancies screened were missed. This may elicit a resentment among mothers who had

hoped for protection against the birth of an affected child despite the risk to the fetus which is implicit in the procedure.

17.3% of pregnancies with ASB were not screened because women declined screening, booked too late or were not screened for other reasons. The proportion of those who declined screening was 6.7%. These women were aware of antenatal screening for neural tube defects, but did not attend the appointment offered. Some refused to be screened for religious reasons or on principle. The proportion of pregnancies with ASB not screened because they attended antenatal clinic too late was 7.8%.

Estimation of gestational age is improved by early attendance (by the use of ultrasonography) and so the potential benefit of antenatal screening is increased. Women who attend late for antenatal care experience a higher than average perinatal mortality and are less likely to benefit from antenatal screening not only for maternal serum AFP but for amniocentesis for chromosomal and other abnormalities, fetoscopy and fetal blood sampling (Pearson, 1982).

A high proportion of the women booked after 20 weeks gestation are more likely to be of immigrant origin and of high parity (Simpson and Walker, 1980). In the west of Scotland in 1981 about 27% of pregnant women did not have MsAFP tested either because they attended before 16 weeks gestation (and were not recalled for screening) or attended after 20 weeks gestation (Ferguson-Smith, 1983). Most of those late attenders are found

to be associated with maternal youth, high parity and poorer socio-economic status (McKinlay, 1970).

In the present study, 2.8% of the women with ASB babies were not screened either because they did not attend antenatal clinics at all or they attended the clinic only minimally. Others concealed their pregnancy because they were single women or had a prenuptial conception. This group also includes those women attending antenatal clinic but without record of antenatal screening for ASB in their case notes.

In order to reduce the proportion of pregnant women not screened, there is a need for an improvement in the administrative arrangements in antenatal clinic appointments such as lost letters or delay in sending appointments. It is also important to increase general practitioners' awareness of the possibility of screening for NTD by measurement of Ms AFP at 16-20 weeks of gestation; facilities could be made more widely available for general practitioners to take blood at the desired stage of pregnancy. General practitioners also need to be reminded of the importance of early referral to hospital when antenatal care is either to be shared or is to become the responsibility of the consultant.

Hospital antenatal clinics should be arranged so that the delay between receipt of the general practitioner's referral letter and an appointment for an antenatal clinic is kept to the minimum.

Health education of the public at different levels through schools, the media and by community nursing and medical personnel might help to persuade women to contact services earlier. Unless a higher proportion of women contact antenatal services early the impact of the prenatal screening programme for NTD will fall short of its potential.

#### 7.4 Efficiency of the Screening Procedure

Maternal serum alphetoprotein and ultrasound are the techniques which are used for the presumptive detection of neural tube defects, while for definitive diagnosis detailed ultrasound and amniocentesis for AFP and AchE are used.

Ultrasound is useful in determining the cause of an elevated Ms AFP. If there is no satisfactory explanation for the elevation of Ms AFP, Am AFP and AchE determination are usually carried out.

The use of ultrasound in the detection and diagnosis of NTD is increasing and some have suggested that screening for NTD by ultrasound has now become a serious alternative to screening by Ms AFP (Harris and Read, 1981; Christie, 1983).

In the present study the proportions of anencephaly terminations detected and diagnosed by ultrasound was increased from 20.2% in 1976-1981 to 67.1% in 1982-1986 (Table 30). In 1982-1986 only 8.2% of spina bifida terminations were detected and diagnosed by ultrasound (Table 30). Most of the terminations were diagnosed by amniocentesis. A possible explanation is that the anencephaly lesion is large, easily detected and diagnosed by ultrasound. The ability of ultrasound to demonstrate spina bifida is related to the resolution of the equipment used, the size of the defect and the experience of the operator. Defects involving more than

three vertebral segments can be easily diagnosed although if only one or two segments are involved the diagnosis is more difficult (Harrison, Golbus, Filly, 1984).

These findings suggest that a combined approach for screening of neural tube defects using both ultrasound and Ms AFP determination is probably worthwhile. This view is also supported by the finding of Persson et al (1983).

The sensitivity for neural tube defects in Glasgow was calculated in terms of both tests combined. For anencephaly sensitivity was 96.7% (Table 31) during 1982-1986 while for spina bifida the figure was 67.9% (Table 31). For ASB the sensitivity was 83.1% (Table 31), which is similar to the figure of Persson et al (1983) who found a sensitivity of 80.0% in Sweden.

The proportions of neural tube defects detected and terminated as a consequence of antenatal screening techniques were 67.7% for both anencephaly and spina bifida during 1982-1986 (93.4% for anencephaly, 45.8% for spina bifida) (Table 32). Thus the efficacy of antenatal screening techniques improved during 1982-1986 when compared with 1976-1981. This was due to an increase in the proportion of pregnancies screened, an improvement in the sensitivity of the screening techniques and an increase in the proportions of those terminated when detected.



### 7.5 The Economics of Screening

With the introduction of screening programmes during the early 1960's the question was frequently asked "Is screening for NTD worthwhile in relation to its cost and the benefit it will yield?"

During the 1960's Wilson and Jungner (1968) and others set out criteria which required to be satisfied if any screening programme were to be justified. One of these is that the cost of contacting the population and carrying out the test must be reasonable.

In assessing a screening programme a decision has to be taken which requires some balance of costs and benefits. The costs and benefits of a screening programme are direct, indirect and intangible:

Direct costs include the direct medical costs (doctors, nurses, hospital treatment, inpatient and outpatient services, physiotherapy and rehabilitation services), cost of facilities, equipment, material, manpower and programme publicity.

Indirect costs include loss of productivity due to patient taking time off work, cost of travelling, loss of earnings and cost of special education.

Intangible costs include pain and anxiety experienced by the patient and their family, psychological effect on siblings and the child's own psychological problem.

Direct benefits include the reduction in the number of liveborn neural tube defect cases leading to a reduction in the care needed which leads to a change in the quality of life of the family and change in the resources used.

Indirect benefits include the reduction in the number of live born neural tube defects and a reduction in the resources needed these resources can be used in other parts of the health service.

Intangible benefits include the reduction of suffering, pain and anxiety.

Cost benefit analysis involves establishing a relationship between the value of benefits generated and the cost that must be incurred to obtain these benefits.

The cost of screening procedures is ascertained and compared with the cost of not doing it in terms of the treatment and care that would be required if the disease were allowed to run its usual course. The screening procedures are judged to be worthwhile if their cost is less than that of treating and caring for the patient.

An economic analysis based on the early years of the West of Scotland screening programme for spina bifida was conducted by Hagar, Carter and Milne in 1976. They took account of a wide range of direct and indirect costs and benefits to the families and the public services arising from screening. They concluded that on economic grounds screening may be worthwhile only in a population with a high prevalence of spina bifida.

Glass and Cove (1978) estimated that public sector costs of a group of spina bifida children would exceed the cost of a screening programme (with a test sensitivity of 45%) within four years.

Henderson (1982) carried out an economic analysis similar to that of Hagar, Carter and Milne (1976). He concluded that the tangible benefits of screening probably outweighed the tangible costs by a substantial amount. The intangible psychological costs and benefits are more difficult to estimate but the balance is likely to be greatly in favour of screening.

Two studies permit a comparison of economic benefits between low and high prevalence areas. Standing et al (1981) found that in a low prevalence area, Ms AFP values had a poor predictive value in detecting open neural tube defects and recommended abandoning the programme. An economic analysis carried out in a high prevalence area (Hibbard et al, 1985) based its analysis on the efficacy data of an earlier study (Roberts et al, 1983) and

concluded that screening for neural tube defects in areas in which the prevalence falls below 5 per 1000 total births is not cost effective.

Spencer and Carpenter (1985) argued that the prevalence is not the only factor determining screening cost. In an area of low prevalence (1.95 per 1000 total births) a high detection rate, good patient compliance, good counselling, result in an efficacy of 75%; adding the psychological benefit of identifying non-viable pregnancies and the benefit from detecting other abnormal pregnancies, they concluded that antenatal screening programmes can be highly cost-effective in low prevalence areas; in other words, prevalence is not the only important factor in determining the screening cost. The detection rate, efficacy, proportion of pregnancies screened, and the provision of genetic counselling services are equally important.

If one accepts the conclusion of Hibbard et al (1985), their arguments are important in assessing the economic work of the Glasgow programme. The combined pregnancy prevalence in 1972-1978 was 5.22 per 1000 of total births but by 1979-1986 this had declined to 3.43 per 1000 total births. On strictly economic grounds, therefore, the benefits of the programme are likely to depend on the factors above and the balance is more likely to be in favour of the screening programme despite the falling prevalence. In addition, there may be other benefits. It is likely that the diagnosis of Trisomy 21, 18 and 13 is likely to

improve following the discovery of an association between these conditions and low Ms AFP. The screening for Down's Syndrome started in the West of Scotland in 1987 provided the possibility of screening all pregnant women with a combination of maternal age and early mid trimester Ms AFP concentration (Cuckle, Wald and Lindenbaum, 1984). This potential is currently being evaluated within the West of Scotland screening programme.

In addition, the introduction of antenatal screening for NTD also helped to improve obstetric services generally by promoting the wide-spread introduction of obstetric ultrasound which helps in dating the pregnancy with a consequent reduction in post-maturity and unnecessary induction of a wide range of fetal abnormalities (Campbell and Pearce, 1983).

If maternal serum AFP testing is extended to later gestational ages to study the relationship between maternal serum AFP levels and intrauterine growth retardation this might lead to the earlier identification of more at risk pregnancies in whom the prognosis would be improved by more intensive obstetric care.

All these potential benefits will extend the usefulness of Ms AFP screening beyond the identification of NTD and add to the cost effectiveness of antenatal screening programmes. Therefore it is important to continue monitoring the pregnancy prevalence of anencephaly and spina bifida.

SECTION VIII - CONCLUSIONS

## SECTION VIII: CONCLUSION

### 8.1 Epidemiology and Natural History of Anencephaly and Spina Bifida

The findings confirm the view that Glasgow suffers a relatively high prevalence of NTD even in British terms. Birth and pregnancy prevalence rates of anencephaly declined significantly during the period 1976-1986. Birth and pregnancy prevalence of spina bifida declined over the same period. There is no evidence that the decline in prevalence has levelled off.

The decline in birth prevalence is partly attributable to antenatal screening, while the decline in pregnancy prevalence is unexplained.

There appeared to be a downward secular trend in prevalence in Glasgow which was independent of intervention during pregnancy. But antenatal screening and termination of affected fetuses have played an increasingly large part in reducing the birth prevalence. The identification of the reasons for the decline in pregnancy prevalence would be valuable for aetiological and preventive purposes. Even if this cannot be achieved, monitoring the extent of the decline is important for health services planning. Antenatal screening appears to have influenced the natural history of both anencephaly and spina bifida.

## 8.2 The Effectiveness of Antenatal Screening

The effectiveness of an antenatal screening programme is judged by its ability to reduce the birth prevalence of NTD in the population.

Monitoring differences between pregnancy prevalence and birth prevalence is one means of estimating the effectiveness of antenatal screening. This difference also gives the proportion of births avoided which is reflected by the proportions of pregnancies terminated with NTD during the same period.

Antenatal screening for NTD made a considerable impact on the birth prevalence of anencephaly and spina bifida and was instrumental in reducing the number of live births with spina bifida and the consequent burden of disability from this condition.

The proportion of both anencephaly and spina bifida pregnancies screened showed a significantly increasing trend from 1976-1986. There was a significant trend in the proportion detected when screened for both anencephaly and spina bifida during 1976-1986.

In the case of anencephaly the proportion terminated when screened and detected was always high, while spina bifida showed a significant upward trend over the same period.



### 8.3 Efficiency of Screening Services

The proportion of pregnant women who utilised the service of antenatal screening for NTD in Glasgow was higher than that for the west of Scotland during 1982-1986, suggesting that geographical proximity to services contributes to their uptake.

Less than one-fifth of NTD pregnancies in Glasgow during 1979-1986 were not screened, and these were mainly due to administrative reasons.

In order to reduce the proportion of those women not screened, general practitioners, obstetricians and health visitors need to put more emphasis on pregnant women under the age of twenty, multiparous women (IV and V) and those from social classes IV and V.

#### 8.4 Efficiency of the Procedures

The techniques used for the detection of NTD. were MsAFP and ultrasound, while for the diagnosis a detailed ultrasound scanning and/or amniocentesis for amniotic fluid AFP and AChE were employed.

The effectiveness of an antenatal screening programme for NTD was improved by the combined use of Ms AFP and diagnostic ultrasound. Antenatal screening for NTD using combined ultrasound and AFP determination was carried out in Glasgow with a sensitivity of 83.1%.

Due to an increase in the proportion of pregnancies screened, an improvement in the sensitivity of the screening techniques, and an increase in the proportion of those terminated when detected, the efficiency and effectiveness of the screening has improved over time.

The combined use of ultrasound and Ms AFP screening with its high sensitivity, specificity and efficacy is worthwhile and will probably reduce the birth prevalence further.

It is clear that in Glasgow during 1986 Antenatal screening for NTD by MsAFP and ultrasound made a major contribution to the reduction in birth prevalence of children with ASB. Nonetheless such programmes are not without problems. They require a

considerable degree of organisation and communication.

## 8.5 Policy Implications

Policy implications will be discussed under three headings: public health monitoring; screening services and research.

### Public health monitoring

Because of the epidemiology of ASB, continued monitoring of its prevalence is essential because changing exposure to an unidentified causative agent could lead to an upturn in the rate. The Glasgow Register of Congenital Anomalies is an example of a validated epidemiological surveillance system (Stone, 1986). Repeated searches for missed ASB births or induced abortions following prenatal diagnosis have failed to yield additional data and this permits a satisfactory monitoring of time trends, so any change in prevalence is unlikely to be due to varying case ascertainment. Monitoring in itself cannot improve health, and so measures to promote health and prevent disease are required.

The specific causes of ASB are unknown but the high risk group in the population are mothers under the age of 20 years and over 35 years, primiparous or multiparous, and those from social classes IV and V (Stone, 1981) but improvements in unemployment and poverty, health education, diet and housing environment may assist the further decline in prevalence of ASB.

Recent evidence shows that there is a possibility of preventing NTD by preconceptional supplementation with folic acid (MRC 1991). But there is a need for continued monitoring of pregnancy

prevalence of ASB in order to identify any acceleration in the decline which might be due to folic acid.

The impact of antenatal screening and therapeutic termination of the affected fetuses (discussed below) also requires continuous monitoring.

#### Screening services

The development of antenatal screening for the detection of ASB in utero represents a major scientific advance. It could assist the disappearance of neural tube defects as a major health problem but its limitations should be made clear to policy makers.

Antenatal screening for NTD requires a considerable degree of organisation and good communication between the pregnant women and the obstetricians and between the laboratory and the obstetrician. Women should be told about the implications of antenatal screening and the limitations of the test since no single test can exclude all fetal abnormalities. Women should always be given adequate information about the procedure and the meaning of false positive and false negative and any anxieties related to the procedure should be resolved. This may lead to a further increase in the proportion screened.

The proportion screened could presumably be increased further by health education and extensive publicity directed at encouraging antenatal screening for NTD. In particular, more emphasis needs

to be placed on meeting the needs of women under 20 years, those who are multiparous and those from social classes IV and V by health services staff, since the success of screening is dependent on the attitude and behaviour of the target population toward the health service.

The use of reliable techniques and skilled staff in performing amniotic AFP and ultrasound with more careful counselling of parents before they enter the screening process would enhance the effectiveness and efficiency of the screening.

Preconception counselling and advice should be offered to all couples intending to have a baby rather than simply to those who seek genetic counselling due to a particular risk. The advice should include the importance of diet (especially folic acid) and nutrition not only in early pregnancy but also before pregnancy. Antenatal screening for anencephaly and spina bifida must be subject to continuous medical audit in order that deficiencies can be identified and rectified promptly.

It would be premature to abandon antenatal screening for ASB given our current state of ignorance of the aetiology. At the same time, children born with NTD, despite anteantal screening, should continue to receive the highest standard of social and medical care.

### Research

Although the birth prevalence is reduced by antenatal screening

and despite the large number of epidemiological, clinical and laboratory studies, the cause of NTD is still unknown. Fundamental research into aetiology should remain a high priority and worthy of policy support and encouragement.

Antenatal screening for NTD makes a contribution to the reduction of both anencephaly and spina bifida birth prevalence, but there is substantial scope for improving the efficiency and consequently the effectiveness of screening for spina bifida by identifying new methods. The present difficulty is the need for AFP testing within the 'window' of 16-20 weeks gestation and the limitations of ultrasound in the diagnosis of spina bifida.

Despite the falling prevalence of NTD, the benefit of Ms AFP screening may have increased after the discovery of the association of low MS AFP in pregnancies with Down's Syndrome. There is a need for an updated economic evaluation of antenatal screening programme which takes account of the epidemiological trends, the effectiveness and efficiency of screening and therapeutic advances in the care of handicapped children.

Examination of the distribution of maternal age parity and social class for the screened and not screened in total pregnancies is needed in order to help service planners to identify and target those least likely to be screened.

## APPENDIX I

The risk of having a fetus with NTD in those with positive test results.

The chance that those with positive results are affected is expressed as an odds ratio of the number of affected to the number unaffected among those with positive results (i.e. 1:2 in every three positive results one is affected). Odds is used because it is easier to calculate and gives a better impression of the reliability of the test.

Odds of being affected for the group of individuals with positive results is necessary for planning a screening programme. It is critically dependant on the prevalence of the disorder in the screened population as well as on the detection rate and false positive rate of the test.

The birth prevalence is expressed as an odds ratio (i.e. prevalence of 4 per 1000 is 4:996). The detection rate is applied to the left-hand side of the ratio and the false positive rate to the right-hand side of the ratio.

Example: Detection rate of 90%; False positive rate of 2.5%; and Prevalence 4:996. The new odds ratio would be  $(90 \times 4):(2.5 \times 996)$  or 360:2490 which simplifies to 1:7 (i.e. in every eight positive results one is affected).



## APPENDIX 2

## NOMOGRAM

Instructions for use

Always use the Maternal Serum AFP scale which corresponds to the appropriate Amniotic Fluid AFP scale (clear, any or blood-stained - regardless of source or extent of blood contamination - amniotic fluid sample). Join the appropriate AFP values on the serum and amniotic fluid scales using a straight edge, and read the odds ratio where the ruler intersects the centre (risk of open spina bifida) scale. The odds indicated are those which apply if birth prevalence in the absence of antenatal diagnosis and selective abortion is 1:1000. If necessary, adjust the odds for different birth prevalences or for other factors as noted below.

Adjustments to the left-hand side of the odds ratio

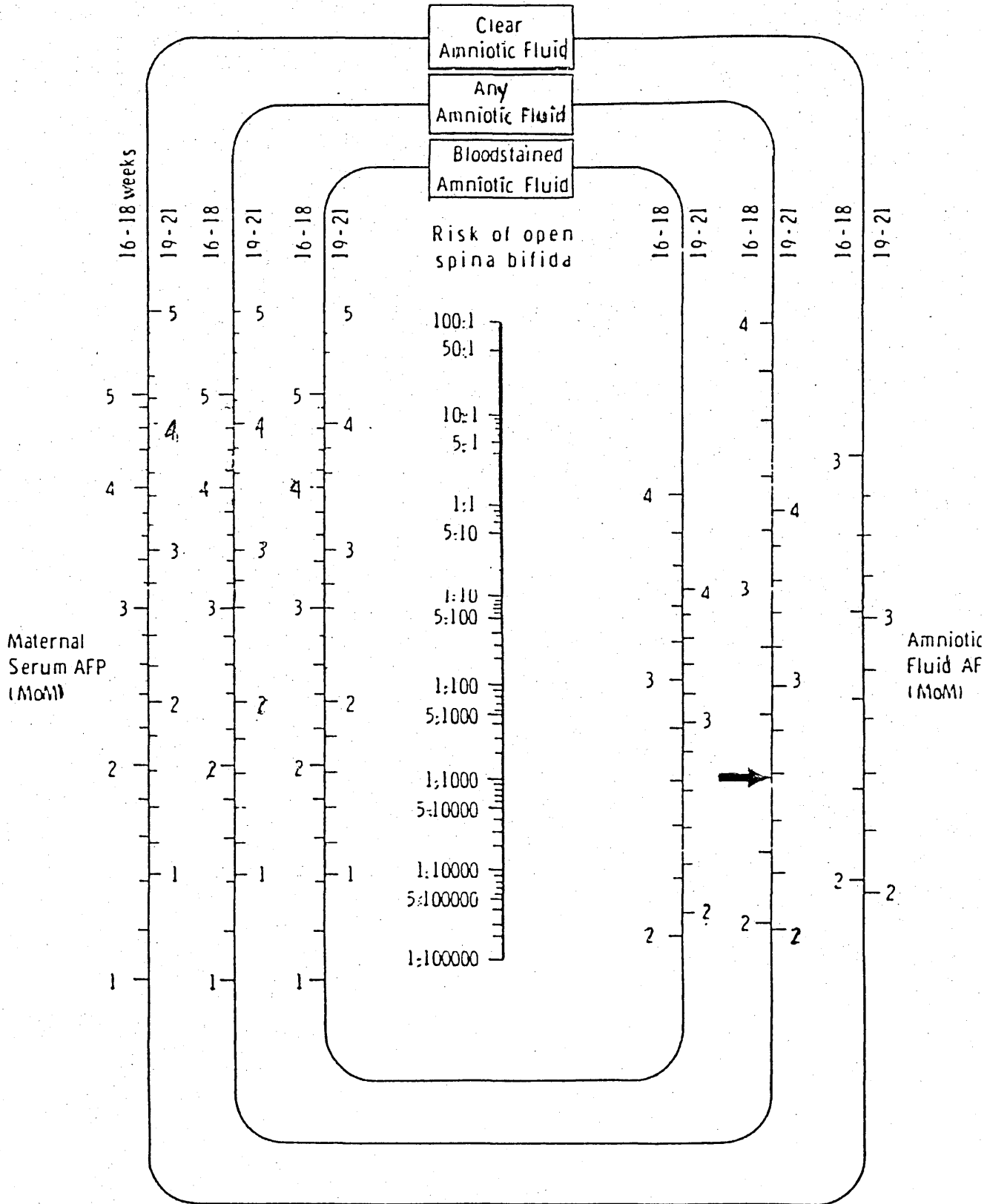
For open spina bifida birth prevalences other than 1:1000: multiply by the number of times the prevalence is different from 1:1000.

For women with one, two, or three previous infants with an NTD: multiply by 10, 20 or 40 respectively.

For positive amniotic fluid gel AChE result relating to 'clear', 'any' or 'blood-stained' amniotic fluid: multiply by 62, 16 or 9 respectively.

For negative amniotic fluid gel AChE result: divide by 150.

Nomogram to estimate risk of open spina bifida from maternal serum and amniotic fluid AFP values between 16 and 21 weeks of gestation (from Wald N.J. 1984)



Example

Given an amniotic fluid AFP level of 3.6 MoM at 19 weeks' gestation in a clear sample, and a maternal serum level of 2.4 MoM taken at 18 weeks' gestation, the straight line connecting the two values on the nomogram (using the clear amniotic fluid scales at 19-21 weeks' gestation for the amniotic fluid AFP and at 16-18 weeks' gestation for the maternal serum AFP) intersects the risk scale at 1:10. The woman lives in an area where the birth prevalence of open spina bifida is 0.5:1000, half that used to construct the central scale. Therefore the risk of her fetus having open spina bifida would be 1:20 ( $0.5 \times 1:10$ ). However, she has already had an anencephalic fetus, so the odds now become 1:2 ( $10 \times 1:20$ ). The gel AChE result is positive, so her final risk of having a fetus with open spina bifida is 31:1 ( $62 \times 1:2$ ) or 97 per cent (31/32).

Though mainly intended for use with women who have borderline amniotic fluid AFP results, the nomogram can also be used for a woman who has not yet had an amniocentesis. This is done, using the 'any amniotic fluid sample' scales, by joining the maternal serum AFP value to the point marked by the arrow.

MEDICAL IN CONFIDENCE

SCOTLAND MATERNITY DISCHARGE SHEET

SMR2  
Revised 1.1.87

1. GENERAL INFORMATION

Hospital Code  1-5

Hospital Case Reference Number  6-15

Surname  16-27

Forename  28

Second Initial  29

Maiden Name  30-41

Age \_\_\_\_\_ Date of Birth  42-49

Marital State  50

Home Address \_\_\_\_\_

Post Code  51-57

Occupation - Patient  58-60

Occupation - Husband  61-63

Date of Marriage  64-69

Obstetrician  70-76

Family Doctor  77-83

Type of Antenatal Care  84

2. PREVIOUS PREGNANCIES

Total Number  85

Therapeutic Abortions  87

Perinatal Deaths  89

Spontaneous Abortions (Miscarriages)  86

Caesarean Sections  88

Children now Living  90

3. CURRENT PREGNANCY

Date of Admission  91-96

Admitted From  97

Number of Previous Admissions to Any Hospital in this Pregnancy  98

Type of Admission  99

Date of Booking  100-105

Original Booking for Delivery  106

Blood Group \_\_\_\_\_ Rh  107

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Type of Abortion  111

Management of Abortion  112

Sterilisation after Abortion  113

Principal Complication of Abortion  114

Last Menstrual Period  115-120

Estimated Gestation at Abortion or Delivery  121-122

Certainty of Gestation based on LMP  123

4. MATERNAL DISCHARGE DATA

Date of Discharge  124-129

Condition on Discharge  130

Discharged To  131

Category of Patient  132

Unit on Discharge  133

\* THESE FIELDS MUST BE COMPLETED WHEN CONDITION ON DISCHARGE = 1 OR 4

5. RECORD OF LABOUR

Method of Induction of Labour  134

Presentation at Delivery or start of Operative Delivery  135

Mode of Delivery  136

Duration of Labour (In Hours)  139

Sterilisation after Delivery  14

Date of Delivery  142

Number of Births this Pregnancy  14

Outcome of Pregnancy  14

Birthweight (GMS)  151

Apgar Score at 5 mins  15

Sex  16

6. POSTNATAL RECORD OF INFANT(S)

Special Care Baby Unit  16

Baby Discharged To  16

Case Record No. in this Hospital  16-17

To be specified by Clinician

Underlying Cause of Stillbirth or Baby Death  187-190

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8. OTHER CONDITIONS

191-194

195-198

199-202

203-206

207-210

211-214

215-218

219-222

9. OPERATION

223-226

National Use  231

Local Use  24

## KEY TO CODED ITEMS

SMR2

Marital State [50]

- 1 = Never married (Single)
- 2 = Married
- 3 = Widowed
- 4 = Divorced
- 5 = Separated
- 8 = Other
- 9 = Not Known

Type of Antenatal Care [84]

- 0 = None
- 1 = GP Only
- 2 = GP care with specialist consultation
- 3 = Hospital Only
- 4 = GP and Hospital Shared
- 8 = Other
- 9 = Not Known

Admitted from [97]

- 0 = Not admitted
- 1 = Home
- 2 = Other hospital
- 3 = GP unit outwith this hospital
- 4 = Other speciality in this hospital

Type of Admission [99]

- 0 = Domiciliary (Not Admitted)
- 1 = Abortion (includes threatened abortion and ectopic pregnancy)
- 2 = Pregnant but not in labour
- 3 = In Labour
- 4 = Born before arrival
- 5 = Admitted after delivery at home
- 6 = Admitted after delivery in any hospital
- 8 = Other (e.g. doubtfully pregnant)

Original Booking for Delivery [106]

- 0 = Not booked prior to this admission
- 1 = Booked for Home delivery
- 2 = This Hospital (Consultant Unit)
- 3 = This Hospital (GP Unit)
- 4 = Other Hospital (Consultant Unit)
- 5 = Other Hospital (GP Unit)
- 9 = Not Known

Blood Group [107]

- 1 = O Rh -ve
- 2 = O Rh +ve
- 3 = A Rh -ve
- 4 = A Rh +ve
- 5 = B Rh -ve
- 6 = B Rh +ve
- 7 = AB Rh -ve
- 8 = AB Rh +ve
- 9 = Not Known

Type of Abortion [111]

- 0 = Threatened Abortion (still pregnant on discharge)
- 1 = Spontaneous or incomplete abortion
- 2 = Missed abortion
- 3 = Hydatidiform mole
- 4 = Therapeutic Abortion
- 5 = Suspected illegal abortion
- 6 = Failed therapeutic abortion
- 7 = Ectopic Pregnancy
- 8 = Unspecified abortion

Management of Abortion [112]

- 0 = Not operative (i.e. management of threatened or spontaneous complete abortion)
- 1 = D+C
- 2 = Vacuum aspiration
- 3 = Hysterotomy
- 4 = Prostaglandin (all forms)
- 5 = Amniotic infusion (other than Prostaglandin)
- 8 = Other (including ectopic pregnancy)
- 9 = Not stated

Sterilisation after Abortion [113]

- 0 = None
- 1 = Laparoscopy
- 2 = Laparotomy
- 3 = Laparoscopy Other hospital
- 4 = Laparotomy Other hospital
- 8 = Other
- 9 = Not stated

Principal Complication of Abortion [114]

- 0 = None
- 1 = Haemorrhage
- 2 = Sepsis
- 3 = Trauma to Cervix or uterus
- 4 = Damage to bowel
- 5 = Retained products requiring re-evacuation
- 8 = Other
- 9 = Not stated

Certainty of Gestation [123]

- 0 = Not applicable
- 1 = Certain
- 2 = Uncertain
- 9 = Not known

Condition on Discharge [130]

- 0 = Domiciliary Delivery
- 1 = Still pregnant
- 2 = Aborted (all types of completed abortion)
- 3 = Delivered
- 4 = Post natal care only
- 5 = Pregnancy not confirmed
- 8 = Other (e.g. known missed abortion)

Discharged to [131]

- 0 = Domiciliary Delivery
- 1 = Home Care
- 2 = Other hospital - GP maternity unit
- 3 = Other hospital - specialist maternity unit
- 4 = Other hospital or institution
- 5 = Other unit in this hospital
- 6 = Died (PM)
- 7 = Died (No PM)
- 8 = Other

Category of Patient [132]

- 1 = Amenity
- 2 = Paying
- 3 = NHS
- 7 = Special arrangement (see manual)

Unit on Discharge [133]

- 1 = Obstetric (Consultant)
- 2 = Obstetric (General Practitioner)
- 3 = Home or Other confinement not admitted to hospital
- 4 = Day Case (for definition see manual)
- 9 = Other or Not Known

Method of Induction of labour [134]

- 0 = None
- 1 = ARM
- 2 = Oxytocics
- 3 = ARM + Oxytocics
- 4 = Prostaglandins
- 5 = ARM + Prostaglandins
- 6 = Prostaglandins + Oxytocics
- 7 = Prostaglandins + ARM + Oxytocics
- 8 = Other
- 9 = Not Known

Presentation at Delivery or start of Operative Delivery (Baby 1 and Baby 2) [135], [136]

- 1 = Occipito - anterior
- 2 = Occipito - posterior
- 3 = Occipito - lateral
- 4 = Breech
- 5 = Face/brow
- 6 = Shoulder
- 7 = Cord
- 8 = Other
- 9 = Not Known

Mode of Delivery (Baby 1 and Baby 2) [137], [138]

- 0 = Normal, spontaneous vertex, vaginal delivery, occipito - anterior.
- 1 = Cephalic vaginal delivery with abnormal presentation of head at delivery, without instruments, with or without manipulation.
- 2 = Forceps, low application, without manipulation, forceps delivery NOS
- 3 = Other forceps delivery. Forceps with manipulation. High forceps. Mid forceps
- 4 = Vacuum extraction ventouse.
- 5 = Breech delivery, spontaneous assisted or unspecified partial breech extraction
- 6 = Breech extraction. Breech extraction: NOS or Total or Version with breech extraction.
- 7 = Elective (planned) Caesarean Section.
- 8 = Emergency, other and unspecified Caesarean Section
- 9 = Other and unspecified method of delivery

Sterilisation after Delivery [141]

- 0 = None
- 1 = Laparoscopy
- 2 = Laparotomy
- 3 = Laparoscopy other hospital
- 4 = Laparotomy other hospital
- 8 = Other
- 9 = Not stated

Outcome of Pregnancy (Baby 1 and Baby 2) [149], [150]

- 1 = Live birth
- 2 = Still birth
- 3 = Live birth died < 7 days
- 4 = Live birth died 7-28 days
- 5 = Live birth died after 28 days

Sex (Baby 1 and Baby 2) [161], [162]

- 1 = Male
- 2 = Female
- 8 = Other or Not Known

Special Care Baby Unit (Baby 1 and Baby 2) [163], [164]

- 0 = Not Admitted
- 1 = Admitted for up to 48 hours
- 2 = Admitted for more than 48 hours
- 9 = Not known

Baby Discharged to (Baby 1 and Baby 2) [165], [166]

- 1 = Home
- 2 = Remaining in Special Care Baby Unit
- 3 = Special Care Baby Unit but home with mother
- 4 = Transfer to Other Hospital
- 5 = Other Unit in same hospital
- 6 = Foster Home
- 7 = Local Authority Care
- 8 = Healthy baby remaining in unit after mother's discharge
- 9 = Dead

APPENDIX 4

PLEASE PRESS FIRMLY WITH A FINE TIPPED BALL-POINT PEN

NEONATAL RECORD (Revised 1.1.87)

SMR11  
(ABBREVIATED)

Hospital of Birth (Name or Code No.) ..... 1

Case Reference No. .... 6

Maternal Reference No. .... 16

Surname ..... 26

Infant Forenames.....

Telephone No. ....

Home Address.....

..... Post Code ..... 38

Ward..... Paediatrician or G.P. .... 47

Family Doctor.....

Address.....

..... Telephone No.....

BIRTH RECORD

Specify Place ..... 55

1. Hospital  
2. Home  
8. Other  
9. N/K

E.D.D. .... Sure Not Sure N/K ..... 56

Gestation (by dates).....

Time Hrs. Date of Birth ..... 58

Appar Score ..... 64

1 min./5 min.  
(for 9 and 10 enter 9, N/K=0)

Resuscitation

1. Nil (with clear airway, funnel O<sub>2</sub>) 5. Intubation, IPPV (with drugs)

2. Mask, IPPV (no drugs) 6. Drugs only

3. Mask, IPPV (with drugs) Specify:

4. Intubation, IPPV (no drugs) 8. Other 9. N/K ..... 70

Birth Weight (g) ..... 71

Number of births this pregnancy ..... 75

Birth Order ..... 76

Sex 1. Male 2. Female 9. N/K ..... 77

O.F.C. cm. .... 78

Transfers within hospital (2 only)

0. None 2. SCBU 9. N/K 1st ..... 90

1. Post Natal Cot 8. Other 2nd ..... 91

Number of days in SCBU ..... 92

Jaundice (bilirubin mg%;  $\mu$ mol/l)

1. Absent 3. Moderate (12.0-19.9; 205-340) 9. N/K ..... 116

2. Mild (5-11.9; 86-204) or not measured 4. Severe (20.0+; 342+)

Absent 1 Present 2 N/K 9 ..... 118

Significant Hypotonia ..... 121

Convulsions ..... 122

Recurrent Apnoea ..... 123

Assisted Ventilation after 30 mins. .... 123

Feeding Difficulty ..... 124

TRANSFER BETWEEN HOSPITALS (Neonatal Only)  
TRANSFER 1

Receiving Hospital Code No. .... 127

Case Reference No. .... 132

Paediatrician or G.P. .... 142

Date of Admission..... 149

Admitted to 1. Post Natal Cot 2. SCBU 8. Other ..... 155

Number of days in SCBU ..... 156

TRANSFER 2

Receiving Hospital Code No. .... 158

Case Reference No. .... 163

Paediatrician or G.P. .... 173

Date of Admission..... 180

Admitted to 1. Post Natal Cot 2. SCBU 8. Other ..... 186

Number of days in SCBU ..... 187

DISCHARGE RECORD

Condition 1. Normal 4. Dead 8. Other ..... 190

2. Doubtful 5. Dead P.M. 9. N/K

3. Cong. Abn. 6. Cong. Abn. & Other

Discharge (Final)

1. Home with Mother 5. Transfer to Residential/Foster Care ..... 191

2. Home after Mother

3. To care of relative 6. Dead

4. To other ward or Hospital (Medical or Surgical). 8. Other 9. N/K ..... 191

Age (Days)..... Weight at Discharge ..... 192

Date of Discharge ..... 196

DIAGNOSIS

..... 202

..... 206

..... 214

..... 220

..... 226

..... 232

..... 236

..... 244

..... 250

..... 256

Operations (2 only) 1. .... 266

2. .... 266

FOLLOW UP 1. None 3. Elsewhere ..... 270

2. This Hospital 4. Multiple

Local Option ..... 271

..... 281

PLEASE NOTE: COMPLETION OF SHADED BOXES IS OPTIONAL

## APPENDIX 4 (cont.)

## NEONATAL RECORD—SMR11 (ABBREVIATED) FOR FURTHER DETAILS SEE MANUAL

Notes for completion of this form.

- General**
1. This form should be completed for every newborn infant discharged or transferred from hospital. The top copy should be sent in monthly batches to Room BO20, Information and Statistics Division, Trinity Park House, South Trinity Road, Edinburgh EH5 3SQ. The second copy may be sent to the General Practitioner and the back copy may be retained in the Hospital Case Records.
  2. Use legible block capitals. A fine tipped ball point pen should be used.
  3. In those instances where the key to the code is not given on the form, you may write comments in the spaces provided in addition to coding.
  4. The use of separate temperature and weight charts will be necessary.
  5. Items which do not have numbered coding boxes will not be included on the computer record. Shaded boxes need not be filled.

Administrative and Clinical Data – Coding Instructions

Box	Item	Instructions																
1	Hospital of Birth	Enter the 5-digit official code																
6	Case Reference No. )	Enter a unique number. All numbers should have a minimum of 6 digits. Preceding zeros should be entered to make the number up to 6 digits. e.g. 12345 = <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td></td><td></td><td></td><td></td></tr></table>	0	1	2	3	4	5										
0	1		2	3	4	5												
16	Maternal Reference No. )																	
26	Surname	Enter the current surname, starting with the left-hand box. Apostrophes and hyphens should be placed in separate boxes. Names containing more than 12 letters should be entered as follows: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td>D</td><td>U</td><td>R</td><td>H</td><td>A</td><td>M</td><td>-</td><td>R</td><td>O</td><td>B</td><td>E</td><td>R</td><td>T</td><td>S</td><td>O</td><td>N</td></tr></table>	D	U	R	H	A	M	-	R	O	B	E	R	T	S	O	N
D	U	R	H	A	M	-	R	O	B	E	R	T	S	O	N			
38	Postcode	Enter postcode if available.																
47	Paediatric Consultant or G.P.	Enter appropriate 7-digit code.																
55	Specify Place	Enter appropriate code.																
56	Gestation	Enter the number of weeks (min. =20, max. =45). If not known, enter "99".																
58	Date of Birth	Enter a 6-digit date, e.g. 010182 for 1st January 1982.																
64	Apgar Scores (at 1 and 5 minutes)	Each box must contain a number in the range 0-9, where "0" means not done. For scores of 9 or 10 enter code "9". If resuscitation is in progress at 1 or 5 minutes, enter 'R'.																
70	Resuscitation	Enter appropriate code.																
71	Birth Weight	Enter the weight in grams, e.g. '0980' (min. =0200, max. =7500). If not known enter 9999.																
75	Number of Births this Pregnancy	Enter in box 74 if the child was a singleton (1), a twin (2) or a triplet (3).																
76	Birth Order	Enter in box 75 the order this child was born, e.g. the second child born in triplets=2																
77	Sex	Enter appropriate code.																
78	O.F.C.	Enter the measurement in cm. (preferably measured on third day of life). Min. =10.0, max. =49.9. If not known enter "99.9".																
90-91	Transfers within hospital	Enter appropriate code. Both boxes should be completed.																
92	Number of days in SCBU	Number of days = day of discharge minus day of admission to SCBU.																
1	Jaundice	Enter appropriate code.																
2	Findings – Any Age	Enter appropriate code.																
	Transfer between Hospitals	(i.e. discharge from one hospital and admission to another) For further details see manual.																
	Transfer 1 and 2 (if appropriate)																	
117	Receiving Hospital Code No.	Enter the 5-digit code if known. Otherwise write name of hospital.																
122	Case Reference No.	Enter a unique 10-digit code. All numbers should have a minimum of 6 digits. Preceding zeros should be entered to make the number up to 6 digits. e.g. 12345 = <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td></td><td></td><td></td><td></td></tr></table>	0	1	2	3	4	5										
0	1	2	3	4	5													
132	Paediatric Consultant or GP.	Enter appropriate 7-digit code.																
139	Date of Admission	Enter a 6-digit date e.g. 070282 for 7th February 1982.																
145	Admitted to	Enter appropriate code.																
146	Number of days in SCBU	Number of days = day of discharge minus day of admission to SCBU.																
180	Condition	Enter appropriate code.																
181	Discharge (Final)	This applies to discharge from the neonatal service. Enter appropriate code.																
182	Weight on Discharge or Death	Enter the weight in grams, e.g. '0980' (min. =0200, max. =7500). If greater than 9998 gm. enter 9998. If not known enter 9999.																
186	Date of Discharge or Death	Enter a 6-digit date e.g. 090282 for 9th February 1982.																
192-246	Diagnosis	The first diagnosis, Classification of Infant, Single twin, etc., must be completed. The codes to be used are in the range V30 to V39 with 0, 1 and 2 used to indicate place of birth. The <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td>V</td><td>3</td></tr></table> have been preprinted leaving the remaining two digits to be filled in. The other diagnoses may be left blank but if filled in should be coded to the BPA supplement.	V	3														
V	3																	
252-256	Operations	Enter code in accordance with the Office of Population Censuses and Surveys Code of Operations.																
260	Follow up	Enter appropriate code.																
271	Local Option	These boxes are for local use only. Unused boxes should be left blank.																

List of Abbreviations

EDD	- Estimated date of delivery	Cong. Abn.	- Congenital Abnormality
IPPV	- Intermittent positive pressure ventilation	N/K	- Not known
SCBU	- Special Care Baby Unit		





## KEY TO CODED ITEMS

FULL INSTRUCTIONS FOR COMPLETING THIS FORM ARE CONTAINED IN THE SMR1 MANUAL

## SEX (SEX)

1. Male
2. Female
8. Other or NK

## MARITAL STATE (MRST)

1. Never Married — Single
2. Married — (Includes Separated)
3. Widowed
8. Other — (Includes Divorced)
9. NK

## ADMITTED/TRANSFERRED FROM (ADTF)

1. Home = Usual Address
2. Other N.H.S. Hospital (In-patient, Short Stay or Day Bed Facilities only)
3. Other Unit in This Hospital (In-patient Facilities or Day Bed Units only)
8. Other

## TYPE OF ADMISSION (TADM)

0. Deferred Admission
  1. Waiting List/Diary/Booked
  2. Repeat Admissions
  3. Transfer
  4. Emergency — Deliberate Self Inflicted injury or Poisoning
  5. Emergency — Road Traffic Accident
  6. Emergency — Home Accident (Includes Accidental Poisoning in the Home)
  7. Emergency — Other Injury (includes Accidental Poisoning other than in the Home)
  8. Emergency — Other (excludes Accidental Poisoning)

## DISCHARGE CODE (DISC)

0. 'Irregular' — eg Self Discharge
  1. Home
  2. Convalescent Hospital or Home
  3. Other hospital
  4. Local Authority Care
  5. Transfer to other specialty in same hospital
  6. Died (P.M.)
  7. Died (No P.M.)
  8. Other

## CATEGORY OF PATIENT (CAT)

1. Amenity
2. Paying
3. NHS
7. Special Arrangements

## TYPES OF FACILITY (TOF)

1. In-patient Admission
5. 5 Day Ward
6. Day Bed Unit
7. Day Case In-patient Facilities
8. Day Case Other

## SPECIALTY (SPEC)

(Read detailed instructions in manual)

- 01 General Surgery
- 02 Orthopaedic Surgery
- 03 ENT Surgery
- 04 Ophthalmology
- 05 Urology
- 06 Neurosurgery
- 07 Thoracic Surgery (incl. Cardiac Surgery)
- 08 Plastic Surgery (incl. Maxillo-Facial Surgery and Burns)
- 11 Orthodontics and Paediatric Dentistry
- 12 Oral Surgery and Oral Medicine
- 16 General Medicine
- 17 Cardiology
- 18 Metabolic Disease
- 19 Neurology
- 21 Gastroenterology
- 22 Poisons Unit
- 23 Dermatology
- 24 Nephrology
- 25 Rheumatology
- 26 Rehabilitation Medicine
- 28 Respiratory Medicine (incl. Respiratory T.B.)
- 31 Communicable Diseases
- 32 VD (STD)
- 33 Diagnostic Radiology
- 34 Radiotherapy (consultative)
- 36 Homeopathy
- 37 Medical Oncology
- 38 Spinal Paralysis
- 39 Surgical Paediatrics
- 40 Medical Paediatrics
- 41 Pain Control (Anaesthetist)
- 42 Gynaecology
- 46 Special/Intensive Care Baby Unit
- 48 Intensive Therapy Unit
- 49 Accident and Emergency
- 50 Geriatric Assessment
- 51 Geriatric Long Stay
- 52 Young Chronic Sick
- 62 Haematology
- 73 GP (other than Obstetrics)
- 76 Acute Mixed
- 98 Other Acute



# Greater Glasgow Health Board

## Health Visitor Child Health Record

1001

**CONFIDENTIAL**

CHILD'S SURNAME

GGHB NO.

FORENAMES

BIRTH DATE

ADDRESS

PLACE OF DELIVERY

BIRTH WEIGHT

MOTHER'S D.O.B.

TEL. NO.

DISTRICT

SAMPLE

CHANGE OF ADDRESS \_\_\_\_\_

GENERAL PRACTITIONER \_\_\_\_\_

GUTHRIE TEST      DATE \_\_\_\_\_ RESULT \_\_\_\_\_

HEALTH VISITOR SCREEN/EXAM.		HEARING TESTS	
AGE	DATE		
10-14 WEEKS		<input type="checkbox"/>	<input type="checkbox"/>
18-24 MONTHS		<input type="checkbox"/>	<input type="checkbox"/>
36-42 MONTHS		<input type="checkbox"/>	<input type="checkbox"/>

### IMMUNISATION RECORD

Antigen	Date	Antigen	Date	Antigen	Date
DTP/DT 1	/ /	Polio 1	/ /	MMR	/ /
2	/ /	2	/ /		/ /
3	/ /	3	/ /		/ /
B.C.G.	/ /		/ /		/ /

Contraindications to Immunisation

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Antenatal Care \_\_\_\_\_

Post Natal Condition/Complications \_\_\_\_\_

**DELIVERY**

Type \_\_\_\_\_

Complications \_\_\_\_\_

**NEONATAL DATA**

Birth Weight \_\_\_\_\_ Kg Discharge Weight \_\_\_\_\_ Kg Date of Discharge \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Gestation (completed weeks) \_\_\_\_\_

	YES	NO	Not Known
Asphyxia (Apgar below 5 at 5 minutes)			
Assisted respiration required after 30 minutes			
Low birth weight ( < 2,500 g)			
Convulsions (any cause)			
Jaundice (serum bilirubin > 200 ( $\mu$ mol) / L or 12 mg/100 ml)			
Tube feeding			
Profound Hypotonia			
Recurrent apnoea or lapses of consciousness			

**CONGENITAL ABNORMALITIES & HANDICAPPING CONDITIONS** (these factors should also be recorded on the reverse side of the consent form)

\_\_\_\_\_

Other conditions \_\_\_\_\_

Feeding \_\_\_\_\_

Examination \_\_\_\_\_

Remarks and Advice \_\_\_\_\_

Date of First Visit \_\_\_\_\_ H.V. Sig. \_\_\_\_\_

DEATHS OF INFANTS RESIDENT IN GCHB

SURNAME .....  
 1st name(s) .....  
 Address .....  
 .....  
 .....

Place of death: 1 - home; 2 - hospital;  
 3 - nursing home; 4 - other

Cause of death (words)

- 1.
- 2.
- 3.
- 4.
- 5 STILLBIRTH

Category of death

1. <24 hours .....
2. 24 hours - 6 days ....
3. 7 days - 27 days ....
4. 28 days <1 year ....

Age at death .....

Father's occupation.....

No. births: singleton - 1  
 twin - 2  
 triplet - 3

Post mortem: yes ...  
 no ...  
 expected ...

D.O.B.  No.  10

Sex  Place of Birth  16

Postcode  Dist.  23

Date of death  29

Place of death  30

Cause of death

1.   
 2.   
 3.   
 4.  50

Congenital defect  51

Category  52

Gestation  54

Parity  56

Birthweight (grams)  60

Social class  61

No. of births  62

Single parent  63 maternal age  65

Gestation certainty  Prev. pregs.  68

Ch. still living  69 Prev SBs  Prev IDs  71

Codes:- Sex: male = 1; female = 2  
 Congenital defect: yes = 1, no = 2  
 single parent: yes = 1, no = 2

**ALPHAFETOPROTEIN ASSAY REPORT**

From: DUNCAN GUTHRIE INST. OF MEDICAL GENETICS,  
YORKHILL, GLASGOW G3 8SJ

Tel: 041-339 8888 ext 393

Date Sample Taken

Lab. Ref. No.



Surname:  
Forename:  
Address:  
  
Weight:            Kg.            Height:            m.  
Date of Birth:

Hospital:  
Address:  
  
Hospital No.:  
Clinic/Ward:  
Consultant:

Previous Serum A.F.P. Report Number

L.M.P.

Weeks Gestation:

By Dates

Exam<sup>D</sup>

Ultrasound

Previous History of Neural Tube Defect

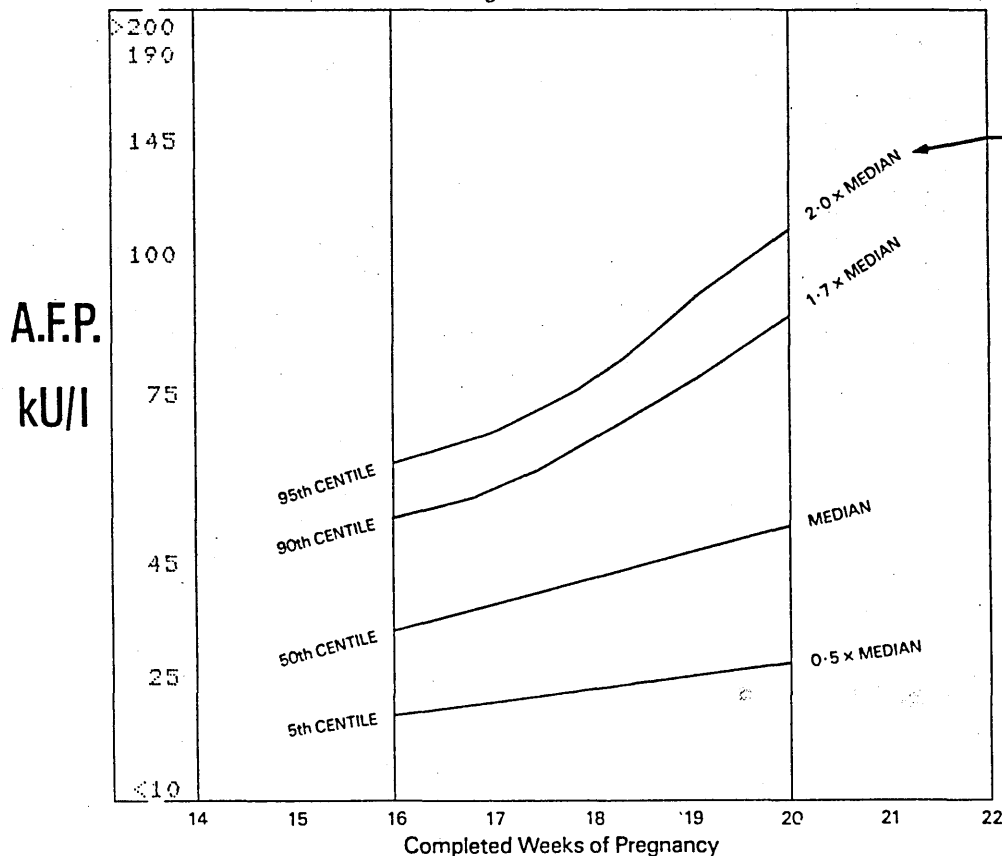
Complication of this Pregnancy

Remarks

Serum A.F.P. Result            kU/l

Comments

Please amend graph if gestation is corrected after sampling.  
Screening Period 16-20 Weeks



RECOMMENDED ACTION ON FIRST SERUM AFP LEVEL:

ABOVE 95th CENTILE:  
CHECK GESTATION BY ULTRASOUND, EXCLUDE TWINS, THREATENED AND MISSED ABORTION, REPEAT SERUM AFP

INTERVENTION LEVEL

BETWEEN 90-95th CENTILE:  
VALIDATE GESTATION

BELOW 90th CENTILE:  
NO ACTION INDICATED IF GESTATION VALID and DOR correct

Date \_\_\_\_\_

Signature \_\_\_\_\_

Local ID No. <b>14</b>	EUROCAT No. <b>14</b>	MALFORMATIONS
Date of Birth	Residence code	Date of discovery
Place of Birth (specify)	Age at delivery (years)	When discovered (see instructions)
Sex (1 = Male, 2 = Female, 3 = Indeterminate, 9 = Not known)	Previous Pregnancies (1 = Spontaneous abortion(s) no., 2 = Induced abortion(s) no.)	Condition at discovery (1 = live, 2 = dead, 9 = NK)
No. of babies delivered	Live births - no.	Syndrome
Birth order (in multiple set) (1 = live, 2 = still, 3 = spont. ab., 4 = induced ab., 9 = NK)	Stillbirths - no.	Malformations present:
Type of birth (1 = live, 2 = still, 3 = spont. ab., 4 = induced ab., 9 = NK)	Total pregnancies - no.	1
Birth weight (grams)	Occupation	2
Date of L.M.F.	Social status	3
Length of gestation (weeks)	Racial type	4
Certainty of L.M.F. (1 = certain, 2 = uncertain, 3 = no L.M.F., 9 = not known)	For boxes 42-46 & 63-66 code: 1 = yes, 2 = no, 9 = NK	5
Pre-natal diagnosis: Amniocentesis (see instructions) (not serum AFP screening)	Chronic illness (specify)	6
Ultrasound	Illness during pregnancy (specify)	7
Other techniques (specify)	Smoking	8
Karyotype of infant/fetus (see instructions)	Alcohol	9
Post mortem examination	Drugs (specify)	10
Sources of information (see instructions)	Consanguinity (1 = 1st cousin, 2 = 2nd cousin, 8 = other relation, 9 = NK, 0 = not related)	11
Date of Death	FATHER	12
Previous sibs notified to EUROCAT (1 = yes, 2 = no, 9 = NK)	Date of Birth	13
Local code nos. 1	Age at delivery (years)	14
2	Occupation	15
3	Social status	16
No. of sibs with same type of anomaly	Racial type	17
No. of sibs with other anomalies (specify)	Chronic illness (specify)	18
Mother - same type of anomaly (1 = yes, 2 = no, 9 = NK)	Smoking	19
Father - same type of anomaly (1 = yes, 2 = no, 9 = NK)	Alcohol	20
	Drugs (specify)	21
	Name	22
	Address	23
	Post Code	24
	(For local use only)	25
	Enter additional malformations/comments below:	26

## APPENDIX 10

**ANENCEPHALY AND SPINA BIFIDA SCREENING****(i) Trends in Pregnancy & Birth Prevalence**

Trends in birth and pregnancy prevalence were modeled using poisson regression models. Details of the significance of the regression slope and fit of the models are given below.

**Poisson Regression**

The form of the poisson model is

$$\log(\text{expected pregnancies or births}) = \text{intercept} + \log(\text{pregnancies at risk}) + \text{slope} * i$$

where  $i = 1, \dots, 11$  represents the years 76 - 86

log = natural logarithm

**ANENCEPHALY****Pregnancy Prevalence**

Trend  $X^2 = 8.68$  1df  $p < 0.005$

Fit of Model  $X^2 = 13.10$  9df  $p > 0.1$

**Parameter Estimates**

intercept	-6.006	ese	0.127
slope	-0.059	ese	0.020

**Birth Prevalence**

Trend  $X^2 = 44.42$  1df  $p < 0.0005$

Fit of Model  $X^2 = 15.72$  9df  $p > 0.05$

**Parameter Estimates**

intercept	-6.345	ese	0.218
slope	-0.306	ese	0.052

ese = estimated standard error

**SPINA BIFIDA****Pregnancy Prevalence**Trend  $X^2 = 3.78$  1df  $0.075 > p > 0.05$ Fit of Model  $X^2 = 8.87$  9df  $p > 0.4$ 

## Parameter Estimates

intercept	-6.037	ese	0.124
slope	-0.037	ese	0.019

**Birth Prevalence**Trend  $X^2 = 20.9$  1df  $p < 0.0005$ Fit of Model  $X^2 = 17.6$  9df  $p < 0.05$ 

## Parameter Estimates

intercept	-6.071	ese	0.142
slope	-0.110	ese	0.024

This regression has a poor fit ( $p < 0.05$ ) and was redone excluding 1981 as this appears to be an 'outlier' (ie an unusual observation with high sensitivity & terminated when detected in that year). The details of this new regression are give below.

Trend  $X^2 = 19.95$  1df  $p < 0.0005$ Fit of Model  $X^2 = 12.18$  8df  $p > 0.1$ 

## Parameter Estimates

intercept	-6.049	ese	0.140
slope	-0.105	ese	0.024

With this year removed the curve fits the data better. This is the curve which is shown on the prevalence graph. Please note - whether or not 1981 is removed would make no difference to the fact that there is a significant decline in birth prevalence, since using all years  $p < 0.0005$ . The fitting of these models is purely to document the fact that there are significant trends within the data.



## APPENDIX 10 (cont.)

**(ii) Trends in Screening, Sensitivity and Terminations when Detected**

Trends in screening, sensitivity and terminations when detected provide insights into the effectiveness of the screening process since -

$$\text{proportion terminated} = \text{proportion screened} * \text{proportion detected when screened (sensitivity)} \\ * \text{proportion terminated when screened \& detected}$$

Changes in the proportion terminated could be due to one or any combination of these three factors. Trends over time were modeled individually for these three factors using logistic regression. The details of the significance and fit of the regression curves are given below.

**Logistic Regression**

The form of the logistic regression model is

$$\log(p/(1-p)) = \text{intercept} + \text{slope} * i$$

where  $i=1, \dots, 11$  represents the years 76-86

log = natural logarithm

$p$  = expected proportion of whatever outcome (ie proportion screened, proportion detected when screened ... etc)

The slope parameter can be thought of as the log odds ratio between successive years for whatever outcome.

**ANENCEPHALY****Proportion Screened**

Fitted without intercept.

Trend                      z-score = 8.5   p < 0.0001

Fit of model                 $X^2 = 15.62$  10df   p > 0.1

**Parameter Estimate**

slope	0.3564	ese	0.042
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**Proportion Detected when Screened (sensitivity)**

Trend                       $X^2 = 6.61$  1df   p < 0.025

Fit of model                 $X^2 = 13.29$  9df   p > 0.2

**Parameter Estimates**

intercept	1.487	ese	0.650
slope	0.338	ese	0.151

## APPENDIX 10 (cont.)

**Proportion Terminated when Screened & Detected**Trend  $X^2 = 0.042$  1df  $p > 0.8$ 

Model fitted as a constant term

Fit of model  $X^2 = 8.876$  10df  $p > 0.5$ 

Parameter Estimate

constant 3.45 ese 0.414

**SPINA BIFIDA****Proportion Screened**

Fitted without intercept.

Trend z-score = 6.45  $p < 0.05$ Fit of model  $X^2 = 13.09$  10df  $p > 0.2$ 

Parameter Estimate

slope 0.144 ese 0.022

**Proportion Detected when Screened (sensitivity)**

Fitted without intercept.

Trend z-score = 4.16  $p < 0.05$ Fit of model  $X^2 = 14.16$  10 df  $p > 0.15$ 

Parameter Estimate

slope 0.097 ese 0.023

**Proportion Terminated when Screened & Detected**

Fitted without intercept.

Trend z-score = 6.03  $p < 0.05$ Fit of model  $X^2 = 14.92$  10df  $p > 0.1$ 

Parameter Estimate

slope 0.239 ese 0.040

## HYDROCEPHALY

terminations

goodness of fit  $\chi^2 = 11.02$  7df  $p > 0.1$ 

## ANENYAL BIFIDA

terminations

goodness of fit  $\chi^2 = 20.04$  8df  $p < 0.05$ 

1981 produces a poor fit for spina bifida. If, however, 1981 is removed  
the new fit is

 $\chi^2 = 11.43$  7df  $p > 0.1$

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