A SURVEY OF PREGNANCIES AFFECTED WITH A NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

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1. INTRODUCTION

Abnormalities of the central nervous system account for up to a third of all congenital abnormalities and include anencephaly, encephalocoele and spina bifida (Smithells et al 1976).

The effect that these abnormalities have on life is variable ranging from incompatibility to minimal or no disability (Hunt 1973, Althouse and Wald 1980, Lorber and Salfield 1981, Chervenak and Isaacson 1989). Most surviving infants have some impairment of function (Lorber 1971). Medical treatment attempts to minimise this but the cure for the failure of development of the spinal cord has not yet been achieved and prevention remains the ultimate aim (Smithells et al 1976). This may be approached in one of two ways; either by primary prevention whereby every child conceived has a spinal column that is perfectly formed, or by secondary prevention whereby the pregnancy with a neural tube defect is terminated thus preventing the child from being born with the defect. The former method is the optimum one but, until the cause of neural tube defect is elucidated, it is likely that secondary prevention will continue to be the only available alternative should termination of pregnancy be acceptable (Smithells et al 1976).

In an attempt to find the cause of neural tube defect many aetiological factors have been identified (Carter 1974,

Elwood and Nevin 1973, Campbell 1986 et al, Smithells 1983, MRC 1991). It has been hypothesised that, in this multifactorial condition, dietary factors have a major role to play (Smithells et al 1977). This has led to studies of periconceptional vitamin supplementation in mothers known to be at risk of a pregnancy affected with a neural tube defect i.e. having already had at least one affected pregnancy (Smithells et al 1980, Smithells et al 1983, MRC 1984, MRC 1991).

Following the results of trials by Smithells et al (Smithells et al 1980, Smithells et al 1983) showing an association between periconceptional vitamin supplementation and the reduction of recurrence risk of neural tube defect, The Medical Research Council began a randomised controlled trial (MRC 1984). A Regional Working Party on neural tube defect was established by The Obstetric and Gynaecological Sub-Committee of The Regional Medical Committee in The North Western Region to co-ordinate a study of prevention of recurrence of neural tube defect. However, a questionnaire sent to obstetricians indicated that vitamins were already being prescribed by over 70% of these clinicians, most of them advising Pregnavite Forte F (Bencard) as in the Smithells protocol (Smithells et al 1980). In view of this it was not possible to recruit patients to The MRC trial but there were a number of questions requiring investigation concerning the management of pregnancies affected with a

neural tube defect and subsequent prevention of recurrence. These were:

1. What was the accurate incidence of neural tube defect in The North Western Region and what was its distribution and epidemiology?

2. What were the counselling and supportive services available to couples following an affected pregnancy?

3. What was the outcome of subsequent pregnancies either supplemented or unsupplemented?

These questions formed the basis of this three year prospective study.

Since this study was undertaken there have been important developments in the field of the prevention of neural tube defect. These will be considered and their implications discussed in the light of the findings of this study.

2. THE AIMS OF THE STUDY

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This study aimed to

1. Establish a regional notification system for cases of neural tube defect

2. Ascertain the incidence of neural tube defect in The North Western Region

3. Identify the immediate level of support that families received surrounding the diagnosis of neural tube defect and the subsequent termination or delivery of the pregnancy

4. Identify information provided about the risk of recurrence of neural tube defect and the use of periconceptional vitamin supplementation

5. Follow up subsequent pregnancies and periconceptional vitamin supplementation received.

3. THE HISTORY OF NEURAL TUBE DEFECT

Neural tube defect is not a problem that only modern day society has to contend with. Skeletons with spina bifida had been identified from The Neolithic Period, The Bronze age and The Late Iron Age. These were adult remains so almost certainly not accompanied by serious handicap. A mummified anencephalic infant had also been discovered from approximately 2000 BC but remains of child skeletons with defects above sacral level were rare as the child would have died prior to adequate bone mineralisation. More recently, medieval cases have been described but anthropological data are minimal making studies into early genetic and environmental factors limited (van Gool and van Gool 1986).

Spina bifida, "separation of the vertebral elements in the midline", is a term that has been used since the 17th. century. Tulp was probably the first to use it in his book Observationum Medicarum Libri Tres - cum Aeneis Figuris. Apud Ludovicum Elzeurum, Amsterdam, 1642 (Rickham 1963). He recognised that the cystic lesion of the infants back involved the nervous system (Furkawa 1987). Anencephaly, "without head" was a term first thought to have been used by Shlegal in 1812 (Taruffi 1891) and, although inaccurate, remains in common usage today. By the mid 18th. century Morgagni had provided a complete review of 16th. and 17th. century literature on spina bifida and was the first to describe the pathophysiology of the defect (Morgagni 1761).

He linked spina bifida with hydrocephalus and appreciated that spina bifida and anencephaly were within a spectrum of the same defect. Abnormalities of the lower limbs, bowel and bladder were acknowledged as being associated with spina bifida.

During this period there were various other works, many Dutch, giving comprehensive descriptions of neural tube defect and its complications (Cleland 1883, van Gool and van Gool 1986).

Until well into the 19th. century it was believed that spina bifida was due to hydrops of the spinal cord resulting in disruption of the shape of the canal and bone (Brocklehurst 1976). Hydrocephaly was thought to cause the hydrops but was also known to occur as a result of spina bifida.

In 1881 Lebedeff experimented with chick embryos and human fetuses and again expressed the view that spina bifida and anencephaly were a spectrum of the same disorder (van Gool and van Gool 1986). Lebedeff believed that the disorder arose as a result of failure of closure of the neural tube.

In 1886 Von Recklinghausen hypothesised that it was an arrest in the development of the nervous system that led to a defective neural tube. Other hypotheses concerning the aetiology of neural tube defect were suggested but failure of

closure of the neural tube became the most acceptable (Brocklehurst 1976). The Arnold-Chiari group of malformations classically associated with spina bifida was described in the late 19th. century by the two workers after whom it was named.

Treatment of spina bifida was attempted in the 19th. century. Morton (1877) injected iodine-glycerine solution into the meningocoele sac but, although initial results were optimistic, it was soon apparent that the complications of hydrocephalus, incontinence, paraplegia, and infection had to be managed. This treatment was not the success it was hoped it would be.

External ventriculostomies were offered as a method of controlling hydrocephalus but infections were almost inevitable. The main change in care came in 1956 in Philadelphia with the development of the Spitz shunt system and the Holter valve (van Gool and van Gool 1986). These became a recognised way of controlling hydrocephalus. The development of a reliable shunt system and more effective antibiotics enabled primary surgical closure of the defect to be feasible.

Aggressive management became a widespread policy but problems were many. Paraplegia, scoliosis, incontinence and renal failure had to be dealt with. Complications from shunts were

high. A cure had not been achieved and the optimism of the 1950's fell. From then multidisciplinary teams were set up to co-ordinate the management of these children and deal with the multitude of problems caused by spina bifida.

Treatment of affected children continues to be recognised as complex, multidisciplinary and far from curative. Prevention must be aimed for. To prevent this common and distressing congenital abnormality the aetiology, epidemiology and outcome must be understood. These factors will be explored in the following chapters.

4. THE DEVELOPMENT OF THE NEURAL TUBE

To enable prevention of neural tube defect to be achieved an understanding of the aetiology of the abnormality is required. Such an understanding must first consider the embryological development of the neural tube, how this development may be imperfect, and what abnormalities may occur as a result of this.

4.1. The Normal Development of The Neural Tube

Following fertilization of the ovum by the sperm the zygote progresses along the fallopian tube increasing its cell number to reach the uterine cavity on day 4-5 after ovulation. The conceptus consists of 20-50 cells enclosed in the zona pellucida known as the morula. Gradually the cells become separated into two groups

1. The outer cell layer or trophoblast
2. The inner cell mass

The conceptus increases in size due to the absorption of fluid from the uterus and the zona pellucida is shed following which implantation occurs. On day 6-8 after ovulation the blastocyst begins to differentiate into deep cuboidal cells, forming the primary embryonic endoderm, and columnar cells which will become embryonic ectoderm and

mesoderm. The cells of the trophoblast form fetal membranes. The fetus is thus composed of a bilaminar disc of cells (Moore 1988).

The bilaminar disc undergoes a heaping up of cells on its upper layer to form the primitive streak. By a process of gastrulation, from day 14-19, notochord and mesoderm interpose between the two layers of the bilaminar disc giving the trilaminar disc.

As the embryo grows the primitive streak takes the form of a linear depression. At its anterior extremity a further collection of cells form the primitive knot. The notochordal process elongates from this on day 16 and hollows out to form the notochordal canal.

The vertebral column develops around the notochord which subsequently degenerates to form the nucleus pulposus of the intervertebral discs (Beck et al 1985).

The ectoderm overlying the notochordal process becomes thickened into the neural plate. By a process of neurulation the neural plate broadens into the neural groove on day 18 and eventually gives rise to the neural tube (Moore 1988).

Closure of the neural tube first occurs at the region that will become the junction between the brain and spinal cord

This extends cranially and caudally until only a small area is open at each end - the anterior and posterior neuropores. The neuropores close soon after the development of the head and tail folds, this being day 25 for the anterior neuropore and day 27 for the posterior. The neural tube will then develop into the central nervous system.

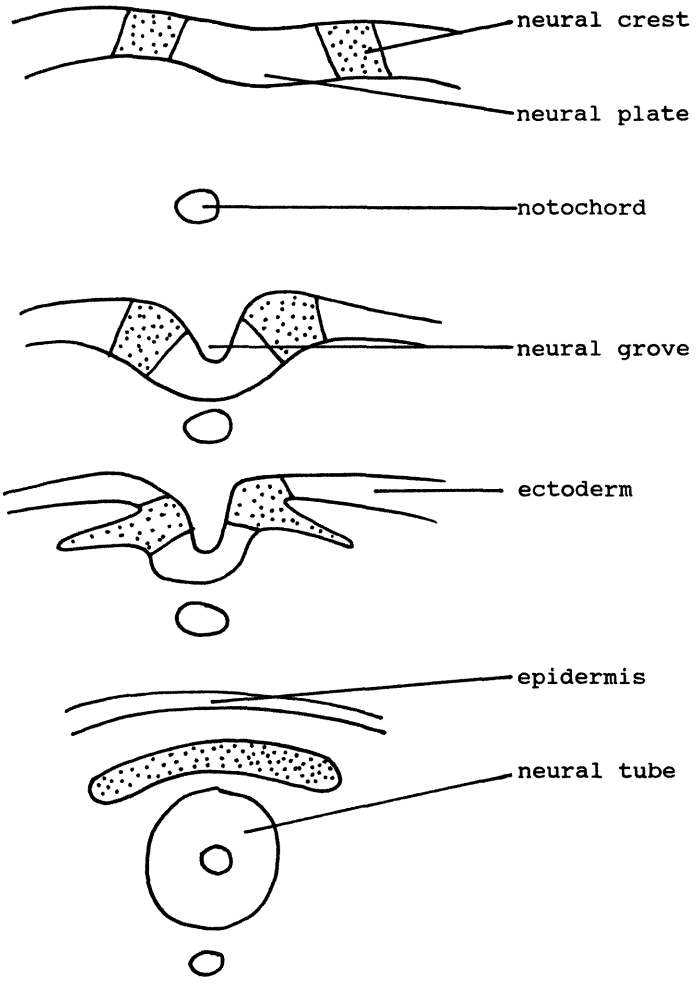
The cranial two thirds of the neural tube are destined to become the future brain whilst the remainder becomes the spinal cord. The walls of the neural tube thicken and the resulting central canal will form the ventricles of the brain and the canal of the spinal cord. This occurs at 9-10 weeks gestation. The wall of the neural tube differentiates into the various components of the central nervous system (Moore 1988).

These events are summarised in table 4.1. and diagram 4.

TABLE 4.1. THE EMBRYOLOGICAL DEVELOPMENT OF THE NEURAL TUBE

DAY POST CONCEPTION	EVENT
1	CONCEPTION
2	ZYGOTE STARTS TO DIVIDE AND FORMS MORULA
4	BLASTOCYST BEGINS TO DEVELOP
6	IMPLANTATION BEGINS
7 TO 9	BILAMINAR DISC FORMED
10	IMPLANTATION COMPLETE
14	GASTRULATION BEGINS
15	PRIMITIVE STREAK STARTS TO DEVELOP
16	NOTOCHORDAL PROCESS FORMS
	DEVELOPS INTO NOTOCHORDAL CANAL
17	EMBRYO NOW TRILAMINAR
18	NEURAL PLATE----->NEURAL GROOVE
19	FORMATION OF NEURAL FOLDS
20	EARLY STAGES OF BRAIN DEVELOPMENT
21	NEURAL GROVE DEEPENS
22	NEURAL FOLDS START TO FUSE
24 TO 25	ANTERIOR NEUROPORE CLOSES
27 TO 28	POSTERIOR NEUROPORE CLOSES

DIAGRAM 4. THE CLOSURE OF THE NEURAL TUBE



4.2. Abnormal Development of The Neural Tube

Abnormal neurulation results in a defect in the developing neural tube; the earlier the abnormality occurs in embryological development the more severe the resulting defect.

There are two theories regarding abnormal closure of the neural tube

1. normal closure fails in all or part of the neural tube
2. The neural tube closes normally but reopens.

These theories are of importance as each will be as a result of a developmental abnormality occuring at a specific gestation.

4.3. Animal Models of Neural Tube Defect

In an attempt to study these and other hypotheses concerning the development of the neural tube, defects have been produced experimentally in a variety of animals using a number of different agents. These include operative interventions in the chick (Jelinek 1960), radiation in the mouse and rat (Hicks 1953, Wilson and Karr 1951) and deficiencies and excesses of vitamins in the rat (Davis et al 1970, Smith et al 1978).

One animal model that has been investigated in detail is the

curly tailed mouse (Seller and Adinolfi 1981). This was first described in 1954 (Gruneberg 1954). The neural tube defect that occurs in this animal closely resembled the defect seen in humans. It is believed to be due to a recessive gene with variable expression that may be influenced by environmental factors (Embury et al 1979). Studies of the curly tailed mouse have supported the hypothesis that vitamin deficiency may contribute to the aetiology of neural tube defect (Seller and Perkins 1982). More recently, growth rates of the tissues forming the neural tube have been studied. The curly tailed mouse has continued to be used for these experimental investigations. Abnormal cell proliferation has been observed in the ventral area of development of the neural tube. Dorsal cell proliferation continues at a normal rate. The imbalance results in stress causing the embryo to curve ventrally and this appears to inhibit neural tube closure. Correction of the proliferation abnormality results in the prevention of neural tube defect. Growth promoting molecules have been hypothesised as being implicated in this (Copp 1991).

These animal models, although not established as being equivalent to human neural tube defect, offer valuable information about the embryology of the neural tube and the abnormalities that occur during its development (Campbell et al 1986).

4.4. The spectrum of defects

A defect in the closure of the neural tube results in a spectrum of fetal abnormalities dependant on the stage at which the neural tube fails to close.

There are many ways in which neural tube defect may be classified. Some terms are clinically descriptive whilst others are purely pathological.

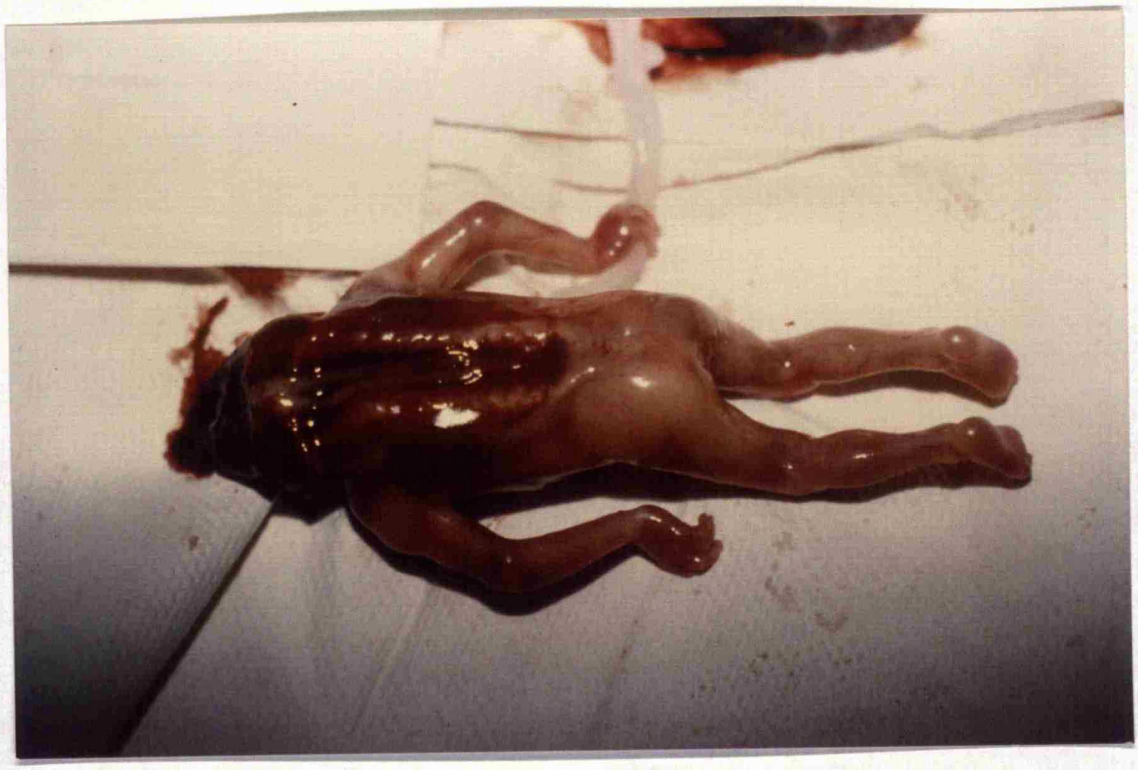
Defects of the cranium will first be considered followed by defects of the spinal cord.

4.5.CRANIUM BIFIDUM

1. Craniorachischisis

This is the most severe form of neural tube defect. It probably occurs during neural fold formation and results in complete exposure of the brain and spinal cord (see photograph 1).

PHOTOGRAPH 1. FETUS WITH CRANIORACHISCHISIS



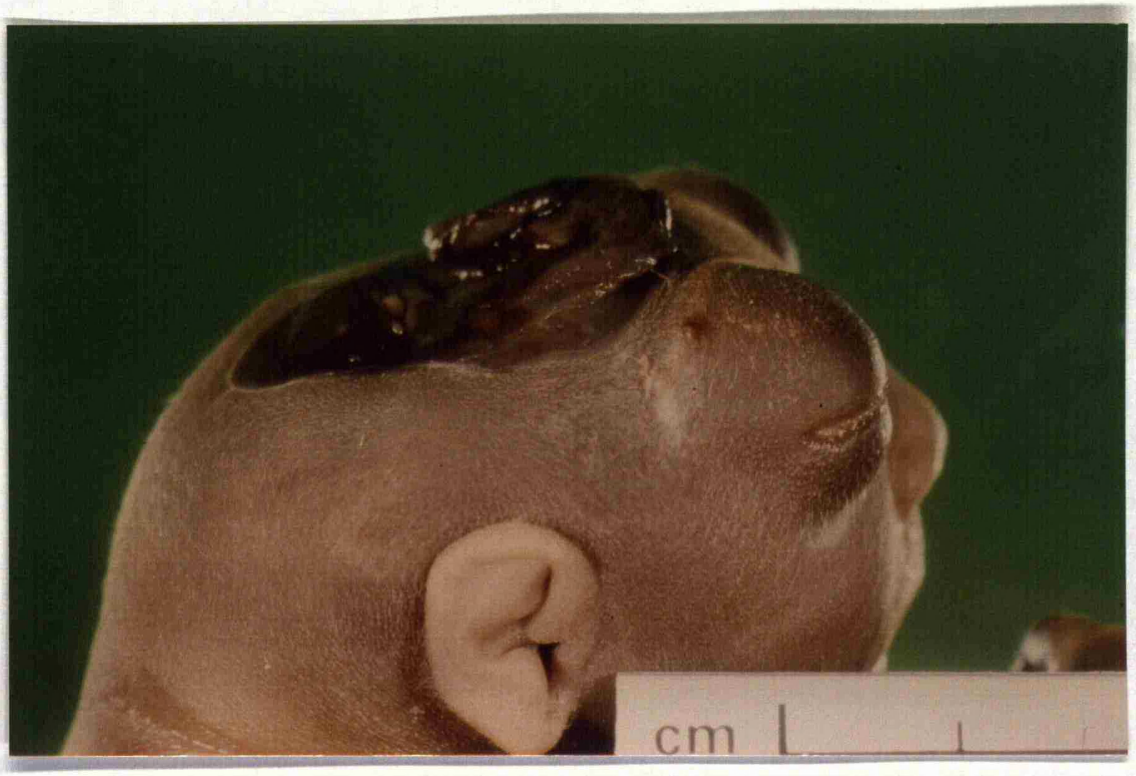
The skull vault is absent and the brain defective. There are a number of subtypes of this defect;

a). Anencephaly; the forebrain and midbrain are absent but the hindbrain complete. The spine is closed.

b). Hemicephaly; the forebrain is absent but the midbrain is partial or complete.

c). Exencephaly; the brain exists outside the skull but parts of the hemispheres are present and the diencephalon is developed. The ventricular surface of the brain is exposed. (See photograph 2).

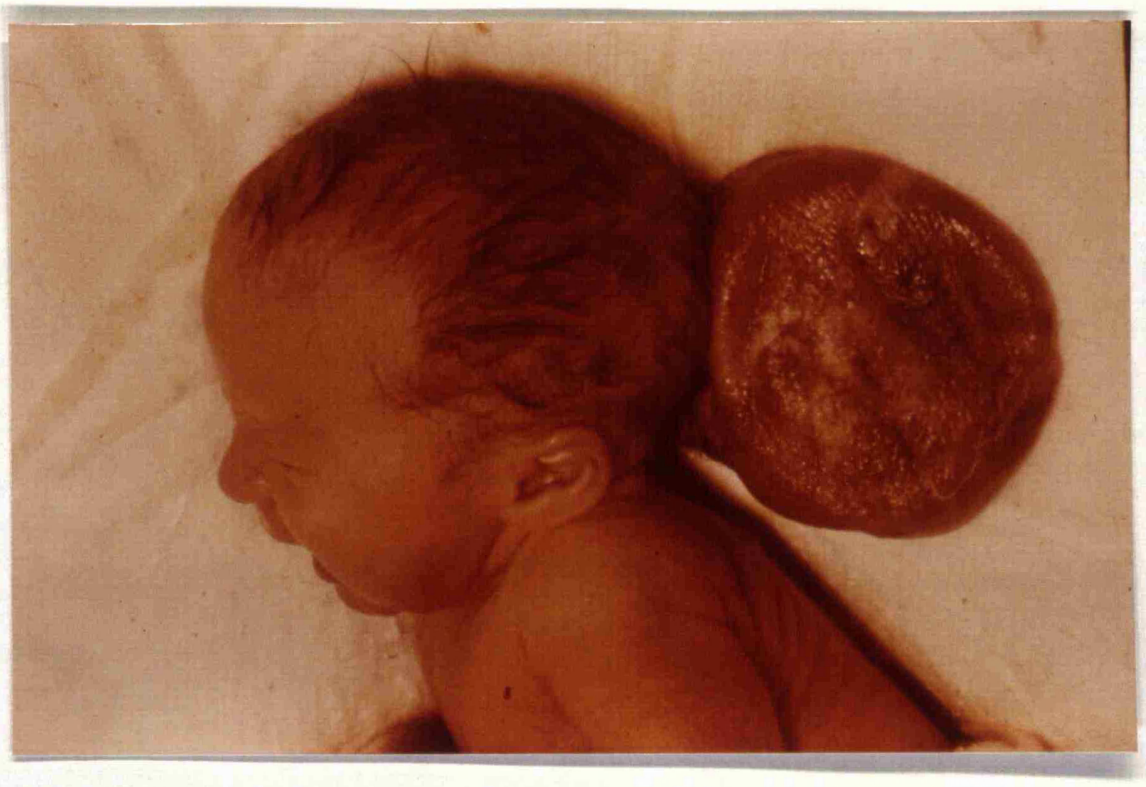
PHOTOGRAPH 2. ANENCEPHALY



2 . Meningoencephalocoele (encephalocoele).

In this case there is a defect in the skull along the suture lines usually in the occipital region. A portion of the brain protrudes through this defect and may contain part of the ventricular system. The brain is covered by meninges and is within a sac. The brain may be defective. (See photogragh 3).

PHOTOGRAPH 3. CHILD WITH MENINGOENCEPHALOCOELE



3. Meningocoele.

Only the meninges and sac protrude through the defect in the skull. The brain may still be defective.

4. Cranium Bifidum Occulta.

There is a bony defect in the skull but no protrusion of intracranial contents through it. The overlying skin may be abnormal.

4.6. SPINA BIFIDA

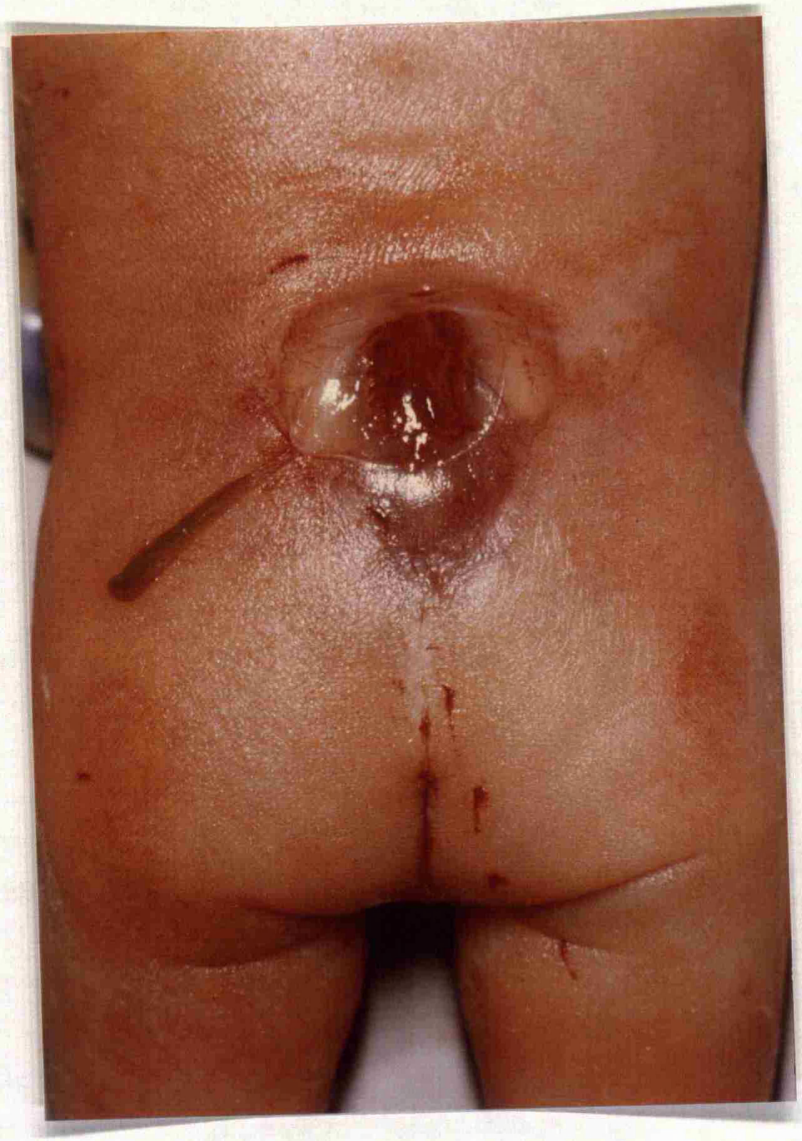
1. Complete Rachischisis.

This may exist as described above but with the skull closed. The spine is open and the spinal cord fully exposed. There is no sac and the spinal cord is grossly abnormal.

2. Meningomyelocoele (Myelomeningocoele).

There is a cystic lesion of the meninges around the malformed neural tube. The neural tissue is abnormal and is adherent to the inner wall of the sac. The overlying ectoderm is not epithelialised and the lesion is open allowing leakage of cerebrospinal fluid. (See photograph 4).

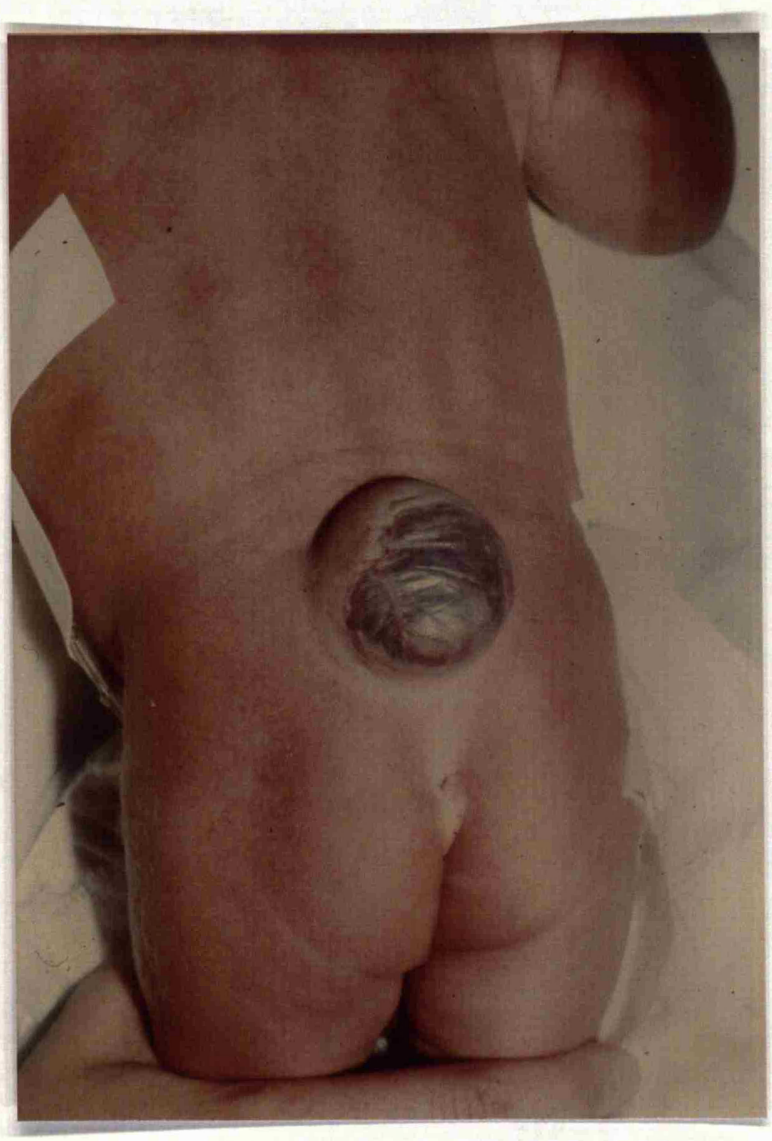
PHOTOGRAPH 4. CHILD WITH MENINGOMYELOCOELE



3. Meningocoele.

A sac protrudes from the abnormal vertebrae but does not contain nerve roots or spinal cord. The posterior spinal processes of the vertebrae at the site of the defect are not fused. The ectoderm may or may not be epithelialised. (See photograph 5).

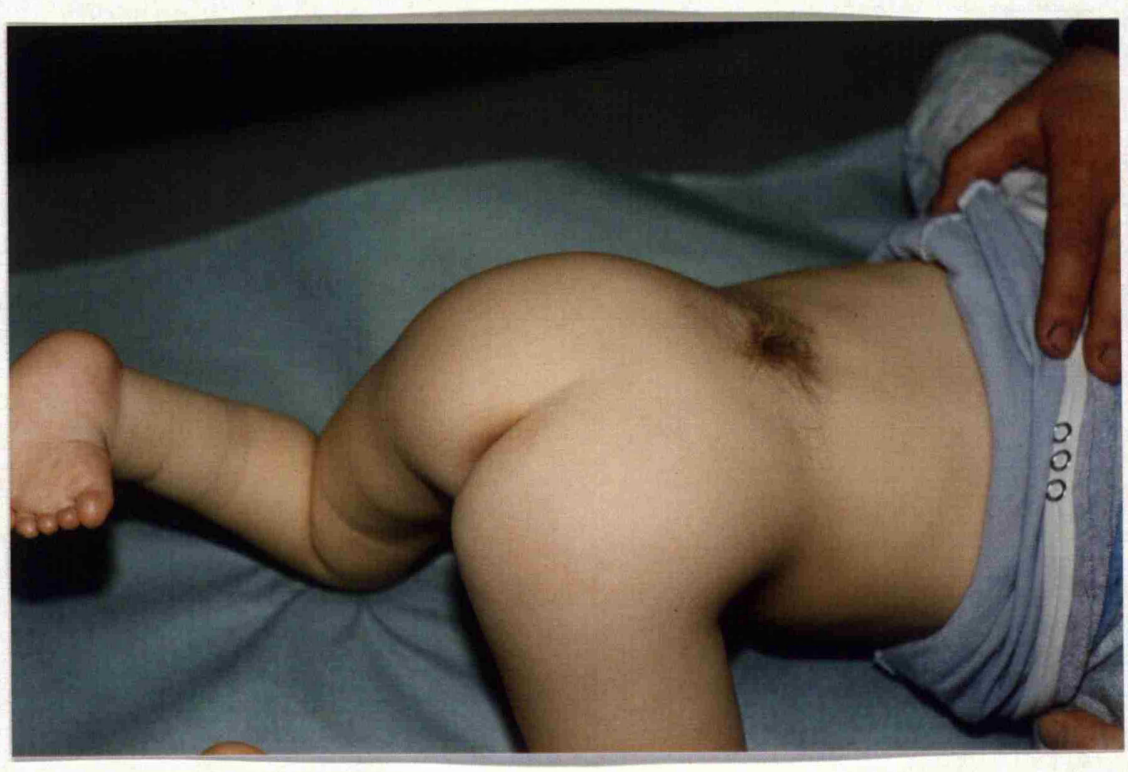
PHOTOGRAPH 5. CHILD WITH MENINGOCOELE



4. Spina bifida occulta.

The canal or vertebrae are defective but there is no sac. There may be a defect of the overlying skin such as a hairy patch or pigmentation. The spinal cord may be imperfectly developed. This defect is often a coincidental finding on radiography and is usually asymptomatic. (See photograph 6).

PHOTOGRAPH 6. CHILD WITH SPINA BIFIDA OCCULTA



Certain other abnormalities have been classified as a neural tube defect including iniencephaly and congenital dermal sinus. It is likely that these have slightly differing aetiologies (Elwood and Elwood 1980). It is recognised that certain anatomical defects occur in association with neural tube defect although not being part of an identifiable syndrome. There are frequently vertebral and rib anomalies surrounding the defect (David and Nixon 1976). In almost all cases of spina bifida there is a hind brain malformation, the Arnold-Chiari Malformation. This consists of

-caudal prolongation of the cerebellar vermis to a varying degree

-displacement of the fourth ventricle into the upper cervical canal

-displacement of the medulla into the upper cervical canal with a dorsally directed kink

-closure of the fourth ventricle to the central canal of the spinal cord.

The cerebellum is reduced in weight and causes obstruction of the flow of cerebral spinal fluid resulting in hydrocephalus (Lemire 1988).

This pathological description can now be related to clinical presentation.

4.7. The Clinical Presentation of Neural Tube Defect

The majority of cases of anencephaly, in all its forms, are incompatible with life for longer than a few hours.

Meningoencephalocoele, depending on the amount of brain tissue in the sac and the extent of damage to the remaining brain, can result in physical and mental deficits. There is often an associated hydrocephalus and the prognosis is generally poor. The extent of pathology in spina bifida is dependent on the damage to nervous tissue and the control of the associated hydrocephalus. The hydrocephalus, if progressive, results in apnoeic attacks, irritability, hypertonicity and gross brain damage (Brocklehurst 1976). Surgical arrest of the hydrocephalus will halt the expansion of the skull. In addition to the above physical problems a specific cognitive profilehas been documented in people with hydrocephalus, the cocktail party syndrome. The person has a higher verbal IQ than performance IQ and is bright and talkative but with little depth of knowledge and lack of concentration. There are also perceptual deficits (Brocklehurst 1976).

The spinal lesion can produce a range of lower limb dysfunctions. If the defect is at the thoracolumbar level it results in complete spastic paralysis or flaccid paralysis dependent on the extent of the lesion. The vertebral column

may be affected because of vertebral body anomalies giving rise to a scoliosis or kyphosis.

As a result of damage to the second to fourth sacral segments of the spinal cord, bladder function is affected producing either a spastic or hypotonic bladder depending on the level of the lesion. This causes progressive renal dysfunction and damage. Bowel function may also be affected.

The spectrum of pathological abnormalities resulting from neural tube defect is wide and infants who survive require a multidisciplinary team approach for themselves and for the family.

4.8. Definitions of The Categories of Neural Tube Defect

For the purposes of this study the following definitions will be used;

Anencephaly. This will include all the subgroups detailed above

Encephalocoele. This will include meningoencephalocoele and meningocoele.

Spina bifida. This includes all forms of spina bifida but excludes spina bifida occulta.

5. ANOMALIES ASSOCIATED WITH NEURAL TUBE DEFECT

Neural tube defect, whilst often occuring in isolation, can exist as part of a wider syndrome. Such a syndrome may have a recognised aetiology such as a chromosomal abnormality (Nisani et al 1981), and a mode of inheritance that results in a recurrence risk that differs from that of an isolated neural tube defect. These syndromes are summarised in Table 5.1.

Certain abnormalities are also known to occur in association with a neural tube defect although not demonstrated as being part of an identifiable syndrome. They include cleft lip and palate, exomphalos, genital anomalies, and renal anomalies. These may reflect the effect of a teratogen exerting a common influence at a vital stage of embryological development (Campbell et al 1986).

To make an accurate diagnosis detailed examination of aborted fetuses and infants with a neural tube defect is essential (Donnai and Farndon 1985).

TABLE 5.1. SOME OF THE SYNDROMES WITH NEURAL TUBE DEFECT AS ONE OF THEIR FEATURES

SYNDROME	FEATURES	INHERITANCE	REF.
MECKEL GRUBER SYNDROME	encephalocoele polycystic kidneys polydactaly micrognathia microgenitalia cleft palate talipes	autosomal recessive	Seller 1978
AMNIOTIC BAND SEQUENCE	anencephaly encephalocoele limb amputation constriction bands	sporadic	Hughes et al 1984
TRISOMY 18	NTD congenital dislocation hip	sporadic	Nisani et al 1981
TRISOMY 13	NTD microcephaly cleft lip\palate polydactaly congenital heart disease	sporadic	Davis & Robertson 1985
TRIPLOIDY	low birth weight multiple abnormalities	sporadic	Wertelecki et al 1976
RUBENSTEIN TAYBI SYNDROME	NTD microcephaly beaked nose broad distal phalanges	sporadic	Wiedemann et al 1985
NEURO-FIBROMATOSIS	NTD cafe au lait patches neurofibromata axillary freckling	autosomal dominant	Wiedermann et al 1985
HARD +/- E	hydrocephalus agyria retinal dysplasia encephalocoele	autosomal recessive	Pagon et al 1978

6. BACKGROUND INFORMATION ON NEURAL TUBE DEFECT - A REVIEW OF THE CURRENT LITERATURE

There have been many studies of neural tube defect ranging from small case reports (Oakshot 1989) to large multicentred research projects (Smithells et al 1976, Hall et al 1988, Eurocat 1991, Czeizel 1992). Aetiological factors have been identified and possibilities for prevention considered (Smithells et al 1983).

The literature available until the submission of this study in 1992 will be reviewed under the following categories;

Ascertainment of neural tube defect

Aetiology of neural tube defect

Periconceptional vitamin supplementation

Prenatal screening and diagnosis

Genetic counselling and support available for families.

There have been important developments since the submission of this study. These will be discussed and their implications considered.

6.1. THE ASCERTAINMENT OF NEURAL TUBE DEFECT

The epidemiological study of any congenital abnormality in a given population must ensure that the definition of the congenital abnormality is comparible with other studies and that there is complete ascertainment of affected cases.

6.1.1. The definition of Neural Tube Defect

Neural tube defect includes three categories of abnormality:

anencephaly
encephalocoele
spina bifida.

A fourth abnormality, spina bifida occulta, whilst recognised as a defect of the neural tube, is not usually included in epidemiological studies (Eurocat 1991). A description of these abnormalities has been considered previously.

Most statistical surveys rely on The International Classification of Diseases (WHO 1992) when defining a disease. In this classification system neural tube defect is included in congenital malformations of the nervous system under the categories anencephaly and similar malformations, encephalocoele and spina bifida. Spina bifida occulta is not included within these categories. Although this classification is comprehensive deficiencies still arise.

The classification does not take into account the aetiology of the disorder or disease and, as a result of this, malformations such as iniencephaly are classified as a similar malformation to anencephaly.

6.1.2. Methods of Ascertainment of Congenital Abnormality.

Complete ascertainment of cases affected with a congenital abnormality has become increasingly more difficult since the availability of prenatal diagnosis and selective termination of pregnancy. Prior to this most cases of neural tube defect would have resulted in a stillbirth or live born infant. These would be documented by the hospital in which the affected infant had been delivered. Home deliveries would escape such documentation although the majority of cases would result in hospital births because of the higher possibility of problematic deliveries in this group of mothers. Even then, some cases would remain unreported (Elwood 1970).

Many countries operate birth defect registers (Fedrick and Butler 1972, Eurocat 1990). In The United Kingdom the birth notification system for congenital malformations has been in operation since 1964 (Weatherall and Haskey 1976). Malformed infants, having been examined by a qualified person, are notified to it within seven days of birth. As this is a voluntary notification system it is not complete.

The cause of death, as defined by the death certificate, may also be used to study neonatal deaths but this lacks accuracy. There is little training given on the completion of death certificates and no standardized method of reporting (Kircher and Anderson 1987). It has been suggested that The International Classification of Diseases could be used to assist reporting (Knight 1986). This, whilst possibly useful for comparison of data, does not solve the problem of contributing factors being omitted. One study of 1656 neonatal deaths demonstrated that the diagnosis of anencephaly was 89% accurate, thus placing doubt on the reliability of the reporting of other, less gross, abnormalities (Fedrick and Butler 1972). The authors highlighted the dependence placed on the doctor when defining the cause of death emphasising the need for adequate training and a greater importance being placed on accuracy of documentation. A study of 55318 death certificates showed that the way in which death certification is carried out should be considered when using mortality data. A congenital abnormality such as spina bifida may not be reported if it did not contribute to the cause of death. This study did not consider how reporting of neonatal deaths may differ from the reporting of deaths occuring in other age groups (Goldacre 1993).

Inaccuracies are likely to occur in all notification systems.

It is important that adequately trained and motivated personel examine and report cases of congenital abnormality if accuracy is to be ensured (Donnai and Farndon 1985,Karwinski and Hartveit 1989).

The reporting system for termination of pregnancy is even less reliable than the birth notification system. There is a legal requirement for each termination of pregnancy to be notified to The Chief Medical Officer giving the indications for the termination as defined by The Abortion Act of 1967. The congenital abnormality need not be defined nor a diagnosis given. The aborted fetus does not legally require examination by a professional. Neural tube defect, although usually occuring in isolation, may be part of a recognised syndrome that will remain undetected without detailed examination (Donnai and Farndon 1985). This has important implications for both epidemiological studies and for the accuracy of genetic counselling provided. It has been suggested that a standardized protocol for the investigation of fetal loss be used. It would include assessment of maternal history, detailed dysmorphic studies of the fetus and chromoseome assay. This would ensure that an accurate diagnosis is achieved (Curry and Honore 1990). Such detailed investigation would also be useful in cases of neonatal death but would require coordination and allocation of resources.

The availability of termination of pregnancy may have

resulted in a less accurate ascertainment of neural tube defect in many studies because of the above factors. Underreporting of cases of neural tube defect would result in a false lowering of the incidence of the disorder and this has to be taken into account when comparing data. This will be discussed further when the incidence of neural tube defect is considered.

The most accurate statistical data on any congenital abnormality are likely to be achieved by reporting from multiple sources (Renwick 1968). Coordination of this requires a substantial amount of time, manpower and expertise (Northern Regional Steering Group 1992). In addition to this accuracy of reporting and classification of data is essental. Expertise and allocation of resources demands consideration if this is to be achieved.

The studies considered above highlight the need for a system of identification of neural tube defect that can ensure accuracy in diagnosis and completeness of data. The first aim of this research is to establish such a notification system. It is hypothesised that such a system with require multiple sources of ascertainment, confirmation of the reported diagnosis by experienced personnel and feedback to those involved with the system to ensure motivation is maintained.

6.2.AETIOLOGICAL AND EPIDEMIOLOGICAL FACTORS ASSOCIATED WITH NEURAL TUBE DEFECT

The aetiology of neural tube defect is multifactorial with genetic and environmental influences. A genetic input is demonstrated by studies of ethnic variation, sexual variation, maternal factors and family studies. The environment, it is hypothesised, then exerts its effects on the already genetically predisposed individual. Environmental factors include diet, drugs or disease.(Carter 1974, Sandford et al 1992, Yen et al 1992).

6.2.1. GENETIC INFLUENCES

Evidence for genetic influences comes from studies of ethnic variation, sexual preponderance, certain maternal factors and family studies (Campbell 1986).

Ethnic Variation

In a simplified manner the variation in incidence of a congenital abnormality reflects person related characteristiccs as opposed to environmental factors (Elwood and Elwood 1980) . In fact ethnic subgroups do have cultural

variations that influence environment factors i.e. dietary habits (Carter 1974). These factors are not always accounted for when the variations in incidence are considered. Additionally it may be difficult to ascertain an individuals ethnic origin (Myrianthopoulos and Melnick 1987). Despite these problems the incidence of neural tube defect has been demonstrated as varying between ethnic groups. Examples of this are seen in Negro populations (Alter 1962), Sikhs (Baird 1983, Hall et al 1988) and those of Celtic origin (O'Dowd et al 1987). These findings are of importance when considering genetic-environmental interactions (Myrianthopoulos and Melnick 1987) although their interpretation is complex.

Variations in Gender

Females are two to four times more commonly affected with neural tube defect than males (Elwood and Nevin 1973, Carter 1974, Myrianthopoulos and Melnick 1987). The reason for this difference is unlikely to be due to any one factor but could be as a result of selective early prenatal loss of male fetuses. Other suggestions include a complex underlying genetic model or a sex specific teratogen (Campbell et al 1986).

Maternal Factors

Maternal factors studied in relation to neural tube defect include maternal age, parity, prenatal health, place of residence and socioeconomic class. The majority of these are multifactorial in nature with genetic and environmental components. The various factors will be considered separately although it will be evident that they are not discrete entities.

MATERNAL AGE

The relationship between maternal age and congenital abnormality is believed to be an indication of the effect of environmental factors on the ovum (Carter 1974). Some researchers have suggested an increase in the incidence of neural tube defect with advancing maternal age whilst others dispute this (Carter 1969). Age related factors must be distinguished from parity and other researchers have documented that age is not an independant variable (Alter 1962). It is evident from the literature that no conclusions have been reached and further research is indicated.

PRENATAL HEALTH

It is recognised that the reporting of prenatal health by mothers is unreliable. Despite this it has been reported

that Influenza A (Pleydell 1960), hyperthermia (Fisher and Smith 1981, Hunter 1984, Sandford et al 1992) and Diabetes (Soler 1976) in the prenatal period all increase the risk of a pregnancy affected with a neural tube defect. These studies were small, retrospective and did not always control for factors such as social class. This places the reliability of the data in doubt. A large prospective study is indicated.

A preceeding spontaneous abortion has been implicated in the aetiology of neural tube defect. In a study of 256 pregnancies preceeded by a spontaneous abortion there were 17 pregnancies affected with a congenital abnormality as opposed to 4 in a control group of 287 (Gardiner et al 1978). Other studies have supported this finding (Cuckle 1983) although other variables, in particular social class and place of residence, had only been taken into account by some. These findings support the hypothesis that residual trophoblastic material may cause disruption of the neural tube during embryological development resulting in a defect. This has become known as the trophoblastic rest hypothesis (Gardiner et al 1978) and has important implications for the reproductive plans of families known to be at risk of neural tube defect with possible implications for the timing of pregnancies following a spontaneous or therapeutic abortion.

SOCIAL CLASS

There has always been an interest in deprivation and social class in relation to congenital abnormality (Alter 1962, Carter 1974). Social class is not an independant variable, neither does it take into account personal life style (Elwood and Elwood 1980).

Social class is divided into five categories as defined by The Registrar General:

Social Class I - Higher professional and administrative occupations

Social Class II - Other professions

Social Class III- Skilled worker

Social Class IV - Semi Skilled

Social Class V - Unskilled

These criteria are related to the head of the household, and do not account for unemployment or single working women. Although there are these problems in defining deprivation in terms of social class, studies have documented that those in the lower social classes are more likely to have a pregnancy affected with a neural tube defect (Nevin et al 1981, Elwood and Nevin 1983). There are many variables that may be due to deprivation including poor housing predisposing to infection, poor diet, larger families, variation in ethnicity and place of residence. None of these variables act independantly. Research has to be directed into looking

at these factors rather than using the arbitary and ill defined classification of "social class" particularly with the inability to account for maternal lifestyle with the current categorisation.

FAMILY STUDIES

Cases have been described in which many siblings from a single family are affected with a neural tube defect (Christakos and Simpson 1969). Studies of consanguinous relationships show an increased risk of occurrence although this is not an indication of straightforward recessive mode of inheritance (Carter 1968, Carter 1974). Wider family studies support a genetic susceptibility to neural tube defect with first degree relatives having a recurrence risk of 4% and second degree relative a risk of 1.5% (Campbell 1986, Connor and Ferguson-Smith 1993)

Twin studies, whilst often helpful in indicating a genetic factor in the aetiology of a condition, have proved inconclusive (Myrianthopoulos and Melnick 1987, Windham and Sever 1982).

Researchers have suggested multigenic and monogenic models to account for the mode of inheritance of neural tube defect (Campbell 1986) or a genetic susceptibility to midline

developmental defects including cleft palate, diaphragmatic hernia and omphalocoele. This is supported by the finding that neural tube defect may occur in association with these midline abnormalities although this may be due to an environmental teratogen acting at the time of midline closure.

At present it is evident that further research is needed if the aetiology of neural tube defect is to be unravelled. Current genetic hypotheses are inconclusive (Seller 1987, Donnai 1993). Researchers need to take into account that neural tube defects are not a homogeneous group of disorders and it is likely that multiple genetic and environmental factors are acting to produce the abnormality (Campbell 1986).

6.2.2. ENVIRONMENTAL FACTORS

Indications of the importance of environmental factors in the aetiology of neural tube defect comes from studies of geographical, seasonal and secular trends. Dietary studies and studies of drug intake have contributed to the understanding of the underlying aetiology of the abnormality.

Incidence

The incidence of neural tube defect varies with time and location. This presents difficulties when comparing data from different studies. Table 6.1. summarises a number of studies that have been undertaken.

Table 6.1. THE INCIDENCE OF NEURAL TUBE DEFECT

LOCATION	INCIDENCE PER 1000 BIRTHS	ASCERTAINMENT	REF
USA	0.6	notification programme	Yen et al 1992
ATLANTA	0.6	notification programme	Yen et al 1992
SCOTLAND	1.1	multiple sources	Davis & Young 1991
WESTERN AUSTRALIA	1.88	defects registery	Bower et al 1993
TASMANIA	1.36	birth notifications and survey	Bower et al 1993
SOUTH WALES	1.9	multiple sources	Laurence 1989
DUBLIN	3.45	multiple sources	Eurocat 1991
GLASGOW	3.74	multiple source	Eurocat 1991
LANCASHIRE	1.5	multiple sources	Bound et al 1991

Comparison of the data from these studies has to take into account variations in the method of ascertainment used. The source of data will influence the calculated incidence. In particular, certain studies have only included hospital births (Coffey and Jessop 1957) at a time when there were deliveries in the community. Inclusion of those pregnancies that are terminated also influence the data. Accurate ascertainment is complicated by women going outside their place of residence for termination as is the case in areas opposed to this method of secondary prevention.

Despite inconsistances in the way in which data was obtained there have been consistant reports of the highest recorded incidence being in Northern Ireland (Elwood and Nevin 1973). The incidence is documented as falling from the North West of England to The South East (Carter 1969). It continues to fall across Europe and low levels have been reported in Japan, Chile, Israel and Australia (Penrose 1957, Myrianthopoulos and Melnick 1987).

The incidence in the North Western Region that was being quoted at the time of this study was 4 per 1000 births this was based on research from over twenty years previously (Carter 1969) and, with the recognised fall in incidence, was likely to be inaccurate. A more recent study in Lancashire estimated the incidence to be 1.5/1000 (Bound et al 1991) which reflects the decline in incidence. This study

ascertained cases prospectively from multiple sources. The diagnosis was confirmed from review of case notes and from autopsy reports.

In addition to geographical variations, changes over time are also evident with both short and long term changes being reported (Alter 1962, Leck 1972, Radic et al 1987). Seasonal variation is also evident (Dallaire et al 1974, Jongbloet et al 1982).

The variation in incidence of neural tube defect may be a reflection of the effects of enviromental factors that are known to alter with time. These include infectious agents (Leck 1972), economic depression (Nevin 1981), alterations in dietary components (Smithells et al 1981) and changes in water supply (Bound 1983). These are clues to an environmental component to the aetiology of the abnormality. Variations in incidence must be accounted for when investigating possible ways of reducing the incidence of the abnormality (Laurence 1985). This will be considered further when discussing methods of prevention of neural tube defect.

One environmental agent that has been studied in detail is diet. For a number of years it has been recognised that diet can have an effect on the developing fetus either because of excesses or deficiencies of its components (Mahotra and Sawyers 1986). Dietary agents would be expected to vary from

region to region and over time as does the incidence of neural tube defect.

Early studies included the association between potato blight and neural tube defect (Renwick 1972). This study hypothesised that, as a result of a correlation between potato blight and the incidence of neural tube defect, a substance in blighted potato tubers was responsible for neural tube defect. Variations in incidence of neural tube defect were considered in the light of this hypothesis. The study did not consider certain inconsistances including high reported incidences in areas of low potato consumption (Emanuel and Sever 1973). Other studies disputed the findings (Elwood 1976) and, following case controlled research (Clark 1973, Spiers et al 1974), evidence has not supported the potato blight hypothesis. Despite remaining unproven, the studies on potato blight paved the way for investigation of other dietary agents.

Preliminary studies looked at dietary intake, linking this to socioeconomic class. The Leeds Nutritional Survey demonstrated, prospectively, that dietary intake was of poorer quality in those of lower socioeconomic class although this study did not use a randomised population and only assayed maternal blood levels of nutrients as opposed to the actual level in the developing fetus (Smithells et al 1976, Schorah et al 1983). Whilst studies of blood vitamin

levels were being carried out others looked at a variety of dietary factors and found positive correlations between neural tube defect and canned meats, peas, and icecream, as well as tea consumption (Knox 1972). Researchers compared the intake of these foods with the incidence of neural tube defect and did not account for variations in absorption. The role of these foods has not been substantiated. Further studies did not confirm the finding of low vitamin levels in association with neural tube defect although, again, those recruited were not a random sample and differing methods of assay of folic acid levels were used making comparison of the findings problematic (Hall 1972).

Despite criticism of the studies of blood vitamin levels (Hall 1972) the authors hypothesised that mothers at risk of having a pregnancy affected with a neural tube defect would benefit from vitamin supplementation surrounding the time of closure of the neural tube (Smithells et al 1976). This was the start of much controversy that will be considered in greater detail subsequently.

From the above review of the literature on the aetiology of neural tube defect it is evident that the situation is complex. It would be convenient to be able to attribute specific genetic and environmental components to causation but this is not possible in the light of current knowledge on the subject (Seller 1987).

6.3. DIET AND PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

Dietary factors are important to consider as aetiological contributors in neural tube defect. They are one environmental agent that may be altered with relative ease and, it has been hypothesised, with dietary improvements the risk of a genetically susceptible individual having a pregnancy affected with a neural tube defect may be reduced (Carter 1974, Knox 1972, Smithells et al 1976).

The work on the prevention of neural tube defect in mothers known to be at risk of an affected pregnancy began with studies of blood vitamin levels (Smithells 1976). These studies were not without problems. The mothers recruited were not from a randomised group and there were concerns over the validity of the methods used to estimate vitamin levels (Hall 1972). Although these points were acknowledged, a non randomised, multicentred trial was commenced which aimed to supplement those mothers at risk of an affected pregnancy (Smithells et al 1980). The mothers were given a multivitamin preparation, Pregnavite Forte F (Bencard), in the following daily doses:-

Dried ferrous sulphate	252mg
Calcium phosphate	480mg
Vitamin A	4000U
Vitamin D2	400U
Thiamine hydrochloride (Vitamin B1)	1.5mg
Riboflavine (Vitamin B2)	1.5mg
Pyridoxine hydrochloride (Vitamin B6)	1.0mg
Nicotinamide	15mg
Folic Acid	0.36mg
Ascorbic Acid	40mg

This was commenced at least one month prior to conception and taken until the second missed menstrual period. In the first cohort of patients studied, 200 were supplemented in this manner. The control group consisted of 300 mothers who were either already pregnant or who did not wish to be supplemented. The results demonstrated a dramatic reduction in the recurrence of neural tube defect to 1 in 200 (0.5%) whilst, as expected, the recurrence in the unsupplemented group was 13 (4%) (Smithells et al 1981). Further cohorts of patients reproduced these results (Smithells et al 1983).

At this stage ethical approval was not given for a randomised trial. It was evident that there were many other factors that could account for this reduction. These includeda recognised declining incidence of neural tube defect, well documented changes in secular trends and particular maternal

characteristics that could be operating in a non randomised group of mothers. The authors suggested other factors that might have accounted for their findings but, whilst commenting on possible social class differences in the two groups and possible geographical influences, they concluded that these factors alone would not account for the almost seven fold decrease observed (Wild et al 1976). There then followed a debate as to whether periconceptional vitamin supplementation was beneficial (Wald and Polani 1984). In addition to this there were concerns about which components of the preparation used by Smithells were operating to reduce the risk of recurrence. Other centres suggested that folic acid alone was the vital constituent (Laurence et al 1981). These authors carried out a double-blind randomised trial of periconceptional folate supplementation and demonstrated no recurrences in the 44 mothers that were supplemented with folate alone. In the 51 mothers unsupplemented there were 4 recurrences. This trial had originally approached 905 mothers with only 12.3% agreeing to participate and, of the 60 allocated to the supplemented group a further 16 were found to be non-compliant. Reasons were not given for failure to recruit although it may be suspected that some of these mothers were being offered periconceptional vitamin supplementation as recommended by The Smithells trial (Smithells 1981). The study was concluded as being unsuccessful in the prevention of neural tube defect although, by adding those who had not complied with

supplementation to the unsupplemented group the authors found the effects of folate to be significant. This study had many methodological flaws including biases in recruitment, lack of compliance and small numbers. The authors concluded that a larger trial was indicated.

Further debate continued with the possibility that dietary advice alone may influence recurrence risk. Assessment of diet was acknowledged as being problematic and unreliable (Laurence 1980).

There were concerns about teratogenicity (Bound 1983) of the vitamin preparation being used. The incidence of congenital abnormality in a series of 1159 pregnancies that were supplemented was not found to be elevated (Seller et al 1985). Long term effects, as occurred with the prescribing of stillboestriol and the development of vaginal malignancy many years later, were not considered. Only long term follow up of the children of supplemented pregnancies will reveal complications of this nature.

In an attempt to resolve the debate ethical approval was eventually given for The Medical Research Council (MRC) Trial to commence (MRC 1984). This aimed to:-

"Investigate whether the administration of extra folic acid or other vitamins before or after conception can reduce the

risk of fetal neural tube defect recurrence among women who have had one or more previously affected pregnancies."

Mothers recruited to the trial were supplemented in one of four ways:

1) mineral alone
2) mineral and folic acid
3) mineral, multivitamin and folic acid
4) mineral and multivitamin

Blood vitamin levels were checked at regular intervals. The mineral component was dried ferrous sulphate and di-calcium phosphate. The dose of folic acid was 4mg which differed significantly to the dosage of 0.36mg used in the Smithells trials (Smithells et al 1981).

The trial did not commence until many obstetricians had begun to act on the results of the Smithells trial (Smithells et al 1981) by prescribing periconceptional vitamin supplementation to the mothers they felt to be at risk. Thus, even from the outset, the MRC trial had problems with recruitment and had to resort to recruiting patients from other countries (Harris 1988). Concerns about the interpretation of the results of the MRC trial were debated whilst it continued. It was well recognised that there were geographical and cultural, variations in incidence complicating the interpretation of an international trial (Smithells et al 1985). Also, with the recognised declining incidence of neural tube defect

interpretation of the results would be problematic (Seller and Nevin 1984). In addition to this media coverage had increased patient awareness with many wishing for supplementation as recommended by the findings of Smithells (Lorber 1982).

The department of medical genetics in The North Western Region decided not to support recruitment of women into the MRC trial. This decision was made following a survey of all obstetricians in The Region. This survey indicated that 70% of these obstetricians were already recommending periconceptional supplementation to women who had had an affected pregnancy. Instead this research was proposed. It was hypothesised that clinicians were already prescribing periconceptional vitamin supplementation in the Region and that women would be aware of the risk of recurrence for an affected pregnancy.

6.4. THE OUTCOME OF THE MEDICAL RESEARCH COUNCIL TRIAL

Since this research was undertaken the results of the MRC trial have become available (MRC Vitamin Study Research Group 1991) and, as predicted both in this research and by others (Leeming 1991,Smithells 1991,Stone 1991, Super 1991), the results have continued to cause debate.

The MRC trial eventually recruited 1817 people, 183 less than expected with it being discontinued as significant results had been achieved. Of those recruited there were 1195 informative pregnancies with supplementation as follows:-

Supplementation	No.	NTD pregnancies
Folic acid alone	298	2
Folic acid and other vitamins	295	4
No supplementation	300	13
Other vitamins alone	302	8

Recruitment occurred from a total of 33 centres, 17 in the UK and 16 in six other countries.

The trial concluded that folic acid supplementation is able to prevent neural tube defects and that, in the trial, 72% of affected pregnancies were prevented by supplementation in this manner.

Criticism raised following the publication of these results included questions concerning whether the findings were applicable to low and high risk areas (Stone 1991). There were questions about the dose of folic acid being recommended (Scott 1991, Smithells 1991) and which vitamin preparation to use (Reynolds 1991). The analysis of the results was also commented upon (Baijal et al 1991).

Despite these criticisms the MRC trial did demonstrate a statistically significant prophylactic effect of folic acid in the prevention of recurrence of neural tube defect.

Following the publication of the results of the trial the Department of Health has recommended that all women at risk of a pregnancy affected with a neural tube defect should be offered supplementation with 4mg of folic acid from before conception (Department of Health 1991). This has presented problems as such a preparation was not available in The British National Formulary at this dose at the time that this directive

was given. In addition to this, fortification of food with folate has been considered (Department of Health 1992, Schorah and Wild 1993).

Research into periconceptional vitamins and the prevention of neural tube defect has not been concluded as a result of the MRC trial. Some studies have supported the findings of the MRC trial including one of 354 women in Ireland although, yet again, problems with lack of randomisation of the control group arise (Kirke et al 1992). Other studies have not replicated the findings (Mills et al 1989).

The dietary implications of the results of the MRC trial are still being considered (Wald 1991). There are implications for those not identified as being at an increased risk of an affected pregnancy. The assay of folate level in all women may be a possible way of screening for those who are at risk (Mills et al 1992). The metabolism of women who have an affected pregnancy is also being studied (Mooij et al 1992, Wild et al 1993). The beneficial effects of periconceptional vitamin supplementation for the prevention of other congenital abnormalities has also been raised (Czeizel 1993).

Clinicians are not united in their recommendations to

women planning a pregnancy (Super 1991) and, as yet, the Government, whilst initially providing a high profile campaign (Department of Health 1992, ASBAH 1993), has not maintained this (Franzen 1994).

The ongoing debate about the role of periconceptional vitamin supplementation in the prevention of neural tube defect demonstrates the complexities of interpretation and application of research findings. The controversies that have arisen may be "blamed" on the implementation of findings following a non randomised trial (Smithells 1976). Some may argue that, as a result of women taking periconceptional vitamins, many pregnancies that would have been affected with a neural tube defect were prevented prior to approval being given for the MRC trial. The results of the MRC trial, as demonstrated above, will continue to be debated.

6.5. PRENATAL SCREENING AND THE DIAGNOSIS OF NEURAL TUBE DEFECT

Prevention of NTD may either be primary resulting in normal pregnancies or secondary by termination of affected pregnancies. Primary prevention can best be achieved if the causes of NTD are known and removed prior to the defect in the fetal neural tube occuring. Secondary prevention may be achieved by the NTD being detected by prenatal diagnosis. Secondary prevention does not reduce the incidence of affected pregnancies, neither is it an acceptable option for a number of parents. Additionally this method of prevention poses ethical dilemmas for the professionals involved in the care of the parents and unborn child (West 1988).

It is important to consider the way in which prenatal diagnosis of NTD is achieved prior to reviewing existing counselling and supportive services.

Prenatal diagnosis of NTD may be carried out by one, or a combination of the following methods:-

1. Amniotic fluid alpha-fetoprotein (AFP) assay
2. Amniotic fluid acetylcholinesterase
3. Ultrasound scanning
4. Fetal X Ray
5. Fetoscopy

For prenatal diagnostic programmes to be effective a reliable method of screening for those at risk has to be instituted as over 90% of cases of NTD occur in families in which a prior risk of an affected pregnancy cannot be identified (Wald and Cuckle 1980).

6.5.1.Screening for Neural Tube Defect

Screening may be defined as "the presumptive identification of unrecognised disease or abnormal conditions by applying tests which are relatively simple, inexpensive and acceptable to apparently healthy individuals". The following criteria must be satisfied by any screening procedure (Connor and Ferguson-Smith 1993).

1. Clearly defined disorder: this being so in the case of NTD.
2. Appreciable frequency: the risk of a NTD affected pregnancy in the population can be of the order of 1 in 250 this varying from place to place.
3. Advantage of early diagnosis: if a NTD is detected early a therapeutic abortion may be offered.
4. Few false positives: the test needs to be specific. For NTD the initial screening procedure of MSAFP assay can be followed up with other investigations such as ultrasound amniotic fluid AFP assay, and acetylcholinesterase gel

electrophoresis.

5. Few false negatives: the test needs to be sensitive. MSAFP screening does not identify all possible affected pregnancies: it has to be supported with other tests.

6. Benefits outweigh costs: Both financial costs and emotional costs need consideration. These are high for children with NTD.

Screening techniques that are available for detection of those pregnancies at risk of being affected with a neural tube defect include maternal serum alphfetoprotein estimation and ultrasonography. The latter is also used as a diagnostic test either alone of in combination with other investigations.

6.5.2.Biochemical methods of screening

Since 1972 prenatal AFP screening for NTD has become one of the major screening programmes offered to pregnant women in the United Kingdom. AFP is an alphaglobulin that is synthesised by the yolk sac and fetal liver. It is present in fetal serum and cerebrospinal fluid (CSF) from the sixth week of gestation and usually reaches a peak concentration in amniotic fluid by the twelth week of gestation via excretion through the fetal kidneys. Levels are raised when there is a leakage of fetal serum or CSF from an open lesion into the amniotic fluid. Amniotic AFP may thus act as a marker

molecule in the diagnosis of an open neural tube defect plus other open lesions such as anterior wall defects, fetal nephrosis and fetal teratomas.

Initial studies showed that, by amniocentesis, the raised level of AFP could be assayed early enough in pregnancy to offer termination of the fetus. (Brock and Sutcliffe 1972) Amniocentesis is not without risk to the pregnancy and the risks have to be balanced against the risk of the pregnancy being affected. For mothers at a low risk of NTD amniotic fluid AFP is thus not a suitable procedure to use for screening purposes but may be used for diagnostic purposes.

AFP is known to cross the placental barrier and can be detected in maternal serum. Elevated levels can be identified. This raised the possibility of using maternal serum AFP (MSAFP) as a method of screening all mothers for neural tube defect (Wald et al 1974). The United Kingdom Collaborative Study on AFP in relation to neural tube defect was set up to investigate this (1981). 18,684 singleton pregnancies and 163 twin pregnancies were studied in which there was no neural tube defect and a further 301 singleton pregnancies with neural tube defect. MSAFP was measured by radioimmunoassay using various methods. The best time of measurement was found to be at 16-18 weeks gestation when 88% of anencephalics, 79% of open spina bifidas and 3% of unaffected pregnancies had AFP levels equal to or greater

than 2.5 times the median value for unaffected pregnancies.

Differences in assays performed by laboratories made it impossible directly to compare results. Instead inter-laboratory variability may be reduced by expressing the AFP result as a multiple of each laboratory's own normal median level at the appropriate gestational age.

There are a number of reasons other than a NTD in the fetus that can result in a raised MSAFP, thus once detected further investigation is indicated prior to a diagnosis of NTD being made (Connor and Ferguson-Smith 1993) and acted upon. Table 6.5.

TABLE 6.5. THE CAUSES OF ELEVATED MATERNAL SERUM AND AMNIOTIC FLUID ALPHAFETOPROTEIN.

CAUSE	MATERNAL SERUM AFP	AMNIOTIC FLUID AFP
Underestimated gestation	+	-
Overestimated gestation	-	+
Fetal blood in amniotic fluid	(+)	+
Multiple pregnancy	+	-
Threatened abortion	+	-
Anencephaly	++	++
Open spina bifida	+	+
Closed spina bifida	-	-
Isolated hydrocephalus	-	-
Anterior abdominal wall defect	+	+
Fetal teratoma	+/-	+/-
Maternal hereditary persistant AFP	++	-
Congenital nephrotic syndrome	+	+
Skin defects	+	+
Placental haemangioma	+	+

Further studies emphasised the benefits of MSAFP screening. One study in Scotland (Thom et al 1985) reported on 18256 pregnancies screened with MSAFP. 36 cases of NTD were identified with 4 cases associated with a normal MSAFP and 5 cases in unscreened mothers. The study comments upon an 80% effectiveness in detection but also highlights that 889

mothers had a first raised MSAFP. No comment is made about the distress and anxiety suffered by this group of mothers nor is there comment on counselling that mothers receive prior to the investigation taking place. This is a central issue in the institution of a screening programme and will be further considered later. Other studies have acknowledged the declining incidence of NTD and have considered the effect of a screening programme in a low incidence area. One study questioned the value of screening (Standing et al 1981) for the prevention of livebirths with a NTD. Cases of anencephaly were excluded as being incompatible with life. Of the four cases detected only two were detected by MSAFP screening. The study highlighted difficulties in co-ordinating a MSAFP screening programme and on the anxieties raised by false positive results. It was felt that the disadvantages of a screening programme in a low incidence area were sufficient for such a programme to cease and concluded with the comment that a screening programme is weighted towards the detection of fetuses that would inevitably die. The effect that the death has on the family is not considered. Other studies have continued to emphasise the benefits of MSAFP screening in high risk areas despite a recognised fall in incidence of neural tube defect (Stone et al 1988)

In another study (Hooker et al 1984) the difficulties of screening a low risk population were again considered. The need for regular reviews of the cost-effectiveness of a

screening programme was discussed and the advantages of ultrasonography as a diagnostic tool. These points were also highlighted in a study from Sweden (Persson et al 1983) in which economic and psychological benefits were considered.

6.5.3.Diagnostic investigations

Amniocentesis permits the amniotic fluid surrounding the fetus to be sampled and studied. As described above, studies from the early 1970's demonstrated that alphafetoprotein acts as a marker for open neural tube defects. It thus became possible to use this as a diagnostic test for neural tube defect. Table 6.5. demonstrated that AFP may be elevated for a number of reasons so additional diagnostic investigations are helpful. One such investigation is the gel electrophoresis pattern of cholinesterases in the amniotic fluid (Collaborative Study 1981). A normal result will give only one band of pseudocholinesterase. Open NTD produces a second faster band of acetylcholinesterase that has been secreted from the immature nerve terminals that are exposed to the amniotic fluid from the open defect. This investigation is almost always positive for open NTD's and also for 50% of anterior abdominal wall defects. Very rarely a second band may exist when there is no recognisable abnormality in the fetus. Acetylcholinesterase is not detectable in maternal serum so this cannot be used in screening (Sorensen et al 1987).

The benefits of amniocentesis are falling as the accuracy of high resolution ultrasonography increases (Laurence et al 1985). It has been demonstrated that in a high risk population all recurrences of NTD would have been detected with MSAFP and ultrasonography (Laurence et al 1985).

6.5.4.Ultrasonography

Biochemical methods of screening for NTD may be interpreted in conjunction with fetal ultrasonography or, rarely, radiography or fetoscopy. Imaging of the fetal skull and spine was one of the earliest uses for ultrasound in the detection of fetal abnormality. Closed defects may be identified that would remain undetected by biochemical means. Ultrasonography also gives an accurate estimate of gestational age which is vital for analysis of MSAFP levels when screening for neural tube defect. Skill and expertise are needed to ensure accuracy of measurement and diagnosis (Dennis et al 1985, Polanska et al 1983, Quinlan 1984) and standardized methods of detection have been suggested by some centres (de Elejalde and Elejalde 1985). As with biochemical methods of detection on NTD, the timing of ultrasonography is important (Toms 1982).

Ultrasonography may also be used to screen all pregnancies

for congenital abnormality but expertise is vital as such reliance is to be placed on this.

6.5.5.Other investigative procedures

Rarely, other invasive procedures may be indicated when the diagnosis is uncertain. Anencephaly can be reliably diagnosed with radiography in early pregnancy but the diagnosis of spina bifida in this way is less reliable and amniography with a water soluble medium may be required. Fetoscopy may also be used in uncertain cases (Rodeck and Campbell 1978). These procedures have a high risk of complications including spontaneous abortion, premature labour and haemorrhage. Both have largely been replaced by ultrasonography.

6.5.6. Acceptability of screening, prenatal diagnosis, and termination of pregnancy

The availability of a screening programme that would result in fewer livebirths of NTD does not automatically mean it is acceptable to the group of people to whom it is being offered or to the professionals caring for that group. Wider implications that have to be considered when offering this secondary method of prevention include the legalities of termination of pregnancy and the religious, ethical and moral

issues that surround the ability to prevent births of children with congenital abnormalities (Seller 1976, Seller 1982, West 1988).

There are benefits in being able to identify neural tube defect in the antenatal period apart from the possibility of termination of pregnancy. In one study in Ireland only 50% of families accepted termination of pregnancy although prenatal diagnosis allowed parents to have time to come to terms with their infants diagnosis. In addition to this clinicians were able to plan the delivery and after care that the child might need. This study was only small (N=34) and the feelings of the families involved were not considered in detail but it demonstrates that all the benefits of prenatal dianosis should be considered particularly prior to the withdrawl of such programmes.

The psychological impact of screening and prenatal diagnosis of neural tube defect will be considered in more detail subsequently.

6.5.7.The Abortion Act

The Abortion Act of 1967 states "a person shall not be guilty of an offence under the law relating to abortion when a pregnancy is terminated by a registered medical practitioner if two registered medical practitioners are of the opinion,

formed in good faith;
a) that the continuance of the pregnancy would involve risk to the life of the pregnant woman, or of injury to the physical or mental health of the pregnant woman or any existing children of her family, greater than if the pregnancy were terminated; or
b) that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped."

Since The Abortion Act of 1967 termination of pregnancy has been an option available to pregnant women should a congenital abnormality be detected at a gestation that termination may be legally offered. Thus secondary prevention is feasible.

There have been a number of attempts to ammend The Abortion Act of 1967 (Bromwich 1987). Most aim to reduce the gestation at which a termination of pregnancy may be legally performed. The object of this would be to reduce the number of "social" terminations occuring in the mid-trimester of pregnancy but amendments like this would also reduce the efficacy of a screening programme for NTD. This is because MSAFP can only be offered between 16-20 weeks gestation. The proposed amendments by Mr. David Alton M.P. would have reduced the gestation to 18 weeks and if had become law would have meant that any MSAFP screening programme would be

impractical if not impossible. The amendment reducing the gestation to 24 weeks still enables a screening programme to exist and it also permits termination of pregnancy at any gestation should there be a substantial risk of the child, when born, suffering abnormalities resulting in a severe handicap.

During the course of this study the House of Lords passed the Human Fertilisation and Embryology Bill which included changes to the upper limit for termination of pregnancy. It states that the upper limit for termination of pregnancy is twenty four weeks gestation although this does not apply if there is risk of grave permanent injury or death to the mother or a substantial risk of handicap to the child (Hall 1990). The issues surrounding serious handicap are complex. In the case of anencephaly the prognosis is not in doubt but in spina bifida and encephalocoele assessment of the risk of serious handicap may pose difficulties and is open to interpretation. Serious ethical dilemmas may occur (Chervenak 1990).

6.5.8 Religious views

Selective termination of pregnancy for congenital abnormality is not an acceptable method of prevention of congenital abnormality for all families. The various religious denominations have laid down guidelines for parents. Some

denominations are opposed to termination for whatever reason, including congenital abnormality, but others support it when the health of the fetus is known to be compromised. The denominations also vary on the acceptable gestation for termination to occur if a serious abnormality is present. The Catholic Church does not accept termination of pregnancy for congenital abnormality, neither does the Islamic faith (Ibrahim 1990). Orthodox Jewish guidelines are that termination may be sanctioned for individual cases (Jackobovits 1988). In Jewish Talmudic law the anencephalic infant is not deemed to have a soul thus allowing termination of the fetus in affected cases. This is not the case for infants with spina bifida (Brown 1990).

6.6. PSYCHOLOGICAL ASPECTS OF SCREENING AND PRENATAL DIAGNOSIS OF NEURAL TUBE DEFECT

The development of prenatal screening and diagnostic techniques has enabled parents to make decisions about whether they wish to continue with a pregnancy that has been identified as likely to result in an infant affected with a congenital abnormality.

These developments have raised many ethical issues (Lilford 1989, Richards 1989, Seller 1982). They have also raised concerns about the stress that is created during investigations and the effects of either a positive or negative finding (Berne-Fromell et al 1983, Robinson 1984). The support needs of families who are undergoing prenatal screening and diagnosis and the subsequent professional input that they require must be considered (Donnai 1987).

Generally, women undergoing screening and diagnosis for neural tube defect have a series of investigations that result in a positive or negative diagnosis of an abnormality. It has been assumed that those undergoing these tests will be anxious although there has been little systematic study of this until recently (Green 1990).

6.6.1.SCREENING FOR NEURAL TUBE DEFECT

Screening for neural tube defect was made possible with the findings that MSAFP could be used as a biochemical marker for the open neural tube (Wald et al 1974). Since then it has also become possible to use ultrasound to screen for defects of the neural tube. The problems of the nonspecificity of MSAFP has already been considered. Should the first assay of MSAFP be elevated further investigations are necessary which may include repeating the MSAFP, detailed ultrasonography or amniocentesis. These events raises uncertainties for the family. The false to true positive ratio of MSAFP has been investigated by a number of authors. It was found to range from 66:1 to 15:1 (Cambell 1987, Wald et al 1979). These figures are dependent on the incidence of neural tube defect in the population being screened. They will thus vary with time and location.

Studies of womens experiences of MSAFP screening have concentrated on anxiety levels or have looked at descriptions of their experiences.

6.6.2. MEASURMENT OF ANXIETY

The measurement of anxiety is complex. Anxiety may be seen as a symptom of a disorder, for example in depression, or as a specific disorder, for example generalised anxiety disorder (Sheehan and Harnett-Sheehan 1990). Two types of assessment

tool are used to assess anxiety disorder, structured interviews or rating scales. Structured interviews may be used for diagnostic purposes whereas rating scales identify the severity of the disorder. Currently the use of structured interviews are prefered with supplementary information being made available from rating scales. The assessment of the distress caused by prenatal diagnostic tests has concentrated on measures of anxiety. This assumes that the symptom or disorder to be studied is anxiety. The most commonly used tool in the assessment of anxiety in pregnancy is the State-Trait Anxiety Inventory (Spielberger et al 1970). This was developed to allow a self-reporting assessment of state and trait anxiety and consists of two sections. State anxiety is the anxiety experienced as part of an unpleasant emotional reaction. It varies with time. Trait anxiety is relatively stable with time and includes personality factors (Spielbergar and Rickman 1990). The State-Trait Anxiety Inventory assessment tool is relatively easy to administer and validity for symptoms of anxiety are well established. Deficiencies of this rating scale have been highlighted. It rates the persons feelings at the time of completion of the questionnaire and cannot account for alterations in anxiety levels at other times. This complicates comparison of data with retrospective documentation of experiences. The place of completion may also influence the ratings (at home as opposed to in the clinic setting). It is essential that the two parts of the

scale are administered to allow trait anxiety to be taken into account (Green 1990).

6.6.3 THE EFFECTS OF SCREENING

The acceptability of screening programmes has been considered (Bennet et al 1980). In one study of 179 women undergoing screening it was found that women had a more positive attitude to their pregnancy following screening than those that were not screened. The State-Trait anxiety Inventory was used to assess anxiety levels and the maternal attitude to pregnancy was also assessed (Burton et al 1985). How their responses related to the management they received during screening was not considered and neither was the support they received . In other studies anxiety levels were found to be raised in women who had both positive or negative results of screening although the anxiety experienced was reduced by good family and social support (Robinson et al 1984). It has also been shown that, following screening, anxiety levels fall during the pregnancy although transient anxiety may still have and effect on the developing fetus and cannot be disregarded (Reading 1983).

A number of studies have raised concerns about the lack of understanding of screening tests that are undertaken by women (Marteau et al 1988). It has been shown that, with the provision of adequate information, uptake of screening

becomes more likely (Marteau et al 1992). Others have found screening to reduce, rather than raise, anxiety levels (Berne-Fromell et al 1983). In this large study of women who did and did not experience screening it was demonstrated that, in those screened, an initially high level of anxiety was experienced which fell after screening. Interpretation of these results was complicated by the differing ultrasound policies that the various districts followed which might influence the level of anxiety experienced but were not accounted for.

Decisions about prenatal diagnosis appear to have been made prior to attendance at antenatal clinics. In one study of 211 women 83% had decided to have investigations before registering at the clinic although the effects of the media were not assessed. This study did not consider a further 15% who decided against prenatal diagnosis but were over 37 years and thus at higher risk of congenital abnormality (Sjogren and Uddenberg 1988)

6.6.4.AMNIOCENTESIS

There have been a number of retrospective and prospective studies that have looked at the anxieties created by amniocentesis. Many of these studies investigated women undergoing amniocentesis because of advanced maternal age (Green 1990). One early study considered those having

amniocentesis as a result of elevated MSAFP and found that these women had more negative views than those being investigated for Down syndrome (Farrent 1980). From studies such as these it is difficult to assess the effects that differences in management has on the level of anxiety that women experience. The amount of information provided about the risks of amniocentesis was not assessed and there have been concerns that women undergoing amniocentesis may be unaware of the complications that may arise as a result of the procedure (Knight 1988). This would, it may be hypothesised, result in those in whom there was lack of awareness of risks to the pregnancy being less anxious than those who had received more detailed information.

Waiting time for the results of amniocentesis has also been studied. One study revealed that 4% of amniocenteses were performed at a gestation of over 21 weeks and a further 26.3% of women undergoing amniocentesis did not receive a result until after 21 weeks gestation. In certain cases delays could have been reduced thus allowing termination to occur at an earlier gestation (Timothy and Harris 1986).

Age related effects were evident in a further study from Denmark (Tabor and Jonsson 1987). In older women anxiety levels were maintained. The reason for amniocentesis did not appear to affect anxiety levels in this study. Other studies have not reproduced this finding (Green 1990).

Despite the anxiety that women experience whilst undergoing amniocentesis this does not result in them refusing the investigation in subsequent pregnancies (Evers-Kiebooms et al 1988).

6.6.5.ULTRASOUND

Ultrasound scanning may be used either for screening purposes or as a diagnostic test. It is routinely used to assess gestational age and fetal growth . In addition to this it is non invasive and, as a result of it, women are able to receive positive images of their baby. One descriptive study of 20 women undergoing ultrasound revealed information about the anxieties women experienced and the positive effects of the procedure (Milne and Rich 1981)). Other more quantitative studies have used psychological testing to demonstrate the benefits of ultrasound investigation. This was particularly so when women were given positive feedback (Reading and Cox 1982, Giovanni et al 1988) although, if the baby is identified as having an abnormality feedback of this nature becomes problematic (Tsoi et al 1987).

There was found to be a reduction in levels of anxiety in women known to be at risk of a fetal abnormality following a ultrasound scan that revealed no abnormality. Further study

was indicated in those who were found to be carrying an affected pregnancy (Tsoi 1987).

These studies confirm the benefits of ultrasonography for those found to have a healthy baby. Further study of those who go on to have a termination as a result of a congenital abnormality is indicated (Green 1990).

6.6.6.EVENTS AFTER A POSITIVE DIAGNOSIS.

The decision that the women and her family make after the diagnosis of a congenital abnormality is influenced by a number of factors. These include the nature of the abnormality, counselling received and the womens own experiences that may be influenced by her religious or moral beliefs.

Some results of prenatal diagnostic tests are relatively easy to interpret. In the case of trisomy 21 or metabolic disorders the family are already aware of a prior risk and have elected to undergo investigation (Donnai 1987). In neural tube defect over 90% of cases occur in those not known to be at increased risk. In addition to this it is not always possible to give an accurate prognosis for pregnancies affected with spina bifida (Donnai 1987). Decision making in the light of a positive diagnosis of congenital abnormality

has been studied although the use of complex mathematical data seems to detract from the emotional issues surrounding decisions of this nature (Pauker and Pauker 1977)

6.6.7.TERMINATION OF PREGNANCY

Usually termination of a fetus with a neural tube defect will be in the mid trimester of the pregnancy and "delivery" will be induced with prostaglandins.

Studies have looked at the psychological and psychiatric sequelae of termination of pregnancy. They have shown that, in patients in whom there is already a psychiatric disturbance, there are more likely to be difficulties post termination (Anon 1976). This complicates interpretation of many studies as it is not possible to ascertain the womens mental state prior to the diagnosis being made and reliance has to be placed on retrospective data. In terminations that have occured as a result of a diagnosis of congenital abnormality it has been demonstrated that, immediately after the termination, the women experiences an acute grief reaction as seen with a stillbirth or neonatal death (Lloyd and Laurence 1985). This study of 48 women used a semistructured interview making comparisons with more standardized methods of assessing grief difficult but, despite this, it was evident that support during the post

termination period was important and needed consideration. Another small study of 15 women undergoing genetic termination of pregnancy confirmed these findings but acknowledged the difficulties of using anecdotal information (Donnai et al 1981). Further studies confirm that, whilst support surrounding the diagnosis of neural tube defect was good, once the women leaves hospital there was little input resulting in isolation and confusion for the family (White-Van Mourik et al 1990). Studies that have looked at supportive interventions have found that adverse emotional consequences may be lessened and, although standardized methods to assess grief were not used, the results were similar to a previous study by the same authors (Elder and Laurence 1991 ,Lloyd and Laurence 1985)

Psychiatric sequelae have been shown to be more likely after a termination of pregnancy and, although these did not persist, grief was found to be prolonged (Iles and Gath 1993).

There has been little study on the benefits of seeing the fetus after it has been terminated although the benefits of seeing an infant who is stillborn have been recognised (Kirkley-Best and Kellner 1982). There has been a recent interest in how fetuses that have been terminated in the midtrimester of pregnancy are disposed of. One questionnaire study assessed the management of fetal loss and revealed

that, in the 28 units that were assessed, there was no single method of disposal. This study raised the issue of the use of a plot in a cemetery for the burial of these fetuses. This would enable parents to have a place to go to to mourn the lost pregnancy (Batcup et al 1988) Others have suggested there should be guidelines for the disposal of these fetuses as for cases of perinatal deaths (Morris 1988).

6.6.8.CONTINUING WITH THE AFFECTED PREGNANCY

There have been many studies on the effects of having a child with a disability (MacKeith 1973, Hannan 1980, Zachary 1977, Bax 1992, Kelter and Ramsey 1993). Some of these consider all types of disability whilst others that have concentrated on specific disabilities such as Down syndrome or spina bifida (Murdoch 1984, Dorner 1985).

Early interest in spina bifida concentrated on treatment criteria (Lorber 1971) and the management of children who did not fulfill these criteria (Althouse 1980, Hunt 1973). There were also studies on the effects of stillbirth and neonatal death and the effects on the family if the child survived (Althouse and Wald 1980)

One study of 107 families looked at the initial responses of having a child with spina bifida. Prospective and retrospective data was used with the mean age of the child

being 16.5 months at the time of first interview of the parents. During the study period 29 families were interviewed at the time of delivery of the affected infant. Although retrospective data might bias the results with recall of bad experiences it was evident that families lacked information at the time of diagnosis and were in need of professional support (Walker et al 1971).

A review of the management of women who had had a stillborn infant highlighted the need for more research on the subject (Kirkley Best 1982) whilst criticising descriptive studies.

One group of researchers investigated the mental health of parents of children with disabilities. 54 mothers were studied using well validated psychiatric questionnaires. The subjects, matched with a control group, were found to have a higher rate of psychiatric morbidity. This study emphasised that the whole family needs support and that the family is an important resource contributing to the care of the child. Further study of how the family unit may be protected were suggested (Romans-Clarkson et al 1986). Others have considered the stigma of having a child with a handicap. Stigma can disrupt parenthood but how to overcome it is a wider social and cultural problem that the author did not attempt to answer (Sensky 1982). A series of detailed interviews with families also highlighted the feelings encountered after the birth of a disabled child (Delight

1988). It is evident from this and other studies that adequate education of professionals is essential if parents are to receive the support they need (Forrest 1981, Forrest 1982).

Many studies concentrate on families of older children whilst attempting to investigate events surrounding the time of diagnosis of the congenital abnormality. The validity of data that is recalled after six years, as in one study of 109 women, must be questioned. It is unlikely that these women were able to accurately recall the amount of time spent with the baby in the immediate postnatal period (Dorner 1985).

Women wish to have time to talk about what is wrong with their baby. This discussion should occurs with people who have the appropriate knowledge and training to answer their questions (Standish 1982, Swerts 1987).

6.6.9.GENETIC COUNSELLING

With the rapid growth of genetic knowledge in the last few years guidelines have been produced that consider the functions of genetic sevices. These may be summarised as

1. To detect and, if possible, exclude risk factors.
2. To make accurate diagnoses

3. To assist in the diagnosis of rare genetic conditions
4. To provide genetic counselling
5. To provide registers of disorders
6. To provide care for those at risk
7. To provide training
8. To provide national professional networks
9. To monitor services
10. To provide a resource for research and development
11. To provide expert advice for purchasers and providers

(Adapted from HMSO 1993)

In the detection and management of neural tube defect genetic services need to identify those at risk, ensure that prenatal diagnosis is available, and be able to offer the care that families require during this period. Services that encourage the development of registers and provide information that can be used to identify aetiological factors are also indicated.

Support at the time of diagnosis and subsequently is important if longterm sequelae are to be avoided (Donnai 1987). The way in which information is provided should be considered. Subjective information may be more readily understood than objective risks (Shiloh and Saxe 1989) and practices need to be adjusted in the light of research findings.

The development of specialist nurses in genetic counselling has helped to ensure families get the support they require (Farnish 1988). Self help groups are also important (Black 1988). Groups such as The Association for Hydrocephalus and Spina Bifida (ASBAH) have an important role in providing information and support. More recently SATFA, Support Around Termination for Fetal Abnormality, has established itself as a national support network which also encourages the development of service provision and research.

This study aims to identify the level of support women receive surrounding the diagnosis and termination or delivery of a pregnancy affected with a neural tube defect. It is hypothesised that, in The North Western Region, women are receiving information about recurrence risks and the use of periconceptional vitamin supplementation to minimise these risks. As a result of this knowledge women undergoing further pregnancies will be being supplemented with periconceptional vitamins.

7. METHODOLOGY

Prior to commencing the research project ethical approval was obtained from The Central Manchester Ethical Committee. Data protection complied with legal requirements. The North Western Regional Health Authority locally organised research committee awarded a grant for the research to be carried out by a Research Registrar with the assistance of a clerical officer.

An introductory letter from the professor of medical genetics in the North Western Region was sent to all consultant obstetricians and paediatricians in the region. These consultants were then approached personally where possible and by written communication otherwise (Appendix A.1.) and the proposed study discussed (Appendix A.2.). Background information was provided about the MRC trial and why it had not been feasible for women to be recruited in The North West Region. Permission was obtained from each consultant allowing their patients to be approached about the project.

7.1. Determination of Incidence

To determine the incidence of NTD in The North Western Region, ascertainment of cases was sought primarily from the obstetrician caring for each case. The obstetricians were requested to return monthly details on the form provided

indicating whether or not there had been any cases of NTD affected pregnancies identified in patients under their care (Appendix A.3.).

At the time of notification of cases permission was obtained to view the notes of the patient concerned and to contact her about the research project. Regular six monthly reminders were sent to obstetricians who failed to return notifications (Appendix A.4.).

At six monthly intervals similar forms were distributed to paediatricians and ultrasound departments to allow detection of any cases that had not been notified by the obstetricians (Appendix A.5.). The sources of notification were matched to ensure completeness.

On viewing the case notes patient particulars were recorded including the mode of diagnosis of the NTD and the outcome of the pregnancy. Autopsy and cytogenetic reports were consulted where available.

7.2. The Interview

Once written permission to contact the woman had been obtained, her general practitioner was informed of the research (Appendix A.6.). If the general practitioner had no

objections, the woman and her partner were contacted by letter with the aim of interviewing them approximately three months after completion of the pregnancy whether by termination or delivery. The woman was offered an appointment and, if this was inconvenient, she was requested to suggest an alternative appointment (Appendix A.7.). All appointments were confirmed by letter.

A semi-structured interview, allowing for unprompted information, took place in the womans home with the partner present whenever possible. It took from one to three hours (Appendix A.8.). The woman was questioned about her past medical, obstetric and family history. The affected pregnancy was discussed and details obtained about the way in which the diagnosis was made and how the woman was informed of the diagnosis. The understanding of the diagnosis and subsequent events were discussed including management preceeding, during and after the delivery or termination of the pregnancy. Time was given to allow the woman to express her feelings. The woman was then questioned about what she had been told about risks of recurrence and whether she was aware of periconceptional vitamin supplementation as a method of reducing recurrence risks. She was asked to rate her satisfaction with the support provided by those involved with her care. The woman was encouraged to ask the interviewer any questions concerning neural tube defect and its inheritance. An information sheet provided and the woman was

asked to make contact with the interviewer when a subsequent pregnancy occured (Appendix A.9.).

Following the interview the obstetrician, general practitioner and other clinicians involved in the care of the woman or child were informed that the interview had taken place. A personal letter of thanks was sent to the woman.

7.3 .Follow-up of Subsequent Pregnancies

If the woman had not been in contact with the interviewer by six months following the interview a letter was sent to her asking if any subsequent pregnancies had occurred (Appendix A.10.) . The use of periconceptional vitamins was also asked about.

At the completion of the two year period of ascertainment all general practitioners were contacted to identify pregnancies that may not have been reported (App A.11.).

At the end of the research project everyone that had participated with the study were sent summaries of the results (App A.12.).

7.4. Analysis of the results

The incidence of neural tube defect in the North Western Region for the study period was calculated as:

Total number of cases identified / Total number of live and still births

The total number of live and stillbirths was obtained from the statistical information department of The North West Regional Health Authority as a result of birth notification data.

The variation in incidence between district was analysed using standardized residuals. Incidences that were found to vary significantly from the expected could be identified. The statistical analysis used is explained in greater detail in appendix A.13.

Information obtained on diagnosis and outcome was verified by review of the case notes. Information on prenatal diagnostic investigations performed was also confirmed in this way.

The women were asked to rate their experiences of the support that they received as either satisfactory or unsatisfactory.

The semistructured interview used yes/no answers to identify information recalled about genetic counselling and periconceptional vitamin supplementation.

8. RESULTS

The results of the study will be presented under the following categories

The ascertainment of affected cases

The incidence of neural tube defect in The North Western Region

Maternal characteristics

The method of diagnosis of affected cases

The care and support experienced by families

The genetic counselling received

The subsequent pregnancy.

8.1. THE ASCERTAINMENT OF AFFECTED CASES

The North Western Regional Health Authority covers a population of 4 million people with approximately 55,000 births per year. It is served by 67 consultant obstetricians, 58 consultant paediatrician, 4 consultant clinical geneticists and 18 ultrasound departments. These services are distributed amongst 19 districts as illustrated by the following map.

THE NORTH WESTERN REGIONAL HEALTH AUTHORITY AND ITS NINETEEN DISTRICTS

8.2. PARTICIPATION FROM CLINICIANS

Information concerning patients diagnosed as having a pregnancy affected with a neural tube defect was provided by 66 obstetricians. Only one obstetrician in the region refused to participate. Of the obstetricians that agreed to participate, three refused permission for their patients to be approached for interview although they did agreed to provide information on cases diagnosed as having a neural tube defect.

All paediatricians in The Region agreed to provide information on the children under their care that had spina bifida or an encephalocoele.

All the ultrasound departments in The North Western Region also agreed to provide the necessary information.

8.3. NOTIFICATION OF CASES

There were 268 cases notified to the study from May 1986 until April 1988. On further investigation 201 (75%) of these cases were found to have an isolated neural tube defect. There were 35 (13.1%) cases that had a congenital abnormality that did not include a neural tube defect and 32 (11.9%) cases had a neural tube defect that was identified as being part of a recognised syndrome.

Permission was given to approach 174 (86.6%) of these families. Of these 132 (75.9%) were interviewed. A further 9 (5.2%) families did not respond to the request to interview them and 6 (3.4%) did not wish to be seen. There were 27 (15.5%) cases notified at least three months after the completion of the affected pregnancy and these were not interviewed as this was outside the interview time identified by the research protocol. These data are summarised in table 8.3.1.

TABLE 8.3.1. RECRUITMENT OF FAMILIES TO THE STUDY AND REASONS FOR FAILURE TO RECRUIT.

Number of families interviewed	132
No response from family	9
Family refused	6
Permission from clinician not given	27
Not NTD	35
Part of a syndrome	32
Notification too late	27
Total no of cases notified	268

The diagnosis and outcome of the 201 cases identified as having an isolated neural tube defect are detailed in Table 8.3.2.

Table 8.3.2.THE DIAGNOSIS AND OUTCOME OF CASES OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION FROM MAY 1986 TO APRIL 1988

DIAGNOSIS	OUTCOME			
	Termination of pregnancy	Stillbirth	Livebirth	TOTAL
Anencephaly	70	12	3	85
Encephalocoele	7	1	6	14
Spina bifida	48	2	52	102
TOTAL	125	15	61	201

Table 8.3.3. gives details of those cases notified to the study that did not have a neural tube defect and Table 8.3.3. illustrates those cases that had a neural tube defect as part of a recognised syndrome

Table 8.3.3. CASES NOTIFIED TO THE STUDY THAT DID NOT HAVE A NEURAL TUBE DEFECT

	NUMBER
Hydrocephalus	21
Turners Syndrome with cystic hygroma	3
Cystic Hygroma	2
Kniest Syndrome	1
Hydrolethalus	1
Mongolian Blue Spot	1
Intrauterine fetal death	1
Nucal cyst	1
Toxoplasmosis	1
TOTAL	35

Table 8.3.4. CASES NOTIFIED TO THE STUDY THAT WERE IDENTIFIED AS HAVING A NEURAL TUBE DEFECT AS PART OF A RECOGNISED SYNDROME

	NUMBER
Amniotic band sequence	8
Meckel Gruber Syndrome	7
Triploidy	3
Trisomy 18	4
Rubenstein Taybi Syndrome	1
HARD +/- E	1
Cloacal Extrophy	1
Amyoplasia Congenita	1
Caudal Regression	1
Short cord exomphalos	1
Roberts syndrome	1
Chordal axis developmental defect	1
multiple anomalies consistant with chromosomal abnormality	2
TOTAL	32

Of those cases having a neural tube defect as part of a recognised syndrome 7 (21.9%) were only identified as a result of the research project.

8.4.THE INCIDENCE OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

The incidence of neural tube defect in The North Western region from May 1986 until April 1988 was 1.76/1000 live and stillbirths. This incidence was found to vary between districts as illustrated by table 8.4.1.

TABLE 8.4.1. THE INCIDENCE OF PREGNANCIES AFFECTED WITH A NEURAL TUBE DEFECT.

DISTRICT	NUMBER OF CASES OF NTD.	TOTAL BIRTHS.	INCIDENCE per 1000 births	STANDARD RESIDUAL
LANCASTER	9	3183	2.83	1.43
BLACKPOOL	5	7482	0.67	-2.25
PRESTON & CHORLEY	16	9214	1.74	-0.06
BLACKBURN	13	8157	1.60	-0.36
BURNLEY	12	7045	1.70	-0.12
WEST LANCS.	3	2940	1.02	-0.96
BOLTON	20	7530	2.66	1.85
BURY	4	4933	0.81	-1.59
NTH MANCHESTER	12	4619	2.60	1.36
CENTRAL MANCHESTER	18	4368	4.12	3.72*
STH MANCHESTER	8	5271	1.52	-0.42
OLDHAM	9	6593	1.37	-0.77
ROCHDALE	9	6687	1.35	-0.81
SALFORD	16	6747	2.37	1.19
STOCKPORT	14	7789	1.80	0.08
TAMESIDE	16	7283	2.20	0.89
TRAFFORD	0	5804	0	-3.2*
WIGAN	17	8482	2.00	0.53
TOTAL	201	114127.	1.76	

*p<0.05

From Table 8.4.1. the following may be seen. The overall incidence of neural tube defect in the North West Region from May 1986-April 1988 was 1.76/1000 live and stillbirths. There was variation between districts during the period of study. With the use of standard residuals it was possible to calculate which variations were unlikely to have occured by chance. A standard residual of greater than +/- 2.58 indicates that the variation of incidence occuring by chance alone has a probability of 1%. A standard residual of greater than +/- 3.29 indicates that this is only likely to occur by chance alone in 1 in 1000 instances (i.e. 0.1%). From the data it is evident that incidences varied greatly in certain districts and the variation seen for Cental Manchester and Trafford would only of had a 0.1% likelihood of occuring by chance alone.

8.5.THE CHARACTERISTICS OF THE WOMEN INTERVIEWED

The characteristics of the women identified were primarily ascertained from the obstetric case notes with supplementary information made available at the time of the interview.

The age of the women ranged from 15 to 46 years. This is illustrated in table 8.5.1.

TABLE 8.5.1. THE AGE OF THE WOMEN INTERVIEWED

AGE	NUMBER INTERVIEWED
under 15	0
15-19	18
20-24	45
25-29	38
30-34	21
35-39	6
40-44	3
45+	1
unknown	0
TOTAL	132

In 116 cases the woman was either married or in a stable relationship and 16 women were single.

The parity of the women is illustrated by table 8.5.2.

TABLE 8.5.2. THE PARITY OF THE WOMEN INTERVIEWED

PARITY	NUMBER INTERVIEWED
0	52
1	48
2	17
3	8
4	6
5	1
TOTAL	132

8.6. THE METHOD OF DIAGNOSIS OF THE AFFECTED PREGNANCY

The information concerning the way in which a diagnosis of neural tube defect was made in the affected pregnancy was obtained from the obstetric case notes with supplementary information being provided by ultrasonographers, paediatricians and from the interview with the woman.

THE METHOD OF DIAGNOSIS OF PREGNANCIES RESULTING IN A TERMINATION OF PREGNANCY

There were 125 (62.2%) pregnancies that resulted in a termination. The diagnoses were anencephaly in 70 (56%) cases, encephalocoele in 7 (5.6%) cases and 48 (38.4%) had spina bifida. The way in which the diagnosis of the neural tube defect was made is summarised by table 8.6.1.

TABLE 8.6.1. The method of diagnosis of neural tube defect resulting in a termination of pregnancy.

METHOD	DIAGNOSIS			TOTAL
	anencephaly	encephalocoele	spina bifida	
scan alone	48	5	10	63
scan & MSAFP	20	2	15	37
scan,MSAFP & amniocentesis	2	0	21	23
unknown	0	0	2	2
TOTAL	70	7	48	125

THE METHOD OF DIAGNOSIS OF PREGNANCIES RESULTING IN A LIVE OR STILLBIRTH

The continuation of an affected pregnancy arose as a result of one of the following situations:

-no screening or subsequent prenatal diagnosis undertaken because of concealment of the pregnancy, the mother booking into antenatal care at a gestation that was too late for investigations to allow termination of pregnancy or because the mother had only general practioner care and was not offered such investigations.

-false negative screening.

-parental wishes to continue with a pregnancy that was identified as being affected with a neural tube defect.

-a twin pregnancy.

This data is summarised by tables 8.6.2. and 8.6.3.

TABLE 8.6.2.THE METHOD OF DIAGNOSIS OF PREGNANCIES AFFECTED WITH A NEURAL TUBE DEFECT THAT RESULTED IN A STILLBIRTH

METHOD	DIAGNOSIS			TOTAL
	ANENCEPHALY	ENCEPHALOCOELE	SPINA BIFIDA	
False negative investigations				
SCAN-ve,MSAFP-ve	0	1*	1*	2*
SCAN-ve,NO MSAFP	1	0	0	1
NO SCAN,MSAFP-ve	0	0	0	0
No screening				
NO SCAN,NO MSAFP	2	0	0	2
Other				
PARENTAL CHOICE	5	0	1	6
CONCEALED PREG.	1	0	0	1
TWIN PREGNANCY	2	0	0	2
UNKNOWN	1	0	0	1
TOTAL	12	1	2	15

*closed lesion

TABLE 8.6.3.THE METHOD OF DIAGNOSIS OF PREGNANCIES AFFECTED WITH A NEURAL TUBE DEFECT THAT RESULTED IN A LIVEBIRTH

	DIAGNOSIS			TOTAL
METHOD	ANENCEPHALY	ENCEPHALOCOELE	SPINA BIFIDA	
False negative investigations				
SCAN-ve,MSAFP-ve	0	2	11(9*)	13(9*)
SCAN-ve,NO MSAFP	1	1	14	16
NO SCAN,MSAFP-ve	0	0	0	0
No screening				
NO SCAN,NO MSAFP	0	0	0	0
Other				
PARENTAL CHOICE	1	1	20	22
CONCEALED PREG.	0	0	1	1
TWIN PREGNANCY	1	1	0	2
UNKNOWN	1	0	4	4
TOTAL	3	5	53	61

*closed lesion

There were two cases of anencephaly, one resulting in a stillbirth and one in a live birth, that were not detected on ultrasound prior to twenty-eight weeks gestation. In both these cases the ultrasound had been carried out at eleven

weeks of gestation with the gestation being estimated by the crown rump length of the fetus. In the first case the mother was told that she would require a further scan but this was not carried out until twenty-nine weeks of gestation at which time a diagnosis of anencephaly was made. In the second case a further scan was carried out at thirty-seven weeks of gestation when there was clinical evidence of polyhydramnios.

There were 28 pregnancies that progressed pass a gestation of twenty-eight weeks as a result of the wishes of the parents. 8 parents had strong religious beliefs that did not permit termination of pregnancy. There were three parents that expressed regret at having continued with the pregnancy. All of these had had a liveborn infant with a neural tube defect one of whom had subsequently died and one who was not expected to survive. At the time of the interview 11 of the 61 infants born alive had died and a further 6 had a very poor prognosis.

At the time of this study 4 of the 19 district health authorities in The North western Region did not offer routine MSAFP screening for neural tube defect. Two other health authorities in The Region were considering the withdrawl of this screening programme. 16 affected pregnancies were not identified by ultrasound and MSAFP was not available. In these cases 12 of the parents would have chosen termination of pregnancy.

8.7. THE CARE AND SUPPORT RECEIVED

TERMINATION OF PREGNANCY

There were 81 women interviewed who had chosen to terminate the affected pregnancy. Of these, two had had a suction evacuation of the uterus as the neural tube defect was identified in the first trimester of the pregnancy. The other women had a midtrimester termination of pregnancy. There were no cases terminated by hysterotomy.

The following aspects of the care that this group received will be considered

- technical aspects of the termination of the pregnancy
-pain relief
-the timing of admission to hospital
-feelings about the fetus
-support received

When questioned about the technical aspects of the procedure 55 (67.9%) women were unaware of what the procedure would involve. In 40 (49.9%) cases they did not realise that they would be awake during the termination of the pregnancy. There were 36 (44.4%) women who did not know how long they

would be in hospital and 40 (49.9%) did not realise that the fetus would "be delivered".

There were 38 (46.9%) women who felt that they would have liked further information about what was going to happen to them during the termination and 30 (37%) would have liked more time to talk about their decisions. It was felt that written information would have been helpful in 62 (76.5%) of cases. There were 16 (19.8%) women who felt it would have helped if they could meet others who had undergone a termination for neural tube defect.

Pain relief was inadequate in 39 (48.1%) cases. There were 8 (9.9%) women that commented that the pain was a punishment and 6 (7.4%) women were told that analgesia would slow down the procedure.

The admission to hospital was rapid once the diagnosis had been made. There were 12 (14.8%) women who expressed the need for more time to think about their decision. In 10 (12.3%) cases there were complaints about the environment in which they had the termination. These complaints included being able to hear babies crying fronm adjacent rooms if the procedure was being conducted in the obstetric unit or having to meet other women who were having "social" terminations of pregnancy if on the gynaecology ward.

There were 15 (18.5%) women who saw the fetus after delivery although a further 17 (21%), in retrospect, would liked to have seen it. Concerns were raised about how the fetus was shown to the women. There were 13 (16%) women who named the fetus and in 10 (12.3%) cases a photograph had been taken.

The level of satisfaction with the support received whilst in hospital and following discharge is summarised by Table 8.7.1.

TABLE 8.7.1. LEVEL OF SATISFACTION WITH SUPPORT THAT WAS RECEIVED

VENUE	SATISFACTORY	UNSATISFACTORY	TOTAL
IN HOSPITAL	48	19	68
AT HOME	23	45	68

Examples of incidents that caused dissatisfaction included one woman that was told by the Catholic doctor on duty that the pain she was suffering was a punishment for what she was doing to her child. Another women was told not to see the fetus as it "looked so awful". There were cases of the fetus being delivered into a bedpan and one women recalled "my baby being brought to me on a fish and chip tray" this describing the disposable receptacle that had been used for

this purpose.

In 44 (54.3%) cases partners were able to be present during the procedure although 11 women had no stable partner at the time of the termination. Of the partners that were able to be with the woman, 38 (86.3%) were made to feel welcome. Comments from partners included the inability to obtain refreshments, lack of telephone facilities to contact other relatives, no facilities for their children and lack of people to talk to about what was happening. In one case there was great appreciation for the nurse who "broke the rules" and allowed the husband to rest on an empty bed.

Once the women had returned home there was a variable amount of support received. This is summarised in Table 8.7.2.

Table 8.7.2. THE SUPPORT RECEIVED AT HOME

SOURCE	SUFFICIENT	INSUFFICIENT	NONE	TOTAL
G.P.	30	33	18	81
HEALTH VISITOR	20	25	36	81
GENETICS DEPT.	22	1	57	81
ASBAH	6	2	60	81

It was evident that much of this support lacked coordination and there was little organised follow-up of these women. In one district these issues had been considered and a specialist nurse saw all women whilst in hospital and following their discharge from hospital. All the women who received this service found it helpful. In other cases there were complaints about the general practitioner being unaware of what had happened and also being unable to provide information that was requested. There were four instances when midwives arrived asking to see the new baby. The Association for Spina Bifida and Hydrocephalus (ASBAH) was found to be helpful for 6 of the 8 of the women that contacted them but in two case they did not provide the support the women had asked for and were felt to be interested in children with spina bifida rather than women who had undergone terminations.

SUPPORT FOLLOWING A STILLBIRTH OR LIVEBIRTH

There were 76 women who had a stillborn or liveborn infant infant with a neural tube defect of which 51 were interviewed.

The women were asked whether their overall experiences had

been satisfactory. This information is summarised in Table 8.7.3.

Table 8.7.3. SUPPORT FOLLOWING A STILLBIRTH OR LIVEBIRTH

	SATISFACTORY	UNSATISFACTORY	N/A	TOTAL
OBSTETRICS	37	14	-	51
PAEDIATRICS	24	6	21	51

Women who had a stillborn infant all said that they were happy with the amount of time they spent with their dead baby. Of the 43 whose baby was born alive 15 (34.9%) felt distressed about the child having to be removed rapidly with 12 of these women feeling they did not receive an adequate explanation for this.

Of those 40 babies that were transfered to a paediatric unit 16 (40%) women were able to remain with the baby and a further 11 (27.5%) stayed on the paediatric unit during part of the time that the baby was there. Of these women 15 (55.6%) were satisfied with the care that they received. Dissatisfaction centred around lack of appropriate facilities for a women who had just delivered including no showering facilities or baths that were too small. In addition to this 8 (29.6%) women complained about having to see different midwives each day.

Women were asked who they felt the main source of support was after being discharged from hospital. This is summarised in Table 8.7.4.

Table 8.7.4. THE MAIN SOURCE OF SUPPORT RECEIVED

SOURCE	OUTCOME			TOTAL
	TOP	STILLBIRTH	LIVEBIRTH	
Hospital staff	3	0	9	12
G.P.	8	2	3	13
Health visitor	6	1	3	10
Genetics Dept.	13	0	2	15
Paediatric dept.	N/A	1	16	17
Other	8	1	4	13
No professional support	43	3	6	52
TOTAL	81	8	43	132

Other sources of support included family and friends. ASBAH and SATFA also provided input.

8.8. GENETIC COUNSELLING RECEIVED

Of the 132 women interviewed 28 (21.2%) were unable to recall having been given any information regarding risks to future pregnancies and 25 (18.9%) had no recall of having received information concerning periconceptional vitamin supplementation. Tables 8.8.1. and 8.8.2. indicate the knowledge of recurrence risks that women had

TABLE 8.8.1. THE KNOWLEDGE OF RECURRENCE RISKS IN SUBSEQUENT PREGNANCIES

OUTCOME OF AFFECTED PREGNANCY	KNOWLEDGE ACCURATE FIGURE	SOME KNOWLEDGE	NO KNOWLEDGE	TOTAL
TERMINATION	48	19	14	81
STILLBIRTH	5	2	1	8
LIVEBIRTH	15	15	13	43
TOTAL	68	36	28	132

TABLE 8.8.2. THE KNOWLEDGE OF PERICONCEPTIONAL VITAMIN SUPPLEMENTATION.

OUTCOME OF AFFECTED PREGNANCY	KNOWLEDGE PREGNAVITE FORTE F.	MULTI-VITAMINS	UNAWARE	TOTAL
TERMINATION	45	23	13	81
STILLBIRTH	5	3	0	8
LIVEBIRTH	12	18	13	43
TOTAL	62	44	26	132

The source of genetic counselling received is given in the following tables.

TABLE 8.8.3. THE SOURCE OF INFORMATION CONCERNING THE RISK OF RECURRENCE IN COUPLES HAVING HAD A TERMINATION OF PREGNANCY

SOURCE	NUMBER		
	AWARE OF ACCURATE FIGURE	SOME AWARENESS OR RISK	TOTAL
OBSTETRICIAN	25	14	39
PAEDIATRICIAN	N/A	N/A	N/A
GENETICIST	20	0	20
MIDWIFE	0	0	0
G.P.	1	4	5
ASBAH	1	0	1
OTHER	0	0	0
TOTAL	47	18	65

There were 16 (19.6%) women who were unaware of the recurrence risks.

TABLE 8.8.4. THE SOURCE OF INFORMATION PERICONCEPTIONAL VITAMIN SUPPLEMENTATION IN WOMEN HAVING HAD A TERMINATION

SOURCE	NUMBER AWARE OF P.F.F.	NUMBER AWARE OF MULTIVITS.	TOTAL
OBSTETRICIAN	22	13	35
PAEDIATRICIAN	0	0	0
GENETICIST	20	0	20
MIDWIFE	0	0	0
G.P.	0	4	4
ASBAH	1	0	1
OTHER	0	1	1
TOTAL	43	18	61

There were 20 (24.5%) women unaware of periconceptional vitamin supplementation

TABLE 8.8.5. THE SOURCE OF INFORMATION ON RECURRENCE RISKS REPORTED BY WOMEN HAVING HAD A STILLBIRTH

SOURCE	NUMBER AWARE OF P.F.F.	NUMBER AWARE OF MULTIVITS.	TOTAL
OBSTETRICIAN	4	2	6
PAEDIATRICIAN	0	0	0
GENETICIST	1	0	1
MIDWIFE	0	0	0
G.P.	0	0	0
ASBAH	0	0	0
OTHER	0	0	0
TOTAL	5	2	7

There was 1 (12.5%) woman who was unaware of her recurrence risks

TABLE 8.8.6. THE SOURCE OF INFORMATION ON PERICONCEPTIONAL VITAMIN SUPPLEMENTATION REPORTED BY WOMEN HAVING HAD A STILLBIRTH

SOURCE	NUMBER AWARE OF P.F.F.	NUMBER AWARE OF MULTIVITS.	TOTAL
OBSTETRICIAN	4	2	6
PAEDIATRICIAN	0	0	0
GENETICIST	1	0	1
MIDWIFE	0	0	0
G.P.	0	0	0
ASBAH	0	0	0
OTHER	0	0	0
TOTAL	5	2	7

One woman who had had a stillbirth was unaware of periconceptional vitamin supplementation.

TABLE 8.8.7. THE SOURCE OF INFORMATION ON RECURRENCE RISKS REPORTED BY WOMEN HAVING HAD A LIVEBIRTH

SOURCE	NUMBER		
	AWARE OF ACCURATE FIGURE	SOME AWARENESS OR RISK	TOTAL
OBSTETRICIAN	3	6	9
PAEDIATRICIAN	2	5	7
GENETICIST	10	0	10
MIDWIFE	0	0	0
G.P.	0	2	2
ASBAH	0	1	1
OTHER	0	1	1
TOTAL	15	28	43

There were 13 (30.2%) women who had had a liveborn infant who were unaware of their risks of recurrence.

TABLE 8.8.8. SOURCE OF INFORMATION ON PERICONCEPTIONAL VITAMIN SUPPLEMENTATION REPORTED BY WOMEN HAVING HAD A LIVEBIRTH

SOURCE	NUMBER		
	AWARE OF P.F.F.	AWARE OF MULTIVITS.	TOTAL
OBSTETRICIAN	2	6	8
PAEDIATRICIAN	0	5	5
GENETICIST	10	0	10
MIDWIFE	0	0	0
G.P.	0	3	3
ASBAH	0	1	1
OTHER	0	3	3
TOTAL	9	31	40

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8.9. SUBSEQUENT PREGNANCIES

52 of the 132 women interviewed were pregnant again by the end of the two year study period. A further 20 not interviewed were known to be pregnant following notification by their obstetrician or clinical geneticist. The source of notification of the subsequent pregnancy is illustrated in table 8.9.1.

3 couples had sought sterilization following the affected pregnancy and in one case adoption was being considered

TABLE 8.9.1. THE SOURCE OF NOTIFICATION OF THE SUBSEQUENT PREGNANCY AND THE NUMBER OF THOSE INTERVIEWED.

SOURCE	NUMBER	%	NUMBER INTERVIEWED
PATIENT	41	56.9	41
OBSTETRIC NOTES	16	22.2	5
GENETICS DEPT.	11	15.3	2
G.P.	4	9.8	4
TOTAL	72	100	52

Periconceptional vitamin supplementation received during the subsequent pregnancies was studied. Women were considered as being either fully or partially supplemented according to the Smithells protocol (Smithells et al 1980). In addition the use of multi-vitamins was documented. These results are illustrated by table 8.9.2.

TABLE 8.9.2. THE OUTCOME OF THE SUBSEQUENT PREGNANCY AND THE VITAMIN SUPPLEMENTATION RECEIVED.

OUTCOME	PERICONCEPTIONAL VITAMIN SUPPLEMENTATION				
	P.F.F.* F.S.#	P.F.F. P.S.+	MULTI-VITAMINS	NIL	TOTAL
NO RECURRENCE	24	1	4	8	37
RECURRENCE	1	0	0	0	1
OUTCOME AWAITED	6	0	0	1	7
SPONTANEOUS ABORTION	5	0	0	0	5
UNKNOWN	2	0	0	0	2
TOTAL	38	1	4	9	52

*Pregnavite Forte F

#Fully supplemented

+Partially supplemented

There was only one recurrence. This involved a baby with spina bifida occulta born to a mother who had been fully supplemented with Pregnavite Forte F. There were two documented cases of other congenital abnormalities both occuring in fully supplemented women. These were one case of sacral agenesis in a non diabetic women and one child with a strawberry naevus.

Two women had two pregnancies following the affected pregnancy. Both these women were fully supplemented during the first pregnancy but were unsupplemented during the second pregnancy.

9. DISCUSSION

9.1 THE ESTABLISHMENT OF A REGIONAL NOTIFICATION SYSTEM FOR CASES OF NEURAL TUBE DEFECT.

For a notification system to be effective there needs to be involvement from multiple sources, high levels of motivation, cross checking of data and adequate resources to fund the system (Fredrick and Butler 1972, Karwinski and Hartveit 1989, Renwick 1968).

In this study the primary source of data was obtained from the obstetricians with additional information being provided by paediatricians, ultrasonographers and clinical geneticists. This is similar to methods used in other studies although the close liaison of the researcher with the notifiers was not reported by other researchers (Eurocat 1990).

The obstetricians in The North Western Region were highly motivated - only one out of 67 refused to participate with the notification system. This level of commitment continued during the two year that the study took place with 58 to 62 notification forms being returned each month without further prompting. Cases other than those with a neural tube defect were also reported e.g. Trisomy 21. This may have been because the individual completing the notification form was not aware of which congenital abnormalities to report.

The method of ascertainment that was used resulted in rapid identification of affected cases although there were 27 cases reported at least three months after the pregnancy was completed. These women were not interviewed as only recent experiences were being investigated.

The other disciplines involved with the notification system were equally committed. The compliance with notification was enhanced by repeated feedback of information to the participating clinicians (See appendices).

The method of ascertainment used required confirmation of the diagnosis. There were inaccuracies in the initial notification. Thirty five cases did not have a neural tube defect and thirty two cases had a neural tube defect as part of an identified syndrome. There were seven cases where the syndrome was identified by the researcher after studying the case notes and descriptions of the fetus or baby.

These deficiencies could be avoided by ensuring that the notifier understands which cases are to be reported and by requesting that all cases of congenital abnormalities are examined by an expert in dysmorphology. This should be supported by chromosomal assay (Donnai and Farndon 1985). A standardized protocol for the investigation of fetuses and infants who are believed to have a congenital abnormality has been suggested by other researchers (Curry and Honore 1990).

In cases that are terminated, a statutory obligation to report the abnormality, as with the birth notification system, would assist identification of cases. Currently, death certificates are an inaccurate source of information (Fedrick and Butler 1972, Goldacre 1992).

Anencephaly, encephalocoele and spina bifida are defined as neural tube defect by the researcher in this study. Spina bifida occulta, iniencephaly and congenital dermal sinus are not included. Encephalocoele is omitted by some researchers. This has implications for the estimated incidence of neural tube defect. The use of standardized diagnostic criteria, such as The International Classification of Diseases, ensures that researchers are consistant in inclusion criteria. Little used is made of classification systems and coding when reporting congenital abnormalities. The implementation of such systems may be one way of enhancing accuracy in the future (Knight 1986).

The notification system used in this study required a high degree of input from the researcher. It was expensive and time consuming but ensured completeness and accuracy. The system achieved the first aim of the study although it was not possible for the system to be maintained following the completion of the study because of lack of resources.

9.2 THE INCIDENCE OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

The incidence of neural tube defect in The North Western Region was reported as 4 per 1000 live and stillbirths prior to this reseach taking place. This figure was based on studies carried out over twenty years ago (Carter 1969). At that time termination of pregnancy was rare and prenatal diagnosis was not yet available. Since then, with the development of prenatal diagnostic techniques, identification of cases affected with a neural tube defect has become more complex. Since 1969 there had been little systematic study of the incidence of neural tube defect in the North Western Region. It was suspected that, as in other regions of England, the incidence was declining (Laurence 1985).

As a result of the notification system that was discussed previously, the incidence of neural tube defect in The North Western Region from May 1986 - April 1988 was found to be 1.76/1000 live and stillbirths. This varied between districts within The Region from none to 4.12/1000. There were two districts that had an incidence that significantly differed for that of the region as a whole, Central Manchester and Trafford. The epidemiological implications of this demand further investigation but were outside the remit of this study.

Other studies have documented a decline in the incidence of neural tube defect. In South Wales there has been a fall from 4.5 per 1000 births in 1956-1957 to 2 per 1000 in 1984 (Laurence 1985). A fall has been recorded in Scotland and Ireland (Eurocat 1990, Davis et al 1991) although the incidence appears to have been stable in other parts of Europe (Eurocat 1990). A decline has also been reported in Australia (Bower et al 1993). There have been falls in the incidence of neural tube defect in the past for which no reasons have been found (Laurence 1985). It is recognised that the incidence of neural tube defect has both short and long term fluctuations over time (Leck, Record et al 1968). A more long term study is indicated to observe whether the decline in incidence is maintained.

It is possible that the decline in incidence is due to environmental factors which change over time. If there is an environmental contribution to the recurrence of neural tube defect then the risk of recurrence may fall. This has implications for the effect of periconceptional vitamin supplementation on the recurrence of neural tube defect and will complicate the interpretation of research findings in the future.

This study aimed to ascertain the current incidence of neural tube defect in The North Western Region. The multiple

sources of ascertainment and repeated cross checking of information is believed to have achieved this. As a result of this, the hypothesis that the incidence of neural tube defect in The North West Region was declining has been confirmed. The study demonstrated fluctuations in the incidence of neural tube defect within The Region demanding further, longterm investigation.

9.3 THE SUPPORT THAT FAMILIES RECEIVED

This study investigated the experiences of women who had had an affected pregnancy as recalled three months after the completion of the pregnancy. A semistructured interview schedule was used which allowed unprompted information to be obtained. Standardized rating scales for the assessment of anxiety were not used as the aim of the study was to investigate the support that the women had experienced. The additional use of descriptive rather than quantitative information enabled unprompted information to be obtained.The women were able to provide detailed descriptions of their satisfactory and unsatisfactory experiences. Unsatisfactory experiences, whether few or many, are then able to highlight

areas of clinical practice that require review.

Termination of pregnancy creates an acute grief reaction the impact of which depends on many factors (Green 1990). In this study it was shown that women perceived a lack of information on investigative procedures and the subsequent events surrounding the termination. They did not realise what the procedure would entail and felt unsupported during it.

There was lack of adequate analgesia in 39 cases adding to feelings of punishment and guilt. In one case the junior doctor was recalled as saying that the pain was part of the punishment for terminating the pregnancy.

In over one third of cases that resulted in a termination, time to consider the implications of the diagnosis and to make decisions about how to proceed with the pregnancy was perceived as insufficient. Other researchers have also commented on this aspect of care (Knight 1988, Marteau et al 1988). Women wanted further information about the diagnosis and how the termination would be carried out. There were 67.9% women who were unaware of what the procedure would involve.

Over three quarters of the women interviewed would have liked written as well as verbal information.

The environment where the termination was carried out caused distress for 12.5% of the women interviewed. If the termination was carried out on a gynaecology unit women were exposed to other patients undergoing "social" terminations of pregnancy. On the obstetric unit crying babies contribute to distress.

There were 18.5% women who saw the fetus after the termination. A further 21% would like to have done so but were not given the opportunity. There were 16% women who named the fetus this helping to give it an identity. In 12.3% cases a photograph of the fetus had been taken. Disposal arrangements were not considered by this study although one district had made available a small area in the local cemetery where women and their families could go. This was appreciated by all the women from that district and has been shown to be advantageous by other authors (Batcup et al 1988).

Support in hospital was variable. There was lack of time to discuss the diagnosis and the options available. Women were not told about the physical changes their body would undergo after the termination of the pregnancy. Concerns about lactation were not dealt with and when to resume sexual intercourse was not considered. Contact with the consultant prior to leaving hospital was rare and explanations by junior

staff were frequently perceived as insufficient. Others have supported this finding (Swerts 1987).

Over half the partners were present during the termination of the pregnancy and over 80% of these were made to feel welcome.

SATFA had just been established when this study was undertaken. There were no groups in the North West Region at the time of the study. Two mothers had been in contact with the organisation and had found it helpful. Since the completion of the study this has become an important additional source of support and advice (Black 1988).

Once discharged from hospital organised support was perceived as lacking. The general practitioner failed to provide input in 18 of the 81 cases whilst a further 33 women experienced a general lack of input. The health visitor failed to visit in almost half the cases. Communication from the obstetrician to the general practitioner was inadequate and there were four instances where the midwife visited to find out how the "new baby" was. One district had employed a specialist nurse to see all women who had had a diagnosis of neural tube defect. This nurse was able to offer support from the time of the diagnosis, during the termination and following discharge from hospital. This ensured that the woman received the support and information she needed and

also optimised communication between the professionals. A service such as this requires the provision of adequate resources but may prevent distress at the time of the diagnosis and termination and may also prevent the development of psychological sequelae after the termination (Elder and Lloyd 1990).

Those with a live infant were occupied with the care of the child and at times their care seemed to be forgotten. This was particularly evident when women were transfered to the paediatric unit with the baby. Facilities were inadequate for a woman in the immediate postnatal period and midwifery care lacked co-ordination. The same midwife could not provide care during the womans stay on the paediatric unit in almost a third of cases.

In the case of those women who had a termination over half felt they had no received professional support. A lack of professional support was only perceived in 14% of those having a live baby.

The study aimed to investigate the support that women receive surrounding the termination or delivery of a pregnancy effected with a neural tube defect. This aim was achieved although it was recognised that objective assessment of the experiences that women have presents problems. Part of the grief experienced when the perfect child a women hoped

for does not become a reality may be expressed as dissatisfaction with the support that she received. Despite this it has been demonstrated that certain aspects of care need further consideration, particularly if termination of pregnancy occurs.

The hypothesis that support following termination of pregnancy lacks coordination was supported by this study.

9.4. GENETIC COUNSELLING AND PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

This study investigated the recall of information that women received following a pregnancy affected with a neural tube defect. One deficiency of this study was that the information that women recalled could not be compared with the information that clinicians believed they were providing.

There were 31 woman who were referred for genetic counselling. It is possible that this is not a true reflection of the practices of the obstetricians in the region. The obstetricians were aware that women, once interviewed for the purposes of the study, would then be

provided with information about the aetiology of neural tube defect, the risks of recurrence and periconceptional vitamin supplementation. A review of referral rates for the preceeding two years did not reflect an alteration in referral practices.

Women were receiving information about their recurrence risks from a variety of sources. In over a quarter of cases they were unaware of their recurrence risks and did not know about periconceptional vitamin supplementation.

A lack of awareness of recurrence risks and periconceptional vitamin supplementation may be for one of two reasons. The woman may have been given the information but did not understand it or recall it or the information may not have been provided. Optimal provision of information can be considered in the light of the guidelines from The Department of Health (HMSO 1993).

These guidelines raise the following issues:

Those at risk of "genetic conditions" should be identified. This study did identify those at risk of recurrence of a pregnancy affected with a neural tube defect. It is important that once identified appropriate and accessible information is available. In the North Western Region the information being provided was variable in quality and

quantity. Some women were fully aware of their risks of recurrence and the available of periconceptional vitamin supplementation. Others had less understanding of their risks. Women mentioned that it must have been "the green potatoes" reflecting the mass attention the media gave to the unproven findings of Professor Renwick (Renwick 1972). Media attention now needs to be directed towards the use of periconceptional vitamin supplementation to increase public awareness.

The diagnosis of the congenital abnormality must be accurate. Neural tube defect, although usually occuring in isolation, may be part of a syndrome that has a recurrence risk that differs from that of an isolated defect. This study demonstrated that, whilst these syndromes may be identified at the time of termination or delivery, a proportion are missed. It is essential that all fetuses and babies with a congenital abnormality are examined by an expert. Chromosome assay may be indicated in certain cases. Accurate diagnosis is important to enable the correct genetic counselling to be offered, to allow the appropriate prenatal diagnostic tests to be provided in subsequent pregnancies and to ensure that epidemiological data is accurate.

Genetic counselling should be avalable for those having a pregnancy affected with a congenital abnormality. In cases of neural tube defect counselling is frequently provided by

other clinicians including the obstetrician or paediatrician. This has the advantage that additional people are not involved with the already distress woman but, in some cases, these clinicians do not have the time or expertise that a clinical geneticist can offer. In this study 31 women were referred to the clinical genetics service. The clinical genetics department may, as seen in certain districts within the North West Region, be able to provide specialist nursing support that can reduce the sequelae of an abnormal pregnancy (Elder and Laurence 1990). In one instance during the study a women delivered a stillborn, premature, infant with an encephalocoele. A postmortem examination was not carried out. In her subsequent pregnancy a fetus with multiple abnormalities was identified by ultrasound and was terminated. On detailed examination this fetus was found to have Meckel Gruber Syndrome. The counselling following the first pregnancy, stating that a risk of recurrence was 1 in 100 with the use of periconceptional vitamin supplementation was thus inaccurate. If the correct diagnosis had been made at the time the family would have been aware of the 1 in 4 recurrence risk of an autosomal recessive disorder. In another case the fetus terminated was found to have trisomy 18. A preceeding pregnancy had resulted in a spontaneous mid-trimester abortion of a fetus with spina bifida. This fetus had not had chromosome assay and may also have had trisomy 18. These anecdotal cases illustrate the importance of detailed investigation of such fetuses.

The Department of Health has recommended that registers of congenital abnormalities are organised. This study demonstrated that this requires co-ordination and allocation of resources. The notification system that this study developed could not be continued after the completion of the research project as a result of insufficient resources.

Care for those at risk of genetic conditions is becoming increasingly more important with the development of molecular genetic techniques that have allowed the identification of a greater number of conditions. The prenatal diagnosis of neural tube defect has been possible since the early 1970's but, as seen in this study, co-ordinated and effective care and support is still lacking. This is particularly true for those undergoing termination of pregnancy with over half of these women feeling that they had received no professional support at this time.

The professionals involved with this group of women need training in all aspects of the care that is demanded by these patients. The results of this study were made available to the obstricians, paediatricians and ultrasonographers in The North West Region and were also considered by the working party that had funded the project. As a result of this study guidelines were produced that aim to improve practices for the care of women with a pregnancy affected with a neural

tube defect.

Research and development is essential in all fields of medical practice. Clinical genetics is a developing speciality that is progressing rapidly with the availability of new techniques. This study has demonstrated that all aspects of the care of the patient demands consideration and that new techniques and research findings must be accesible to the patients who they are designed to benefit. The research into the prevention of neural tube defect has taken many years and many aetiological factors have been hypothesised. The findings of a dietary link resulted in unrandomised and controversial studies (Smithells et al 1976). These studies have lead to confusion for the medical profession. The randomised trial that followed was criticised and condemned (Super et al 1991). As predicted by many, although completed, it has continued to cause debate. This research has demonstrated that clinical practices vary. Many clinicians have offered periconceptional vitamin supplementation to women at risk prior to the results of the randomised trial.

9.5. THE SUBSEQUENT PREGNANCY

This study aimed to follow up women who had had an affected pregnancy. Reliance was placed on the woman to report when she was pregnant again. This method of follow up was not satisfactory and almost one fifth failed to notify the researcher of the next pregnancy. Other methods that could be used are antenatal clinic notifications or communications from the general practitioner. A further possiblity, and one that would encourage women to take periconceptional vitamins, is to ensure regular contact with the woman is maintained. A health visitor or specialist nurse could be employed for this purpose. This did occur in one of the districts being studied, as already discussed, and all the women in this district took periconceptional vitamin supplementation.

This study could not offer prolonged follow up of cases. It was not possible to ascertain whether interventions had been effective. In addition to this the effects of the publication of the results of the MRC trial could not be assessed.

9.6. THE FUTURE

Since this study was undertaken the results of the MRC Trial have been published (MRC 1991). These results show that periconceptional folic acid offers protection against recurrence of neural tube defect. Despite this, clinicians remain divided in their practices and research continues (Mills et al 1989, Smithells et al 1991, Super et al 1991).

This study has demonstrated a decline in the incidence of neural tube defect in The North Western Region with local fluctuations in incidence. It has also shown that the support that women receive is variable and that genetic counselling is being provided from a variety of sources. Many women have been offered periconceptional vitamin supplementation.

The Government is now recommending folic acid to those at risk of an affected pregnancy. Clinicians will need to organise services to ensure that women are aware of this recommendation and are able to obtain folic acid prior to becoming pregnant. Despite the availability of folic acid, there will still be pregnancies conceived that are affected with a neural tube defect. These women and their families will require support from those caring for them. Services will need to ensure that this support is optimal and readily available.

10. CONCLUSIONS

This research has established that the incidence of neural tube defect in The North Western Region has declined.

It has also demonstrated that women, having had an affected pregnancy,appear to lack organised support. This is particularly evident if the affected pregnancy is terminated. Women are being advised about their recurrence risks and are being offered periconceptional vitamin supplementation.

There is a need for support and counselling to be co-ordinated. In addition, resources need to be allocated to allow the appropriate training of staff in this field.

With the results of the MRC trial now available, there is confirmation that periconceptional vitamin supplementation can offer primary prevention of neural tube defect. Clinicians need to ensure their patients are aware of this although the needs of those with an affected pregnancy must not be forgotten.

11. APPENDICES

APPENDIX A.1.

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

The North West Regional Health Authority Research Advisory Committee has approved the proposal by a working party of the Regional Obstetrics and Gynaecology Sub-committee to set up a system of surveillance for neural tube defect in the Region. This has received ethical approval. The object is to have complete ascertainment of couples who have had a NTD pregnancy, and to find out the extent of any counselling received, any dietary modification suggested, and the outcome of future pregnancies. For this we hope to create a register of couples known to be at risk because they have had a previous NTD conception. Such couples, if you wish, may then be offered counselling and appropriate information about prophylactic periconceptional vitamin supplementation. The vitamin preparation which we currently advise is Pregnavite Forte F following our published research findings (Seller et al Lancet 1, 1985: 1392-3, Smithells et al Lancet 1, 1980: 339-40.).

Dr. Sarah Bernard has been appointed as Research Registrar for three years from 1.2.86 to work on this programme under the general direction of Dr Maurice Super, Consultant Clinical Geneticist.

Dr Bernard will contact you in the next few months and I shall greatly appreciate your co-operation in referring to her appropriate patients with the necessary background information.

Any information supplied will be treated in the strictest confidence, and no action will be taken concerning your patients without prior discussion with you.

If you have any comments or questions about this work please do not hesitate to contact me or one of the research group.

Yours sincerely

Professor Rodney Harris

on behalf of: Dr J Walsworth-Bell, Dr A P Read, Dr M Super, Dr S Bernard.

APPENDIX A.2.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

I enclose a copy of the letter that you will have received from Professor Harris describing the research work that we are undertaking.

We are hoping to be made aware, via the Obstetricians, of all newly diagnosed pregnancies in which there is a neural tube defect. This will identify patients to us and then, approximately three months after the delivery, I will be arranging to meet with the couple. This will only be done with the full agreement of all clinicians involved with the case.

I look forward to hearing from you soon and would be happy to discuss this project with you.

Yours sincerely

Dr S Bernard
Research Registrar

APPENDIX A.3.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

Further to my discussion with you regarding the above research, I now aim to commence gathering data on pregnancies affected with a neural tube defect. I will be using the enclosed form for this purpose.

Please would you return a completed form for next month in the envelope supplied. I will forward you a similar form at the beginning of every subsequent month.

Many thanks for your help.

Yours sincerely

Dr S Bernard
Research Registrar

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

Monthly returns for.....

Dr.....

NAME	ADDRESS	G.P.	DIAGNOSIS	DATE	OUTCOME

APPENDIX A.4.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

Once again we would like to thank you for your co-operation with our research project.

We are attempting to ensure that our figures are as accurate as possible. We did not receive the following monthly return forms from you and we would be grateful if you could return the enclosed form for the months indicated.

Enclosed is a summary of our preliminary findings.

Thank you

Yours sincerely

Dr S Bernard
Research Registrar

APPENDIX A.5.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

Once again we would like to thank you for your co-operation with our research project.

We are attempting to ensure that our figures are as accurate as possible. We did not receive the following monthly return forms from you and we would be grateful if you could return the enclosed form for the months indicated.

Enclosed is a summary of our preliminary findings.

Thank you

Yours sincerely

Dr S Bernard
Research Registrar

APPENDIX A.6.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

We are undertaking the above research project in the North Western Region. I enclose a letter that has been circulated to Obstetricians and paediatricians concerning this.

I have been notified by.....
that your patient.....
has recently had a pregnancy affected with a neural tube defect.

I intend to see this patient and her partner within the next month unless you feel there are reasons this should not occur. If I do not hear from you by..... I will assume you are happy for me to go ahead with this visit, the outcome of which I will communicate to you shortly.

If you wish to discuss the project with me please do not hestitate to contact me.

Yours sincerely

Dr S Bernard
Research Registrar

APPENDIX A.7.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

I am a doctor who has recently been appointed to investigate the help and support available to couples who have had a pregnancy affected with spina bifida or anencephaly.

Dr.....has informed me that unfortunately your recent pregnancy resulted in this outcome.

Would it be possible for me to visit you to discuss you experiences? The information that you give me will be strictly confidential. As a result of it, we hope to ensure the best possible services for people such as yourself in the future.

I enclose a stamped, addressed envelope and a form to indicate when I could visit. Please could you return it to me. If the date is not convenient please suggest an alternative. I am able to visit in the evening.

Thank you for your help.

Yours sincerely,

Dr S Bernard
Research Registrar

APPENDIX A.7.

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

Name.....

Address.....

.....

.....

I would/would not* be happy for Dr Bernard to visit

Appointment on.....

This is/is not* convenient.

If this date is inconvenient please suggest an alternative

.....

Your appointment will be confirmed by letter prior to the visit.

*please delete

APPENDIX A.8.

INTERVIEW SCHEDULE

IDENTIFICATION NUMBER.....

DISTRICT.....

OBSTETRICIAN.....

PAEDIATRICIAN.....

CLINICAL GENETICIST.....

GENERAL PRACTITIONER.....

MATERNAL DETAILS

AGE

SOCIOECONOMIC CLASS

ETHNICITY

PAST MEDICAL HISTORY

PAST OBSTETRIC HISTORY

FAMILY HISTORY

MEDICATION

DETAILS OF DIAGNOSIS

DIAGNOSIS

OUTCOME

AFP

AMNIOCENTESIS

SCAN

TOLD BY WHOM?

UNDERSTANDING

PARTNER PRESENT

COMMENTS

TERMINATION OF PREGNANCY

EXPERIENCES

PAIN RELIEF

SEEN

HELD

NAMED

PHOTOGRAPH

SUPPORT

In hospital .....satisfactory/unsatisfactory

At home.....satisfactory/unsatisfactory

G.P.

Health visitor

Genetics

Other

STILLBIRTH/LIVEBIRTH

EXPERIENCES

TRANSFERRED WITH BABY

SUPPORT

In hospital.....satisfactory/unsatisfactory

Obstetrician

Paediatrician

At home.....satisfactory/unsatisfactory

MAIN SOURCE OF SUPPORT

COUNSELLING

AWARE OF RECURRENCE RISKS

AWARE OF VITAMIN SUPPLEMENTATION

EXPERIENCES

FUTURE PLANS

SUPPORT

SOURCES

EXPERIENCES

APPENDIX A.9.

ADVICE TO COUPLES WHO HAVE HAD A PREGNANCY RESULTING IN SPINA BIFIDA OR ANENCEPHALY

This leaflet is designed to supplement what you will have been told by the doctors looking after you. It aims to briefly explain what spina bifida and anencephaly are and ways in which the diagnosis may be made in the antenatal period. Methods that are believed to reduce the risk of recurrence of the abnormality for subsequent pregnancies are also explained.

WHAT IS SPINA BIFIDA AND ANENCEPHALY?

As your baby develops the spinal column or backbone begins as a flat sheet of cells, like a ribbon, down the babys back. Two ridges along each side of the ribbon grow upwards leaving a "valley" in the middle. These ridges grow over the valley and join forming a tube - The neural tube. This tube is formed about 28 days after conception, before many people realise they are pregnant. If the tube does not close a defect (neural tube defect) results.The spinal column goes from from the babys head to its bottom so a defect can result

in a malformed skull (anencephaly) or an open spine (spina bifida) depending where it occurs along the tube. The open valley may be a large defect or it may be small and covered with skin so it is not immediately apparent. Either way, because the neural tube encloses the brain and spina cord, if it remains open damage will result to the nerves going to the babys legs, bladder and bowel. The baby may not live or may have a range of handicaps. If the skull does not close the baby will die before or shortly after birth.

WHY DOES IT HAPPEN?

There have been a number of suggestions as to why neural tube defect occurs.

1). Genetic factors are known to play a part. If a couple have had one affected pregnancy, or if their close relatives have had a neural tube defect, they are at an increased risk of another affected pregnancy.

2). Environmental factors are important. Many factors in the environment have been implicated in the cause of neural tube defect. Some cannot be altered but, of those that can, diet is believed to be important. Adequate vitamin levels may have a role in the closure of the neural tube and even if levels are satisfactory supplementation with vitamins around the time of closure of the neural tube may help to reduce recurrence risks in at risk pregnancies.

ANTENATAL DETECTION OF NEURAL TUBE DEFECT

Most neural tube defects can be detected antenatally by a combination of investigations.

1). **Alpha-fetoprotein (AFP).** AFP is a protein that is lost from the open skin defect present in anencephaly and spina bifida. A blood test done on the mother at sixteen weeks of pregnancy is able to detect high levels of it. Should the level be high the mother will be asked to have the test repeated as AFP may be raised for a number of reasons other than neural tube defect i.e.: the wrong dates, bleeding during the pregnancy, twins, other rare abnormalities in the baby. Often no cause will be found for the raised AFP and the mother will go on to have a healthy baby.

2). **Amniocentesis.** AFP also passes into the fluid around the baby, the amniotic fluid. Your doctor may want a sample of this to test. This can be done by inserting a small needle through the mothers abdomen and into the sac around the baby. Fluid may then be drawn off and tested. This procedure causes little pain to the mother but does carry with it a very small risk of miscarriage.

3). **Ultrasound scan.** Scans are of use for a number of reasons in pregnancy. They give an accurate estimation of the age of the pregnancy and, in skilled hands, allow the spinal column to be seen. They may accompany the above tests.

Your doctor will discuss the results of your tests with you and advise on further management should they be abnormal.

No investigation is 100% reliable but if all of the above are negative then it is very unlikely that your child has an open neural tube defect.

PREVENTION OF NEURAL TUBE DEFECT

As indicated above it is believed that vitamins may play a part in the closure of the neural tube. Women who have had an affected pregnancy are being offered a vitamin preparation - Pregnavite Forte F. This is prescribed by their doctor and is taken for at least one month before attempting a pregnancy until the date of the second missed menstrual period. Research has shown that this reduces the likelihood of having another baby with a neural tube defect but it has to be started before conception because neural tube defect occurs so early in the pregnancy.

The above information is a brief outline of what is meant by neural tube defect and ways of detecting it in pregnancy. Your doctor will be able to provide more details and answer any questions you might have.

You are welcome to contact me to talk about this further.

APPENDIX A.10.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

I am writing to find out how you have been since I visited you. I am particularly interested to know if you have become pregnant again.

Please could you complete the enclosed form. This is a vital part of the research that I am carrying out. If you would prefer to talk to me I can be contacted at the above address.

All information is strictly confidential.

We are almost at the end of the research and, once the results are analysed, you will be receiving a copy of them.

Thank you for your help.

With best wishes,

Yours sincerely

Dr S Bernard
Research Registrar

APPENDIX A.10.

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

FOLLOW UP SURVEY OF RESEARCH INTO THE PREVENTION OF SPINA BIFIDA AND ANENCEPHALY

NAME.....

ADDRESS.....

.....

.....

PLEASE INFORM RESEARCHER IF YOUR ADDRESS HAS ALTERED SINCE LAST SEEN.....

.....

.....

SINCE YOU WERE SEEN BY DR. BERNARD HAVE YOU BEEN PREGNANT YES/NO*

PLEASE GIVE DETAILS OF ANY PREGNANCIES BELOW

a) Miscarriages

Date..... Stage of pregnancy.....

Did you take vitamins during this pregnancy Yes/No*

Please give the dates that you took vitamins

from.....until.....

Name of vitamin preparation.....

Dose.....

b) Currently pregnant

Date baby due.....

Did you take vitamins during this pregnancy Yes/No*

Please give the dates that you took vitamins

from.....until.....

Name of vitamin preparation.....

Dose.....

c) I had a baby on.....

Did you take vitamins during this pregnancy Yes/No*

Please give the dates that you took vitamins

from.....until.....

Name of vitamin preparation.....

Dose.....

Is this baby well Yes/No*

If the baby has any illnesses or problems please describe below

.....

.....

.....

.....

*delete as appropriate.

Please make any additional comments below

signed.....

Thank you for your help.

Please return this form in the envelope provided. All information is strictly confidential.

APPENDIX A.11.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WEST REGION

Re.....

A three year prospective study on neural tube defect is nearing its completion. The above patient under your care has participated in this study. Please would you let us know if she has had any further pregnancies and whether periconceptional vitamin supplemwentation was offered.

All information is strictly confidential.

We will be forwarding you the results of our study shortly

Thank you for your help.

Yours sincerely

Dr S Bernard
Research Registrar

APPENDIX A. 12.

Dear

PREVENTION OF NEURAL TUBE DEFECT IN THE NORTH WESTERN REGION

You might remember that I visited you some time ago regarding our research project on spina bifida and anencephaly.

This research is almost completed and I would like to thank you for participating with it.

I enclose a copy of our findings.

If you have any points that you would like to discuss please contact me. I shall be available until the end of January after which time you should discuss any issues with your own doctor.

I would like to thank you for your help. It has been greatly appreciated.

With best wishes for the future.

Yours sincerely,

Dr S Bernard
Research Registrar.

APPENDIX A. 12.

PREVENTION OF NEURAL TUBE DEFECT IN
THE NORTH WESTERN REGION

A SUMMARY FOR PARTICIPATING FAMILIES

Spina bifida is the name given to a group of conditions in which there is an abnormality in the developing spine of the baby. If this occurs in the area of the head it is called anencephaly and results in the brain being under developed. Babies with this severe form of spina bifida can only live for a few hours. If the defect occurs along the spine it is called spina bifida.

Some babies with spina bifida are unable to survive. Those that do survive have a range of disabilities. These disabilities are as a result of damage to the nerves at the site of the defect. Many children with spina bifida also have a condition known as hydrocephalus. This is a build up of fluid around the brain. It may be relieve by an operation that helps this fluid to circulate.

Studies have demonstrated that women at risk of having a baby with neural tube defect may need extra vitamins in their diet when attempting a pregnancy. These vitamins need to be commenced prior to becoming pregnant until two months of pregnancy to ensure that levels are adequate at the time that the spine is developing. Women who have had one affected pregnancy are at an increased risk of subsequent affected pregnancies. It may be possible that this risk can be reduced by taking vitamins in this way.

OUR RESEARCH

Obstetricians in The North Western Region were concerned about women who had had a pregnancy affected with spina bifida. They wanted to know how common the condition was and how the women felt about the care that they had received when the diagnosis was made. Another important question that needed answering was whether this group of women had been told about vitamins as a possible way of reducing risks to future pregnancies.

A research project was commenced. Women who had had an affected pregnancy were approached and asked if they would be willing to be interviewed about their experiences. Those that agreed were seen in their own home. A large amount of information was made available as a result of this.

This is a report of the findings of the project.

THE RESULTS OF THE RESEARCH PROJECT

201 cases of neural tube defect (spina bifida or anencephaly) were identified during the two year period of the project.
125 of these pregnancies were terminated (aborted).

15 babies were still born.

61 babies were born alive.

132 women were interviewed.

The incidence of neural tube defect was found to be 1.76/1000 births i.e. In every thousand babies born there were approximately two affected with either spina bifida or anencephaly.

The incidence reflects a known decline in the number of babies being affected with the condition.

EXPERIENCES OF WOMEN HAVING A TERMINATION OF THE AFFECTED PREGNANCY

125 of the affected pregnancies were terminated (aborted).
At interview the following comments were made:

-Insufficient information was available about the tests offered that detect the abnormality.
-Explanation of the abnormality should be in terms that are easily understood.
-Insufficient time was given to talk about the diagnosis
-Insufficient explanation was given about how the pregnancy would be terminated.
-Women varied in their desire to see the "baby" after the termination.
-Some women were unaware of the increased risk of a recurrence in subsequent pregnancies and the availability of vitamin supplementation.
-Support after leaving hospital was frequently lacking.

The comments made by this group of women highlighted the following needs:
-Adequate time should be given to discuss the diagnosis
-Women should be told what will happen during the

termination.
-There should be an opportunity to see the "baby"
-General Practioners and health visitors should be aware of the diagnosis so that support after discharge from hospital can be coordinated and counselling arranged.

EXPERIENCES OF WOMEN HAVING A BABY THAT WAS STILLBORN OR ALIVE

15 babies were still born and 61 were born alive.
At interview the following comments were made:
-Adequate information should be available.
-It was helpful to see the pardiatrician prior to the birth of the baby if the diagnosis was made at this stage.
-Support at home was generally satisfactory

Comments about vitamin supplementation were similar to the group of wome having a termination of the pregnancy.

The following needs were highlighted:

-Time must be allocated for discussion with professionals.
-Coordination of support is important.

CONCLUSIONS

Our research has demonstrated that, in The North West of England, the number of pregnancies affected with spina bifida or anencephaly is falling.

Women need adequate time to discuss the diagnosis and subsequent management of the affected pregnancy. Support is needed when making decisions and following the termination of the pregnancy or the delivery of the baby. Women need to be aware of the risks to future pregnancies and ways of reducing these risks.

Doctors in The North West will be made aware of these findings and will be requested to act on them to ensure that the care of women that have had a pregnancy affected with neural tube defect is optimised.

ACKNOWLEDGEMENTS

This research has only been possible because of the cooperation of so many women who have had a pregnancy affected with a neural tube defect. We would like to express our very great thanks to these women who have discussed their experiences. Their assistance with this research has been appreciated.

APPENDIX A.12.

PREVENTION OF NEURAL TUBE DEFECT IN

THE NORTH WESTERN REGION

A SUMMARY FOR PARTICIPATING CLINICIANS

Spina bifida, anencephaly, encephalocoele and other abnormalities of the central nervous system are responsible for nearly a third of all congenital abnormalities. Secondary prevention of this important groups of defects is available with screening, prenatal diagnosis and selective termination of pregnancy but primary prevention continues to be the ultimate aim (Smithells et al 1976).

Following reports by Smithells et al (Smithells et al 1980, Smithells et al 1983) on the association between periconceptional vitamin supplementation and a reduction of the risk of recurrence of neural tube defect the Medical Research Council began a randomised controlled trial . A working party was set up to coordinate a study of the prevention of neural tube defect in The North Western Region of England. It was discovered by questionnaire that approximately 70% of obstetricians in The Region were already prescribing vitamins for women

known to be at risk of neural tube defect because of an affected pregnancy, and most were prescribing Pregnavite Forte F because of existing collaberation with the Smithells trials. In view of this established clinical practice it was not possible to randomise people as in the Medical Research Council trial. The working party therefore addressed a number of other important questions concerning neural tube defect and its prevention. These were:

1. The true incidence of neural tube defect.
2. The support and counselling given to women following an affected pregnancy.
3. The extent to which women were being offered periconceptional vitamins for subsequent pregnancies.
4. The outcome of subsequent pregnancies.

A three year prospective study was initiated. This is a report of the findings.

METHOD

Ascertainment of affected cases was through reports from obstetricians with supplementary information provided by paediatricians, ultrasonographers, pathologists and clinical geneticists.

Obstricians were asked to provide details on a monthly return form. Once a case was identified the case noted were examined to confirm the diagnosis.

Permission was obtained to interview the women.

This interview was conducted in the womans own home and took place approximately three months after the completion of the affected pregnancy. The interview schedule used was semi-structured and asked about the way in which the woman became aware of the diagnosis of neural tube defect and details of her subsequent management. The woman was asked about her knowledge of the risk of recurrence in future pregnancies and whether she was aware of periconceptional vitamin supplementation.

The woman was asked to inform the interviewer if she became pregnant again.

RESULTS

The North West Regional Health Authority is served by 67 consultant obstetricians. 66 of these obstetricians agreed to provide information on their patients. of these, three requested that patients identified as having an affected pregnancy were not approached for interview.

201 affected pregnancies were reported from May 1986 until April 1988 giving an incidence of 1.76/100 for The Region. The diagnosis and outcome of these pregnancies is illustrated by table 1.

TABLE 1. THE DIAGNOSIS AND OUTCOME OF CASES AFFECTED WITH A NEURAL TUBE DEFECT.

	anencephaly	encephalocoele	spina bifida	TOTAL
TOP	70	7	48	125
stillbirth	12	1	2	15
livebirth	3	6	52	61
TOTAL	85	14	102	201

Excluded from this are those cases reported that, on review of the case notes, were found either not to have a neural tube defect (35) or to have the defect as part of a recognised syndrome (32).

Table 2 illustrates the regional distribution of cases.

TABLE 2. THE REGIONAL DISTRIBUTION OF CASES AFFECTED WITH A NEURAL TUBE DEFECT.

DISTRICT	NUMBER OF CASES OF NTD	TOTAL BIRTHS	INCIDENCE
LANCASTER	9	3183	2.83
BLACKPOOL	5	7482	0.67
PRESTON & CHORLEY	16	9214	1.74
BLACKBURN	13	8157	1.60
BURNLEY	12	7045	1.70
WEST LANCS.	3	2940	1.02
BOLTON	20	7530	2.66
BURY	4	4933	0.81
NTH MANCHESTER	12	4619	2.60
CENTRAL MANCHESTER	18	4368	4.12
STH MANCHESTER	8	5271	1.52
OLDHAM	9	6593	1.37
ROCHDALE	9	6687	1.35
SALFORD	16	6747	2.37
STOCKPORT	14	7789	1.80
TAMESIDE	16	7283	2.20
TRAFFORD	0	5804	0
WIGAN	17	8482	2.00
TOTAL	201	114127	1.76

Of the 201 cases identified permission was given to contact174 women. 132 of these were interviewed.

EXPERIENCES OF WOMEN INTERVIEWED

A common group of deficiencies in the management of women undergoing a termination of pregnancy were identified which may be summarised under the headings
-understanding od diagnosis
-management of the termination
-support and counselling.

From the comments that women made it was evident that time is needed to discuss the diagnosis and subsequent management of the pregnancy. Women felt that there was insufficient time allowed to ask questions and they were left not fully understanding the situation.

Women were unaware of what the procedure involved. Frequently they believed that they would be anaesthetised for the termination and were distressed to realise that they would go through a "labour" and would have to "deliver" the baby.

Women appreciated the opportunity to see and hold the "baby".

In general there was a lack of perceived support on returning home. Support that was give lacked coordination.

Women who had a stillbirth or livebirth appeared to be more satisfied with the information and support that they received.

PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

The information recalled about periconceptional vitamin supplementation is summarised in table 3.

TABLE 3. RECALL OF INFORMATION ON PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

	PPF*	MV*	NIL	TOTAL
TOP	45	23	13	81
STILLBIRTH	5	3	0	8
LIVEBIRTH	12	18	13	43
TOTAL	62	44	26	132

It was shown that 31 women had been referred to the clinical genetic service for counselling and 68 recalled having received information from their obstetrician, paediatrician or general practitioner. In 33 cases women were unaware of periconceptional vitamin supplementation or the risks of recurrence.

52 women have become pregnant again with 38 of these having delivered. Of those who have delivered 26 have taken Pregnavite Forte F and a further 4 an alternative form of vitamin supplement.

DISCUSSION

It is believed that this study achieved virtually complete ascertainment of neural tube defect pregnancies. This was as a result of a combination of multidisciplinary involvement, positive and negative monthly returns of information and close personal contact with participating clinicians and departments at all stages of the study.

The results reported suggest that The North West Region shares in the general fall in incidence of neural tube defect (Laurence 1985, Lorber 1985, Owens 1981) which cannot be explained simply as a consequence of a successful screening programme as terminations of

pregnancy have been included in the data.

Once an affected pregnancy is detected it is vital that supportive services are provided for women, whether or not they decide to continue with the pregnancy. This study demonstrated that there is a lack of coordinated support for women undergoing a termination of pregnancy whilst those having a live or stillbirth appear to be absorbed into a network of paediatric support.

Having had an affected pregnancy women should be provided with information on recurrence risks and periconceptional vitamin supplementation. This study demonstrated a lack of recall of this information having been provided. On possibility is that uncertainties about the benefits offered by periconceptional vitamin supplementation may result in clinicians not emphasising their availability (Harris 1988).

Adequate counselling cannot be accommodated for in a busy antenatal clinic. A suitable venue should be available. The counsellor must provide time for discussion and be able to offer women realistic hope for a future healthy pregnancy.

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APPENDIX A.13

THE CALCULATION OF STANDARDISED RESIDUALS

The estimation of the standardised residual (SR) of a series of data is a way in which an individual observed value may be identified as differing considerably from the expected value. A statistical significance may then be attached to the observed difference (Strike 1991, Woodward and Francis 1988).

The standardised residual (SR) is calculated as:

SR = (observed - expected)/square root of expected value

In this study this statistical test was used to identify significant variations in the incidence of neural tube defect between districts of the North Western Region. The observed incidence was that calculated for each district. The expected incidence was the calculated incidence for the region.

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