REVIEW OF LITERATURE
Congenital anomalies may be caused by genetic factors or by environmental factors. Most anomalies are a result of complex interaction between genetic and environmental factors. The causes of most anomalies are unknown.

During the first two weeks of development, exposure to teratogenic agents usually kills the embryo rather than cause congenital anomalies. During period of organogenesis, teratogenic agents disrupt development and may cause major congenital anomalies. During fetal period teratogens can produce morphological and functional abnormalities, particularly of the brain and eye (Jenne E. Bell et al 1978, Moore L. Keith et al 1993).

The overall incidence of congenital defects varies between 2-3% and central nervous system malformations constitute about 30% of total defects (Cunningham F G et al 2001). In India congenital malformations have emerged as the 3rd most common cause of perinatal mortality (M. Ravi Kumar et al 1996, K. Park 2002). 2.5% of newborn babies have birth defects in India (K. Park 2002).

There is a wide geographical variation in the occurrence of central nervous system anomalies all over the world. The prevalence of anencephaly and spina bifida at birth varies from about 0.3% in South East England to 0.9% in North Ireland, Cater (Cater C. O et al 1973, Cater C. O et al 1976). Creasy and Alberman (Creasy M.R. et al 1976) reported an incidence of 3% in spontaneous aborting fetuses. Singh and Carr (Singh R.P. and Carr D.H 1967) found the incidence of central nervous system anomalies as 2% in Canada and Ontario in spontaneous aborting fetuses. 1.3% incidence was found in 3715 specimens of induced abortions by Nishumura (Nishimura H. 1970) in
Japan. In 1976 Verma I C et al (Verma I C and Jacob T T 1976) compiled all studies available on congenital CNS malformations. They found the maximum incidence in Chandigarh which was as high as 12/1000 and minimum in Calcutta 0.5/1000 births.


Ajay Kalra et al (Ajay Kalra et al 1984) conducted a study on 2720 newborns over a period of 14 months and reported the rate of congenital malformations as 19.85/1000. CNS malformations were the commonest 6.98/1000, followed by gastrointestinal tract anomalies 5.51/1000. Musculoskeletal system anomalies were the third commonest. Among CNS malformations anencephaly was found to be the commonest, 2.57/1000 followed by spina bifida 2.2/1000, hydrocephalus 1.8/1000 and meningocele 1.47/1000. They observed a higher rate of occurrence of congenital malformations in the offspring of mothers in the age group of 16-20 years.

Arti Chaudhary et al (Arti Chaudhary et al 1984) conducted a retrospective study on 1,15,851 births in five hospitals of West Bengal from 1976 to 1987 and a prospective study from 1986 to 1987. They found the overall frequency of malformations as 4.42/1000 live births. Neural tube defects (CNS malformations) were the commonest, 1.05/1000 live births. Anencephaly was
found in 0.49/1000 live births. Other CNS defects were hydrocephalus, meningomyelocele and microcephaly. The highest rate of neural tube defects was seen in births during rainy season followed by winter and summer. Neural tube defects were common in babies born to mothers of 21-25 years of age. They observed a variable sex ratio in these babies with neural tube defects.

J.P. Goravalingappa and H.K.Nashi (J.P. Goravalingappa et al 1979) conducted a study on 2398 consecutive births in Hubli, Karnataka over a period of 15 months during 1976-77. They observed congenital malformations rate as 31.27/1000. Congenital CNS malformations were highest, as high as 6.67/1000. They found hydrocephalus and meningocele as the most common CNS malformations (2.0/1000) followed by anencephaly (0.83/1000). Other anomalies observed by them were of the gastrointestinal system (cleft lip and palate, esophageal atresia, tracheoesophageal fistula, pyloric stenosis, ileal atresia), cardiovascular system, respiratory system, genitourinary system and facial defects. The incidence of malformations, in relation to social class, was found to be higher in lower social classes (class III, IV, V).

In 1991 Manorama Verma et al (Manorama Verma et al 1991) published a retrospective study done on 10,000 consecutive births in Ludhiana. They found congenital malformations in 4.3% newborns. Malformation rate was 12.6% in still births as compared to 3% in live births. CNS was the most common system involved, 4.7/1000. Anencephaly was found to be 3.6/1000, followed by hydrocephalus 2.2/1000, meningomyelocele and meningocele 1.0/1000 and microcephaly 0.2/1000. Other system anomalies seen were GIT, urogenital and skeletal system. Gastrointestinal malformations included cleft lip, cleft palate, omphalocele, imperforate anus, diaphragmatic hernia, atresia
of bowel, esophageal atresia, tracheoesophageal fistula.

P.C.Mishra and R Baweja (Mishra P C et al 1989\textsuperscript{53}) studied 4098 deliveries in SRN hospital, Allahabad between 1983 to 1987. They observed the incidence rate of congenital malformations as 14.64/1000 births (this included both live births and still births). Commonest malformations were of CNS, 1.95/1000 followed by cardiovascular malformations, 1.46/1000. Limb and skin anomalies were almost as equal as CNS malformations. Multiple malformations were seen in 5.36/1000 births. Spina bifida was the commonest CNS malformation followed by hydrocephalus, meningocele and microcephaly. Cleft lip and palate were the commonest gastrointestinal anomalies seen in their study followed by tracheoesophageal fistula, imperforate anus and umbilical hernia. They suggested exposure to drugs, chemicals and radiation and material infections during pregnancy as the possible risk factors for these malformations.

Parul Patel et al (Parul Patel et al 2001\textsuperscript{64}) conducted a study in central Gujarat over a period of 2 years. They observed central nervous system malformations as the commonest 10.77/1000 births. This was followed by musculo-skeletal, gastrointestinal, cutaneous, genitourinary and cardiac malformations ranging from 0.11/1000 to 2.36/1000 births.

Swain S et al (Swain S et al 1994\textsuperscript{77}) observed CNS malformations as the commonest congenital malformations at birth in their study.

S.S.Aggarwal et al (S S Aggarwal et al 1991\textsuperscript{75}) conducted a study in Lucknow which included 9405 consecutive single births (9123 live births and 282 still births). They found an over all rate of congenital malformations as 2.8%. In live births the incidence
was 1.6% whereas in still born babies the incidence was 16.4%. Defects of CNS system were most common, 31.7% of all births (4.7/1000). Anencephaly and meningomyelocele each were 1.5/1000 followed by hydrocephalus 1/1000. Other defects seen were spina bifida and microcephaly. Anencephaly with spinabifida and encephalocele were also seen. Neural tube defects were seen more in female babies. Female to male ratio was 1.9:1. Rate of neural tube defects was observed to be higher at 33-36 weeks of gestation. It was 5.95/1000. Below 32 weeks it was 1.7/1000 and in more than 37 weeks it was observed as 1.6/1000. GIT defects included trachoesophageal fistula, duodenal atresia, multiple intestinal atresia, exomphalos and imperforate anus. Skeletal and urogenital system anomalies were also observed.

Verma M et al (Verma M et al 1991) conducted a retrospective study on 10000 live births and observed CNS defects as the most common congenital malformation in them.

B.Vishnu Bhat and Lokesh Babu (B.Vishnu Bhat and Lokesh Babu 1998) studied 12,797 consecutive deliveries from September 1989 to December 1992 in Pondicherry. They observed the overall incidence of congenital malformations as 3.7%. It was 3.2% among live births and 15.7% among still births. Malformations were higher among male babies (69%). Consanguinity among parents of congenitally malformed babies (45.2%) was significantly more common than those with out birth defects. Congenital malformations accounted for 10% of perinatal deaths and 13.8% of neonatal deaths. They observed musculoskeletal malformations as the commonest defects (9.69/1000 births). This was followed by cutaneous (6.33/1000), genitourinary (5.47/1000), CNS (3.99/1000) and cardiac (2.03/1000 births) defects. Postmortem examination was useful in detecting internal malformations and it increased the total number of defects by 1½ times.
Hydrocephalus (1.56/1000) was seen as the commonest CNS malformation in their study. This was followed by microcephaly (0.78/1000), meningomyelocele (0.70/1000), anencephaly (0.55/1000), spinabifida (0.16/1000) and encephalocele (0.16/1000).

P. Chaturvedi and K.S. Banerjee (P. Chaturvedi and K.S. Banerjee 198565) (64) conducted a prospective study in rural Maharashtra from April 1985 to March 1986. They observed 27.2/1000 as the overall incidence of congenital malformations among 3000 consecutive deliveries. Musculoskeletal malformations were the most common followed by CNS malformations (3.96/1000), gastrointestinal and urogenital malformations. Among CNS malformations, anencephaly and hydrocephalus were the commonest (1.32/1000 each) followed by microcephaly, meningocele and meningomyelocele. All anencephaly babies were still born. Maximum still born babies had CNS malformations.

P. Dash Sharma (P. Dash Sharma 197066) conducted a retrospective study on records of 5554 births at Holdsworth memorial Hospital, Mysore from 1967 to 1969. He recorded the incidence of congenital malformations as 0.25%. He concluded that this low incidence was because the hospital did not cater to the poor socioeconomic group, thereby excluding a large majority of at risk population.

Creasy and Alberman (Creasy M.R and E.D. Alberman 197615) conducted a study on 2620 pregnancies ending up in spontaneous abortions in London. The rate of CNS malformations in organized fetuses (more than 20 weeks) was found to be 3% while the total incidence of malformations was 3.6%. Anencephaly and spina bifida were the most common CNS malformations noted. Other CNS malformations were craniorachischisis, hydrocephalus, exencephalus, encephalocele. Encephalocele was more frequent in younger abortuses. Typical anencephalus was seen in older
abortuses. 40% abortuses with CNS malformations were found to have some chromosomal abnormality while among abortuses without CNS malformations only 13% had an abnormal chromosomal pattern.

Machin and Crolla (Machin G.A and Crolla J.A 1974\textsuperscript{30}) also reported chromosomal aberrations in perinatal deaths with spina bifida and hydrocephalus.

In 1978, Jenne.E.Bell et al (Jenne.E.Bell and Christine M.Gosden 1978\textsuperscript{35}) studied 509 spontaneous abortuses in Scotland. They reported the rate of CNS malformations as 4.1%. Male fetuses outnumbered female fetuses among CNS defects. The ratio was 3:1. On histological examination they found that in fetuses with localized external CNS defects the internal abnormality was more extensive while CNS was abnormal in some fetuses with no visible external defect. Higher rate of pregnancies with abnormal fetuses were detected in summer and winter. The defects noted were anencephaly, spinabifida, encephalocele, complete rachischisis, and iniencephaly.

J.H.Edwards (J.H.Edwards 1958\textsuperscript{36}) collected data from the registrar general in Scotland regarding still births due to anencephaly, spinabifida and hydrocephalus from 1939 to 1950. He noted very low incidence of these CNS malformations in social class I. Anencephaly, spinabifida and hydrocephalus were 40% more common in the first order births than second order births. Anencephaly and hydrocephalus were common in mothers under 20 years of age. He noted that anencephaly was relatively less frequent in illegitimate babies. Regional variation within Scotland was seen for all these 3 conditions. The pattern showed that an area with a high incidence of any one of the three CNS malformations tended to have a high incidence of the other two as well and that association between anencephaly and spinabifida
was particularly high. Urbanity increased the risk of spina bifida. There was a marked seasonal variation in the incidence of anencephaly, the peak incidence occurring between October and late February.

M.L. Kulkarni, Mathew Kurian (Kulkarni M.L., Kurian M 199044) followed 3700 consecutive live and still births from 1985 to 1987 in Davengeree, South India, for consanguinity and its effects on occurrence of congenital malformations. They observed the congenital malformation rate as 39.1/1000 births. A significantly high incidence among consanguineous groups (8.01%) was seen as compared to the non-consanguineous group (2.42%). Incidence of malformations was higher in uncle-niece marriages (9.34%) as compared with first cousin marriages (6.18%). Central nervous system malformations had an unusually high incidence (11.8/1000 births). Still births were also more common in consanguineous group. Central nervous system malformations were associated with other defects also. On necropsies they observed that 7 anencephaly babies had pulmonary hypoplasia, 3 had hydrenephrosis, 1 had bicornuate uterus, 1 had diaphragmatic hernia.

R.Kulshrestha et al (R.Kulshrestha et al 198371) conducted a community based study on congenital malformations from 1976 to 1977. They covered 15 villages near Delhi (north India) having a population of 31000 which belonged to the same ethnic group and there was no history of consanguinity. There were a total of 2409 births during the study period. In this study only live born infants were included. Multipurpose workers were chosen as the first contacts for this population. They found the rate of congenital malformations as 34.1/1000. Gastrointestinal tract malformations were the commonest, 21.6/1000. This was followed by genitourinary system anomalies, 5/1000 and CNS
Length of gestation was observed to be maximum in fetuses with anencephaly. There was a positive correlation of occurrence of malformations with the winter season and a lower rate was found during summers.

Jean Fedrick et al (Jean Fedrick et al 1971\textsuperscript{33}) noted the evidence of clustering of cases of hydrocephalus in space and time. They found no similar evidence for the occurrence of spina bifida and anencephaly. This study was conducted in Glasgow from 1964 to 1968. They also noted geographical variations in the occurrence of congenital CNS malformations.

I.D.G.Richards et al (I.D.G.Richards et al 1972\textsuperscript{30}) investigated 92,980 births (live and still births) in 8 areas of South Wales over a period of 3 years. They observed variations in the prevalence of congenital CNS malformations from 5.20/1000 to 10.03/1000 in all these 8 areas. Spina bifida rate was highest and ranged from 2.97/1000 to 5.05/1000 in these areas, followed by anencephaly ranging from 0.76/1000 to 3.72/1000 and hydrocephalus 0.37/1000 to 1.35/1000.

Jean Fedrick et al (Jean Fedrick et al 1976\textsuperscript{34}) analysed the data of the surveys 1958 and 1969. They observed that women reporting abortions were higher in number in areas with a lower incidence of CNS malformations as compared to the areas with a higher incidence of CNS birth defects. They suggested that low incidence of anencephaly, spinabifida in low incidence area may be due to high rate of spontaneous abortions in these areas.

Ian Leek (Ian Leek 1969\textsuperscript{28}) conducted a study in Birmingham by collecting data from 1960-1965. He investigated 133,539 births (including still births) and divided the population into different ethnic groups namely European, West-Indian, Indian...
or Pakistani, British and Irish. He observed the rate of anencephaly in Indian population as 0.6/1000, in European population as 1.6/1000, in British & Irish population as 0.3/1000. No anencephaly was born to the West-Indians. He concluded that in children of European, Indian or Pakistani parentage, anencephaly, spina bifida and cleft lip and palate were much common than those of West-Indian origin. Environmental influences may contribute to this variation in incidence observed amongst the Caucasoid population, but the much greater contrast between Negroid and Caucasoid children is probably due to genetic differences.

Ian Leck et al (Ian Leck et al 196729) analyzed data collected from 3 hospitals studying 246,356 live and still births between 1936 to 1965. They observed the anencephaly rate to be 3.79/1000, 3.62/1000 and 5.81/1000 in these three hospitals. They observed peak incidence of anencephaly during 1940-41 and 1960-61 ranging from 4-7/1000. They concluded that environmental changes may have been partly responsible for the fluctuations in the incidence observed.

Farly T F (Farly T F 200222) reported that low maternal education is an important predictor of having a child with neural tube defect. He suggested that in order to further reduce the incidence of neural tube defects intervention should target women of low education status.

Surez L (Surez L 200376) conducted a case control study on 184 cases and 225 controls and observed that occurrence of stressful life events was associated with neural tube defects. Stress may exacerbate risk in population with poor nutritional status and meager economic resources.
A study was conducted by Hendricks (Hendricks K.A 2001) on 149 cases and 189 controls in Texas, Mexico during 1995 to 2000. Cases consisted of fetuses with anencephaly, spina bifida and encephalocele. He concluded that hyperinsulinemia was a strong risk factor for neural tube defects and may be the driving force for the observed risk in obese women.

J.H.Elwood (J.H.Elwood 1970) analyzed 147,825 births (live + still births) of 28 or more week gestation in Belfast from 1956-1966. 584 anencephalic still births and infant deaths were observed. He observed an over all incidence of anencephaly as 3.95/1000 births, ranging from 3.18/1000 to 5.23/1000 from 1956 to 1966. The incidence in first order births (3.95/1000) was greater than in all subsequent births (1.83/1000). The incidence of anencephaly in summer births was 3.2/1000 as compared to winter births 2.78/1000. The maximum number of anencephaly were born in October months (6.03/1000 to 7.87/1000) and minimum in February & March (1.86/1000 to 3.43/1000). He observed that maximum incidence was seen in social class IV, 5.15/1000 births and class V, 4.9/1000 births while it was minimum in class I, 1.60/1000 births.

Jean Fedrick (Jean Fedrick 1970) analyzed data collected from March to May 1958 in London in which he compared 491 anencephalic babies with 16,994 controls. The incidence of anencephaly was 2.43/1000. Anencephaly was seen more in teenage mothers (less than 20 years of age) and in mothers above 45 years of age. He found that anencephaly was more common in primipara especially young primipara. Older mothers, especially para three or more were also at a higher risk. He observed a higher incidence of anencephaly in social class V (3.06/1000) followed by class IV (2.60/1000) and class III (2.39/1000). He concluded that anencephaly was more common in lower social classes.
Victoria P. Coffey and W.J.E. Jessop (Victoria P. Coffey and W.J.E. Jessop 1957) presented results of a study of 137 cases of anencephaly that occurred in three Dublin maternity hospitals between March 1, 1953 and April 30, 1955. They observed incidence of anencephaly as 5.9/1000, ranging from 4.7 to 8.6/1000, in these three maternity homes. The ratio of male to female babies was 1: 4.2. The preponderance of females was less in babies of mature gestation and absent in those born alive or recently dead and weighing 2000 gm or more. A high proportion of fetuses were immature, judged either by weight or by period of gestation (37 weeks was taken as standard for maturity). Other congenital anomalies were present in 13% of anencephaly. Majority had spina bifida and meningomyelocele. Exomphalus was also seen.

The incidence of anencephaly was significantly higher in babies of mothers over 30 years of age. Allowing for the influence of maternal age, differences between affected and controls in relation to parity was not significant. The mothers of anencephaly had significantly lower haemoglobin levels and plasma protein levels. 10% of husbands of mothers of these anencephaly babies were unemployed.

The incidence of congenital deformities in previous births in mothers of anencephaly babies was 4 times higher than in mothers of controls. The incidence of abortions and miscarriages was also almost double.

N.C. Nevin, et al (N.C. Nevin, et al 1981) conducted a study in Belfast and northern Ireland on 41,351 births from 1964 to 1968. They observed the incidence rate of anencephaly and spina bifida as 8.7/1000 births. They found that the incidence of CNS malformations was more in low socio-economic class (5.5% in class I & II and 9% in class III, IV & V). They also concluded that there is a higher risk of recurrence of CNS malformations.
malformations in class III, IV and V.

M.S.T.Hobbs (M.S.T.Hobbs 196959) observed that mothers born in areas of British Isles where high still birth rates due to neural tube abnormalities prevail, had a significantly greater risk of anencephalic still births than mothers born in low risk areas. He conducted a study on 46,651 births occurring in the Oxford record linkage study area from 1962 to 1966. He concluded that the geographical variations in the incidence of anencephaly in British Isles was due to long term influences that were possibly genetic.

Lechaim Naggan et al (Lechaim Naggan and Brian MacMohan 196748) conducted a study on babies with anencephaly and spinabifida born in one of the four Boston maternity facilities from 1930 to 1965. They analyzed a total of 3,11,437 births above the gestational age of 20 weeks. They found the over all rate of anencephaly and spinabifida as 2.24/1000 births (still births included). High rate (3.1/1000) was found among the offsprings of parents of Irish ancestry. The offsprings of Jewish mothers had the lowest rate in any ethnic group examined (0.77/1000). Marked increase in rates with decreasing socioeconomic status was observed. They also noted that females outnumbered males among anencephaly and spinabifida.

Penrose (Penrose L S 194667) suggested 8 groups of environmental influences causing CNS anomalies. These were infection, malnutrition, chemical agents, hormones, mechanical trauma, radiation, fetal anoxia and climatic conditions.

Lauri Saxen et al (Lauri Saxen et al 199047) conducted a population based study on data of recorded influenza epidemics and one particular marker defect, anencephaly. Analysis included
all mothers whose last menstruation occurred between October, 1968 and March 31, 1982 comprising 858,917 deliveries. 248 cases of anencephaly were recorded, 201 had single defects and 47 had additional malformations. They concluded that influenza virus infection of the mother might not be a major cause of neural tube defects: serological screening of mothers of affected children did not show elevated titers against influenza virus antibodies as compared with matched paired controls.

Kari Kurppa et al (Kari Kurppa et al 1991) studied the risk of anencephaly related to common cold during pregnancy. A case control study was done on 393 Finnish mothers of anencephalic children, with time and area matched controls in the period 1964 through 1982. They concluded that common cold in the second trimester was not associated with anencephaly.

T.W.Sadler (T.W.Sadler 1995) described the following teratogens associated with congenital central nervous system anomalies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Anomaly associated</th>
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<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cytomegalovirus</td>
<td>Microcephaly, blindness, mental retardation</td>
</tr>
<tr>
<td>2. Herpes simplex virus</td>
<td>Microcephaly, retinal dysplasia, microphthalmia</td>
</tr>
<tr>
<td>3. HIV</td>
<td>Microcephaly, growth retardation</td>
</tr>
<tr>
<td>4. Varicella virus</td>
<td>Hydrocephaly, microcephaly</td>
</tr>
<tr>
<td>5. Toxoplasmosis</td>
<td>Hydrocephaly, cerebral calcification, microphthalmia</td>
</tr>
<tr>
<td>6. Treponema pallidum</td>
<td>Hydrocephaly</td>
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<tr>
<td><strong>Drugs</strong></td>
<td></td>
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<tr>
<td>7. Aminopterin</td>
<td>Anencephaly, Hydrocephaly, cleft lip and palate</td>
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</tbody>
</table>

REVIEW OF LITERATURE
CONGENITAL CENTRAL NERVOUS SYSTEM MALFORMATIONS - A PROSPECTIVE STUDY

<table>
<thead>
<tr>
<th>8. Valproic acid</th>
<th>Neural tube defects, cranio-facial anomalies</th>
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</thead>
<tbody>
<tr>
<td>9. Warfarin</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>10. LSD</td>
<td>CNS defects</td>
</tr>
<tr>
<td>11. Cocaine</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>12. Isoretiloin</td>
<td>Neural tube defects e.g. spina bifida cystica</td>
</tr>
<tr>
<td>(13-cis retinoic acid)</td>
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</table>

**Radiation**

| 13. X-rays | Spina bifida, microcephaly, cleft palate |

**Trauma**

| 14. Hyperthermia | Anencephaly |

**Maternal disease**

| 15. Maternal diabetes | Neural tube defects |

A retrospective case control study was conducted by A.S.S.T. Leger and P.C.Elwood (A.S.S.T. Leger and P.C.Elwood 1980⁶) to test the hypothesis that there is an association between trace element content of domestic tap water and the occurrence of neural tube malformations in infants. 11 elements (Pb, K, Mg, Na, Ca, Cu, Fe, Zn, Al, Mn) were examined. A notable difference was found only for zinc, which was lower in the cases than controls.

M.S.Morton et al (M.S.Morton et al 1976⁵⁸) conducted a study on 20 trace elements (As, Cd, Co, Fe, Ni, Li, Tl, Be, Na, Mg, Al, Si, K, Ca, Cr, Mn, Cu, Zn, Ba, Pb) in tap water samples of 48 local authority areas of South Wales. Concentration was tested by atomic absorption spectrometry method. Significant correlation between the occurrence of congenital CNS malformations and four trace elements was observed. Of these, Al was positively correlated while for the remaining three-Ca, Ba and Cu-negative associations were found. Regression analysis
of data suggested that the relationships between Ba and Cu with CNS malformation was more important than those of Al and Ca.

A case control study was conducted by J. Mark Elwood and Andrew J. Coldman (J. Mark Elwood and Andrew J. Coldman 1981) in Canada from 1969 to 1972 in order to identify any correlation between the water composition and occurrence of anencephaly. It included 468 dead babies with anencephaly and a random sample of 4129 live births in the same period. They observed no significant relationship with the concentrations of any of the 14 elements studied in drinking water samples (Ca, Mg, Cu, Li, Zu, Ni, Pb, Si, Hg, Cr, Ag, Co, Cd, molybdenum) with occurrence of anencephaly.

E.G. Knox (E.G. Knox 1972) analyzed the data collected from registrar general statistical review to establish any correlation between dietary deficiency or any toxin exposure with anencephaly. This study was conducted in England and Wales. Data was collected from 1961 to 1967. This included still births and infant deaths due to anencephaly and total births. He found a negative association with the total intake of cheese, meat and apples. The first two have either a direct dietary or an indirect social explanation. Bread, cereals, ice cream, canned peas and varieties of canned meat products demonstrated positive association with the occurrence of anencephaly. The geographical distribution of consumption of both canned peas and meats was similar to the regional variations in the incidence of anencephaly. They concluded that food additives like magnesium salts in the case of canned peas and nitrates and nitrites in the case of canned meats may be responsible for the same.

Lynn B. Jorde et al (Lynn B. Jorde, John C, Carey, Michel J.
Bamshad, Raymond L. White 2003 have described the following:

- Neural tube closes at about the 4th week of gestation. A defect in closure or a subsequent reopening of the neural tube results in neural tube defects. Spina bifida is the most common defect.

- Anencephaly is characterized by partial or complete absence of the cranial vault and calvarium and partial or complete absence of cerebral hemispheres. 2/3rd of anencephaly are still born.

- Encephalocele consists of protrusion of brain into an enclosed sac.

- Prevalence of neural tube defects is 1 to 3/1000

- Neural tube defects are caused by genetic and environmental factors.

- Empirical recurrence risk in sibling is 2 to 5%.

- Prevalence of neural tube defects in Hungary is 1 in 300

- The sibling recurrence risk is 3%, 12%, 25% after 1, 2 and 3rd affected offsprings respectively.

- Anencephaly conception increases the risk for spina bifida & vice versa.

- 50% to 70% neural tube defects can be avoided simply by dietary folic acid supplements.

- There is a genetic variation in the response to folic acid which helps to explain why most mothers with folic acid deficiency do not bear children with neural tube defects and why some who ingest adequate amounts of folic acid nonetheless, bear children with neural tube defects.

- Periconceptional use of folic acid and vitamin is an effective prevention strategy for neural tube defects.

- All women in reproductive age group should take 0.4 mg per day folic acid throughout their reproductive years.

- Fortification of wheat and gram with folic acid should be done (As in United States)
R.W. Smithells et al (R.W. Smithells et al 1980) conducted a study on 185 women who had had one or more babies with neural tube defects and were planning a further pregnancy. These women were given full vitamin supplementation started periconceptionally. Vitamin supplement included B complex, vitamin D, vitamin A and folic acid. A control group was taken comprising of 264 mothers with history of delivery of one or more babies with neural tube defects in past. It was noted that the rate of occurrence of infants born with neural tube defects in mothers who had taken the vitamin supplements was 0.6% while the rate seen in the control group was 5%. Authors concluded that multivitamins given periconceptually had a role in the prevention of neural tube defects.

Monica Holmes-Siedle (Monica Holmes-Siedle 1982) conducted a study on the lines of Smithells and concluded that vitamin supplementation in the periconceptional period of mothers who had borne infants with neural tube defects in past, prevented the recurrence of the same.

Ellen M. Velie et al (Ellen M. Velie et al 1999) investigated the association between maternal preconceptional supplemental and dietary zinc intake and risk of neural tube defects in a population-based case control study conducted between 1989 and 1991 in California. Cases were 430 fetuses/infants affected with neural tube defects and controls were 429 randomly selected non-malformed infants. Mothers of these selected babies were given a 98-item food frequency questionnaire which included history of intake of vitamins, minerals and any food supplements. It was noted that a higher preconceptional zinc intake was associated with a reduced risk for neural tube defects. Phytate intake, a constituent of diet known to impede zinc absorption, appeared to modify the zinc-neural tube defects association.
In addition, increased servings of animal products, the more bioavailable food source of zinc, was associated with reduced risk of neural tube defects. Risk estimates for zinc intake changed little after controlling for multiple socio-demographic factors and total folate intake, but were attenuated after controlling for intake of nutrients with a higher dietary content of zinc such as protein. The analysis indicated that risk of neural tube defects in infants and fetuses decreased with increasing maternal preconceptional zinc intake.

MRC vitamin study research group (MRC vitamin study research group 199157) showed in their randomized control trial that increased consumption of supplemental synthetic folic acid will prevent approximately 375,000 of neural tube birth defects each year.

Persad V. L (Persad V. L 200268) conducted a retrospective study to evaluate the reduction in incidence of neural tube defects after the introduction of folic acid fortification of food grains (in 1998) in Nova Scotia in Canada. He obtained the total number of births and the number of lives and stillbirths with open neural tube defects in Nova Scotia from January 1, 1991 to 1994 (before supplementation of folic acid), from 1995-1997 (after introduction of program of supplementation with folic acid) and from 1998 to 2000 (after folic acid fortification of food grains). The incidence of occurrence of neural tube defects during these three time periods was 2.55/1000, 2.58/1000 and 1.17/1000 respectively. He found a 50% reduction in the annual incidence of open neural tube defects after folic acid fortification of food grains.

Laura Martnex de Villarreal et al (Laura Martnex de Villarreal et al 200246) conducted a study in Nuevo Leon, Mexico from 1999
to 2001. In August 1999, a neural tube defect prevention program was initiated with the free distribution of bottles containing 5.0 mg tablets of folic acid to 250,000 low-income women of childbearing age. Physicians from the state secretary of health prescribed folic acid and recommended the intake of one tablet of 5.0mg folic acid per week. All women were encouraged to take folic acid permanently. Public awareness campaign and education programs for health professionals and volunteers were also implemented. People were informed through mass communication, media, brochures, subway tickets and posters placed in public areas. At nine months after program initiation, 44% of women were aware of the benefits of folic acid. Health professionals informed 73% of these women and volunteers informed 16%.

Authors compared the cases and rates of neural tube defects from 1999 to 2001. Cases were obtained from hospitals and obstetric and gynecology clinics by immediate notification, death certificates or fetal death registers. Only isolated cases of neural tube defects were included. They found a significant reduction in the rate of occurrence of neural tube defects from 1.04/1000 in 1999 to 0.58/1000 in 2001. Anencephaly and spinabifida rates decreased from 0.55/1000 to 0.29/1000 and 0.49/1000 to 0.22/1000, respectively from 1999 to 2001. Decrease in female cases was higher than male cases for both phenotypes. Authors concluded that there was a 50% decrease in the incidence of anencephaly and spinabifida with significant reduction of infant mortality and disability. These results encourage proposing the use of a single tablet of 5.0 mg of folic acid per week as an alternate supplement to tablets taken on a daily basis.

In 1992, the United States public health service recommended that all women of childbearing age consume 400 μg of folic acid
daily. The food and drug administration authorized the addition of synthetic folic acid to grain products in March 1996 with mandatory compliance by January 1998. The impact of these public health policies on the prevalence of neural tube defects needed to be evaluated (Centre for disease control and prevention 199214). Therefore, Laura J. Williams et al (Laura J. Williams et al 20C245) decided to determine the prevalence of spina bifida and anencephaly during this transition to mandatory folic acid fortification. Authors used twenty four population-based surveillance systems to identify 5,630 cases of spina bifida and anencephaly from 1995-1999. Cases were divided into three temporal categories depending on whether neural tube development occurred before folic acid fortification (Jan 1995 to Dec. 1996), during the optional period (Jan 1997 to Sept 1998) or after the mandatory fortification (Oct. 1998 to Dec. 1999). Prevalence for each defect was calculated for each time period. Data was also stratified that did and did not ascertain prenatally diagnosed cases. Prevalence of spina bifida was decreased by 31% from pre to the mandatory fortification and the prevalence for anencephaly decreased by 16%. They concluded that decline in the prevalence of spina bifida was temporally associated with folic acid fortification of US grain supplies. But temporal association between fortification and the prevalence of anencephaly was unclear.

H.E.K.de Walle et al (H.E.K.de Walle and L.TW de Jong-Van de Berg 200225) did four awareness studies in Northern Netherlands from 1995 to 1998 after the implementation of advice of Dutch inspectorate of public health to all women planning a pregnancy to take 0.5 mg folic acid daily from 4 weeks before conception and upto 8 weeks thereafter. In their cross sectional study, pregnant women filled out a questionnaire. Out of 461 pregnant women 77% had heard about folic acid before being pregnant, 63%
knew about its protective effect on neural tube defects and 33% knew about the entire advised period for folic acid supplementation. 61% had used folic acid in some part of the advised period and 35% used it in the entire advised period. Higher educated women knew more about folic acid and used it significantly more often in the periconceptional period than lower educated women. They concluded that compliance to proper use of folic acid was poor and food fortification in the Netherlands must be seriously considered. The fortification of specific products instead of staple foods was however a missed chance to reduce neural tube defects and possibly other birth defects like cardiovascular defects.

Godfrey P. Oakley (Godfrey P. Oakley 200223) summarized in his article the different randomized clinical trials of folic acid fortification and the need for active, universal implementation of folic acid fortification of food grains. He concluded that there is proof that folic acid fortification will prevent a large proportion of spinabifida and anencephaly and folate deficiency anaemia. There is also strong evidence indicating that folic acid fortification may prevent cardiovascular disease including strokes. There is less but interesting evidence that folic acid may also prevent colon cancer. The UK committee of medical aspects of food and nutrition policy (COMA) reviewed the evidence and recommended that flour in UK be fortified with folic acid in the quantity of 2.4 parts/1,000,000. Fortification of wheat flour with 240 μg of folic acid/100 gm of flour (2.4 ppm) should be implemented as quickly as possible in UK and across Europe and rest of the world to prevent CNS birth defects and folate deficiency anaemia.

Mathias B. Forrester, Ruth D. Merz (Mathias B. Forrester, Ruth D. Merz 200052) conducted a study on data collected from Hawaii
CONGENITAL CENTRAL NERVOUS SYSTEM MALFORMATIONS - A PROSPECTIVE STUDY

birth defect program, a population based surveillance system for birth defects in the entire state of Hawaii. 245 pregnancies affected with neural tube defects were identified between 1986-1997 in Hawaii. These included 36% anencephaly, 45% spina bifida and 18% encephalocele. Total prevalence of neural tube defects was seen as 0.995/1000 births (live births plus fetal deaths). Anencephaly was 0.362/1000, spina bifida was 0.451/1000 and encephalocele 1.183/1000.

Ultrasound at any time during pregnancy was reported in 90% of total cases while 96% of pregnant women who had anencephaly, 85% with spina bifida and 93% with encephalocele gave history of ultrasound. Thus 74% of the total cases were diagnosed prenatally and 65% of these cases were electively terminated. Cases of anencephaly were most likely to be prenatally diagnosed and to be terminated. Spina bifida was least likely to be prenatally diagnosed and to be terminated. Half of the women with pregnancies affected with neural tube defects reported to have had maternal serum α fetoprotein screen performed. In the majority of these, maternal serum α fetoprotein levels were elevated. Prenatal diagnosis of a neural tube defect was made 93% of the time in the presence of an elevated maternal serum α fetoprotein screen. This suggests that maternal serum α fetoprotein screen was useful in Hawaii for evaluating the risk for neural tube defects.

James Walters et al (James Walters et al 199731) looked into all the aspects of anencephalic fetuses as organ donors. They presented a review of the neurological aspects, ethical aspects and the role of law in America with respect to anencephaly as an organ donor. They concluded that in 1995 the American Medical association ethics council issued an opinion calling for direct procurement of organs from anencephalic newborns, making them an exception to the "dead donor" rules. Present
studies convincingly demonstrate that the brain stems of these infants are almost completely devoid of any evidence of even primitive functional organization. New studies also indicate that cerebral absence causes unusual behaviors such as stiffening and hyperirritability that can be detected prenatally. There are two schools of thought on the permissibility of using anencephalic newborns as organ sources: physicalism and personalism. Physicalism holds that all human beings are equally precious and that no exceptions can be made regarding organ procurement not even cases of anencephaly. Personalism sees the moral worth related to one’s potential and actual mental capacities and because of anencephalic newborn’s uniqueness, believes that considerable liberties can be taken here. Most bio-ethicists are themselves in the personalist camp; many have questioned any changes in the existing law issued by the American Medical Association Council, because of the social impact of that change.

The successful transplant in 1987 of a heart obtained from baby Gabriel (anencephaly) into a Canadian Baby named Paul at Loma Linda, California provoked both interest and controversy in the possibility that infants born with anencephaly might act as organ donors.

Bioethics committee, Canadian Pediatric society (Bioethics committee, Canadian Pediatric society 1990, 2000) published the following recommendations for organ donation from anencephaly newborns.

Recommendations

➤ Any program involving organ donation from anencephalic infants should be reviewed by the institution’s research ethic committee and if present, its clinical ethic committee. In addition, we strongly encourage external review of such protocols, especially if the institution has no research...
or clinical ethic committee.

➢ The families of donors and recipients must be made aware of the investigative nature of these programs and of the likelihood that the number of babies with anencephaly who become successful donors will be very small.

➢ The short term and long-term outcomes of transplantation programs involving newborns should be evaluated with regard to the effects on the donors, the recipients and their respective families.

➢ After brain death has been declared, the use of extraordinary supportive measures such as mechanical ventilation and total intravenous feeding to prolong organ viability should be limited to a finite period (to be defined by each centre).

➢ There should be no modification of the criteria for establishing whole-brain death. The absence of forebrain should not be considered equivalent to whole-brain death. The definition of brain death should not be specific to or specifically modified for any group of patients, including anencephalic infants.

➢ The provision of aggressive life support in the anticipation of brain death should be managed in separate units by separate professional teams.

➢ Basic research and animal studies are needed to determine and prevent the effects of hypoxia and ischemia on the viability and functioning of organs before and after transplantation.

However, the bioethics committee strongly opposed the proposal to allow the removal of organs before the anencephalic infant reaches a stage equivalent to conventional brain death.
Parisi F et al (Parisi F et al 1999) transplanted a heart on the first day of life, with a graft harvested from an anencephalic donor, at Bombino Gesu hospital (Rome). The transplant was performed 9 hours after birth. The recipient died of necrotizing enterocolitis on the 10th postoperative day. Despite failure, this case supports the concept that heart from anencephalic donors can work normally and indicates that heart transplantation on the first day of life may have a favourable outcome if postoperative maintenance of multi-organ balance and function in successful.

A.M. Vare and P.C. Bansal (A.M. Vare and P.C. Bansal 1971) conducted an anatomical study on 41 anencephaly fetuses collected over a period of 6 years (February 1963 to December 1969) from medical college, Aurangabad. Total 13814 deliveries were screened during this period. They observed the incidence of anencephaly as 3/1000 deliveries. The incidence of anencephaly was highest in babies born to mothers in the age group of 20 - 30 years. 50% of anencephaly were born to primi, second and 3rd gravida. Frequency of abortions was noted as 30 %. Male:female ratio was 1:1.5, number of female anencephaly babies were higher. They observed that anencephalic babies were common in summer conceptions. Associated anomalies observed by the authors were spina bifida, spinal rachischisis, hare lip, umbilical hernia, diaphragmatic hernia, hydronephrosis, hydroureters, enlargement of liver and unicorneate uterus.

Authors observed the following defects in different systems:

**CNS**-Complete absence of cerebral hemispheres was noted in 19 anencephaly. In 22 anencephaly, cerebral hemispheres were rudimentary in size. 2 cerebral hemispheres could not be identified separately. Cerebellum was absent in 35 anencephaly and rudimentary in 6. Where the cerebrum was found to be rudimentary, cerebellum was absent. Brain stem was absent in
31 and rudimentary in 10 cases. 13 anencephaly had associated with spina bifida also. This was present either in the cervical or lumbar region. In 6 cases spina bifida was present throughout the vertebral column. In 6 anencephaly fetuses, neural tube was open throughout the length (spinal rachischiasis).

**Neck** - Neck was absent in 18 cases and short in 19 cases. In 4 anencephaly neck was found to be normal.

**Endocrine glands** - Pituitary gland was missing in 21 and hypoplastic in 10 fetuses. Thyroid gland was found to be normal in 20 anencephaly, hypoplastic in 12 and absent in 9. Supra renal glands were abnormally small in 39 and absent in 2 cases.

**Thymus** - Thymus gland showed hyperplasia in 29 fetuses.

**Face** - 1 had hare lip, 2 had both hare lip and cleft palate.

**Abdominal wall** - 3 had umbilical hernia and 2 had diaphragmatic hernia.

**Limb deformities** - 2 fetuses had talipes equino-varus of right foot, 3 had syndactyly of left hand and 1 had polydactyly of right hand.

**Genitourinary system** - A total of 11 genitourinary anomalies were seen. 3 had hydronephrosis, 1 hypoplasia of kidney, 2 unascended kidneys, 2 hydroureter and 3 cases showed hydronephrosis. Unicornuate uterus was found in 2 cases.

**Cardiovascular system** - Dextrocardia, patent interventricular foramen and coarctation of aorta were seen in 3 different cases.

**GIT** - Malrotation of gut, abnormal position of appendix and enlargement of liver were seen.

P.S. Michaelson et al (P.S. Michaelson et al 1972) performed a histological study in 11 cases of trisomy 17-18 for the associated CNS anomalies. They observed abnormalities at various sites namely isocortical gyral pattern, hippocampus, lateral geniculate body and inferior olivary nucleus.
S.Ry Andersen et al (S.Ry Andersen et al 1967) conducted a systematic study on 40 eyes of 21 anencephaly infants. They also studied the skull and brain tissue of the same. On examination of the brain, authors observed free brain tissue exposed to amniotic fluid. It consisted of humpy, dark red tissue masses resembling an angioma, covering the flattened base of the skulls. The microscopic appearance was also reminiscent of an angioma with venous vessels of varying caliber interposed with connective tissue and islets of neurogenic tissue comprising mainly of astroglia and cavities lined with ependyma. Rarely, degenerated nerve cells and fragments of myelin were also seen. The surface was lined with epidermis. The underlying connective tissue was devoid of a cutaneous structure or any division into corium, subcutis and meninges. It merged directly into the angioma like tissue underneath. It was not possible either macro or microscopically to recognize the optic nerve with certainty.

In cases without rachischisis, the spinal cord was often well preserved with normal looking anterior horn cells and some degree of myelination which corresponded roughly to the gestational age. No gross abnormalities were noticed in the eyes. Optic disc was small, pale and often wholly or partially covered with retinal folds on gross examination. In some cases it was impossible to locate optic disc macroscopically. Retina showed distinct layer of rods and cones with normal inner nuclear layer. Nerve fiber layer was hypoplastic. In 14 cases there was coloboma of optic disc. Majority of coloboma were very small and could be demonstrated on serial sections. No uveal coloboma was seen and cornea was unremarkable. Sclera was normal and no visible cataract was seen.

Ashwal S et al (Ashwal S et al 1990) conducted a neuropathological study on 12 anencephaly and revealed the
malformed in 1. Persistent pupillary membrane was present in 10 globes and 1 globe had malformed iris and ciliary body. Three globes showed cataractous lens. All globes showed severe atrophy of retinal ganglion cells and nerve fiber layer.

Elizabeth S. Gray et al (Elizabeth S. Gray et al 198020) conducted a study on adrenal glands of 12 anencephaly fetuses of gestational age less than 21 weeks. They observed that the size of the anencephaly adrenal glands was smaller than the control group. They noticed the early involution of fetal cortex in them as compared to the normal fetuses. Authors observed different cell types in the adrenal glands of anencephaly fetuses constituting fetal zone, definitive zone and intermediate zone. Neuroblasts were also recorded. They concluded that involution of fetal zone of adrenal glands of anencephaly fetuses starts at 16th week and is marked at 19th week of gestation while in the normal fetuses of 15 to 21 weeks gestation there is an increase of volume of fetal zone.

Dragana Pilavdzic et al (Dragana Pilavdzic, Kalman Kovacs, Sylvia L. Asa 199718) examined the pituitaries of 10 anencephalic fetuses at various stages of gestation using formalin fixed paraffin embedded tissue. They concluded that all pituitary cell types differentiate in anencephaly and are present by the 17th week of gestation. Hypothalamic factors appear to be essential for the maintenance of corticotropes and gonadotropes during development.

DEVELOPMENT OF NERVOUS SYSTEM (T. W. Sadler 199578, William J. Larsen 199783)
Development in 4th week of intrauterine life
- The first event in the formation of the future central nervous system is the appearance of a thickened neural
neuroepithelium and the adjacent surface ectoderm is pulled dorsally. The opposing margins of surface ectoderm also meet and fuse. As soon as the surface ectoderm fuses, the neural tube separates from it and sinks into the posterior body wall.

- The lips of the neural folds first make contact on day 22 in the area of the first five somites. The newly formed neural canal communicates with the amniotic cavity at either end through two large openings called the cranial and caudal neuropores. The neural folds may initially fuse at several separate points in the occipital region. The small intervening openings rapidly fill in to produce a continuous canal. As neurulation continues, the cranial and caudal neuropores close on day 26. Closure of the cranial neuropore is actually bidirectional and final closure occurs in the area of the future forebrain. Closure of the caudal neuropore is strictly craniocaudal and finishes at the level of second sacral segment.

- The caudal most portion of the neural tube is formed by secondary neurulation of the caudal eminence. Gastrulation through the regressing primitive streak produces the mesodermal caudal eminence by day 20. The caudal eminence gives rise to caudal neural tube and to the caudal entrance of spinal cord and coverings. The formation of caudal end of the neural tube is completed by about 8 weeks of development. Caudal eminence also produces the somites of the most inferior levels of the embryo.

- Cytodifferentiation of neural tube commences in the rhombencephalic region just after the occipitocervical neural folds fuse and proceeds cranially and caudally as the tube zippers up. Precursors of most of the cell types of the future central nervous system, the neurons, some
types of glial cells and ependymal cells that line the central canal of the spinal cord and the cerebral ventricles of the brain are produced by proliferation in the layers of neuroepithelial cells that immediately surround the neural canal. This layer is called the ventricular layer of differentiating neural tube. The first wave of cells produced in the ventricular layer consists of neuroblasts which will give rise to the neurons of the central nervous system. These neuroblasts migrate peripherally to establish a second layer, the mantle layer, external to the ventricular layer. This neuron containing layer develops into the gray matter of the CNS. The neuronal processes that sprout from the mantle layer neurons grow peripherally to establish a third layer, the marginal layer. This layer does not contain any neuronal cell bodies and it later becomes the white matter of CNS.

- As soon as the neuroepithelial layer lining the neural canal ceases to produce neuroblasts, it begins to produce a new cell type, the glioblasts. These cells differentiate into a variety of glial cells. Neuroepithelium also differentiates to produce ependymal cells that line the cerebral ventricles and central canal of spinal cord.

Development of Dorsal and ventral columns of spinal cord
Starting at the end of fourth week, the neuroblasts in the mantle layer of spinal cord become organized into four columns that run the length of the cord: a pair of dorsal or alar columns and a pair of ventral or basal columns. Laterally, the alar and basal columns are separated by a groove called the sulcus limitans. Dorsally and ventrally they are separated by acute thinnings of the neural tissue called, respectively, the roof plate and the floor plate. The cells of the ventral columns become the somatic motor neurons of the spinal cord and
innervate somatic motor structures such as the voluntary (striated) muscles of the body wall and extremities. The cells of the dorsal columns develop into association neurons, which will interconnect the motor neurons of the ventral columns with neuronal processes that soon grow into the cord from the sensory neurons of the dorsal root ganglia. In most regions of the cord, all 12 thoracic levels, at lumbar levels L1 through L2 and at sacral levels S2 through S4 - the neuroblasts in the more dorsal regions of the basal columns segregate to form distinct intermediolateral cell columns. The thoracic and lumbar intermediolateral cell columns contain autonomic motor neurons of the sympathetic system while the intermediolateral cell columns in the sacral region contain central autonomic motor neurons of the parasympathetic system. In general, at any given level of the brain or spinal cord the motor neurons form before the sensory elements appear.

Development of the brain and cranial nerves—summary
Even before neurulation begins, the primordial of the three primary brain vesicles - the prosencephalon, mesencephalon, and rhombencephalon - are visible as broadenings in the neural plate. During the fifth week, the prosencephalon subdivides into telencephalon and diencephalon and the rhombencephalon subdivides into metencephalon and myelencephalon. Thus, along with the mesencephalon, this creates five secondary brain vesicles. During this period the brain is also transiently divided into smaller segments called neuromeres. The primordial brain undergoes flexion at three points. The forebrain folds back under the rest of the brain at the mesencephalic (cranial) flexure. Ventral folding occurs at a cervical flexure between the myelencephalon and the spinal cord. Reverse or dorsal bending at the pontine flexure in the region of the future pons folds the metencephalon back against
Cytodifferentiation of the neural tube begins in the rhombencephalon at the end of the fourth week. The neural tube neuroepithelium proliferates to produce in succession, the neuroblasts, glioblasts, and ependyma of the central nervous system. The neuroblast migrate peripherally to establish a mantle zone, the precursor of the gray matter. In the regions of spinal cord and brain stem, the mantle zone immediately overlies the ventricular zone of proliferating neuroepithelium, and the growing neuronal fibers establish a marginal zone (the future white matter) peripheral to the mantle zone. In the higher centres of the brain, including the cerebellum and cerebral hemispheres, the pattern of cytodifferentiation is more complex.

The mantle zone of the brainstem, like that of the spinal cord, is organized into a pair of ventral (basal) columns (or plates) and a pair of dorsal (alar) columns (or plates). Laterally the two columns are separated by a groove called the sulcus limitans; dorsally and ventrally they are separated by thinnings of the neural tissue called respectively, the roof plate and the floor plate.

The nuclei of the 3rd to the 12th cranial nerves are located in the brain stem. Some of these cranial nerves are motor, some are sensory while some are mixed and therefore, some of them arise from more than one nucleus. The cranial nerve motor nuclei develop from the brain stem basal plates and the associational nuclei develop from the brain stem alar plates. The brain stem cranial nerve nuclei are organized into seven columns which correspond to the types of function they subserve. From ventromedial to dorsolateral, the three basal columns contain somatic efferent, branchial efferent and visceral efferent motor neurons and the four alar columns contain visceral afferent, special visceral afferent (subserving the special
most prominent function of which is to control visceral activities such as heart rate and pituitary secretion. Dorsal to the hypothalamic sulcus, the large thalamic swelling gives rise to the thalamus which serves as a relay center, processing information from subcortical structures before passing it to the cerebral cortex. Finally, a dorsal swelling, the epithalamus, gives rise to a few diminutive structures, including the pineal gland.

A ventral outpouching of the diencephalic floor plate, called the infundibulum, differentiates to form the posterior pituitary. A matching diverticulum from the stomodeal roof, called Rathke's pouch, grows to meet the infundibulum and becomes the anterior pituitary. Diencephalic outpouchings also form the eyes. The two cerebral hemispheres arise as lateral outpouchings of the telencephalon and grow rapidly to cover the diencephalons and mesencephalon. The hemispheres are joined by the cranial lamina terminalis (representing the zone of closure of the cranial neuropore) and by fiber tracts called commissures, particularly the massive corpus callosum. The layered cellular architecture of the cerebral cortex arises by a complex mechanism. The olfactory bulbs and olfactory tracts arise from the cranial telencephalon and synapse with the primary olfactory neurosensory cells which differentiate in the nasal placodes.

The expanded primitive ventricles formed by the neural canal in the secondary brain vesicles give rise to the ventricular system of the brain. The cerebrospinal fluid that fills the ventricle system is produced mainly by choroid plexuses in the lateral, third and fourth ventricles which are formed by the ependyma and the overlying vascular pia. The third ventricle also contains specialized ependymal secretory structures called circumventricular organs.
- Abnormalities of neural tube closure not only affects the development of the CNS but also interferes with the vertebral arch morphogenesis.

- Neural tube defects originate generally in the 3rd week of development. A failure of part of neural tube to close (called dysraphie zone) disrupts both the differentiation of the central nervous system and the induction of the vertebral arches and can result in a number of developmental anomalies. These anomalies generally involve part of the cranial or caudal neuropores, resulting in a defect of the cranial or lower lumbar and sacral regions of the CNS respectively. Failure of the neural tube to close disrupts the induction of the overlying vertebral arches, so that the arches remain underdeveloped and fail to fuse along the dorsal midline to enclose the vertebral canal. The resulting open vertebral canal leads to the condition called spina bifida. In some cases of spina bifida the contents of the vertebral canal bulge into a membranous sac (cele) that is continuous with the surrounding skin. The fact that spina bifida is quite common in the lower lumbar and upper sacral region suggests that neuropore closure or secondary neurulation may be involved in the etiology of these malformations. Approximately 2,500 infants with these defects are born each year in United States. Additional fetuses affected with these malformations are aborted. Approximately 400,000 infants with spina bifida are born worldwide each year.

Spina bifida and related defects of cranial neuropore closure result in a range of malformations

The clinical consequences of defects in neural tube closure range from mild to fatal. In its mildest form it presents as
neural tube, a defect results in which the brain is represented by an exposed dorsal mass of undifferentiated neural tissue. This condition is called exencephaly, anencephaly or craniorachischisis. Anencephalic embryos often survive till late fetal life or to term but invariably die within a few hours or days of birth. The analogous defect of spinal cord development, rachischisis or myelochisis, is not always fatal but presents very difficult clinical problems. Failure of the neural tube to properly differentiate and close in the occipital and upper spinal regions is called an inionschisis.

Herniation of the brain may also occur in an unrelated spectrum of anomalies

In a class of anomalies not related to failure of neural tube closure, differentiated brain and meninges may bulge from an unossified gap in the skull. This malformation is called a meningoencephalocoele. If the ventricular cistern as well as the brain and meninges protrude from the skull, the condition is called a meningohydroencephalocele.

The cause of neural tube defects are variable and possibly multifactorial

Neural tube defects (NTDs) have no single genetic or teratogenic cause. The karyotype usually appears normal although some animal mutants expressing similar defects exhibit chromosomal anomalies.

A genetic basis for some NTDs in humans is postulated based on evidence that the frequency of meningomyelocele appears to be greater in siblings of affected individuals, although familial cases of NTDs may represent only about 3% of the total. However, the frequency of NTDs is higher in some populations and racial groups than in others. For example the frequency of
NTDs is approximately 0.1% in the United States as a whole, but it is 0.0335% among African-Americans. In contrast, the frequency of NTDs in some parts of India and in Ireland is of the order of 1.1%. Moreover, a rare condition called Meckel’s syndrome, which is inherited as an autosomal recessive condition, may also present with craniorachischisis while the autosomal dominant disorder called brachydactyly syndrome may be characterized by presence of exencephaly. In addition, an autosomal dominant spectrum of malformations called Waardenburg syndrome sometimes includes spina bifida. It is characterized by mutations of the PAX3 gene, which also appears to be the basis for NTDs in splotch mouse mutants.

Teratogens that induce NTDs in animals and humans have also been identified, opening the possibility that some human NTDs may be caused by environmental toxins or nutritional factors. For example, studies on experimental animals have implicated retincic acid, insulin, high plasma glucose levels and trypan blue in development of NTDs. Factors implicated in the induction of NTDs in humans include the use of antiepileptic drug valproic acid, maternal diabetes and hyperthermia. It has been suggested that valproic acid may interfere with folate metabolism. A substantial body of evidence now shows that administration of 0.4 mg of folic acid per day during pregnancy significantly reduces the risk of spina bifida and anencephaly, even in the babies of mothers who have previously given birth to infants suffering from NTDs.

DEVELOPMENT OF THE EYES (William J. Larsen 1997*3)

The eyes first appear in the early fourth week in the form of a pair of lateral grooves, the optic sulci, which evaginate from the forebrain neural folds and grow toward the surface ectoderm to form the optic vesicles. As soon as the expanded
tip of the optic vesicle reaches the surface ectoderm, its
distal face (called the retinal disc) invaginates transforming
the optic vesicle into a goblet shaped optic cup that is
attached to the forebrain by a narrower, hollow optic stalk.
The adjacent surface ectoderm simultaneously thickens to form
a lens placode, which invaginates and pinches off to become a
hollow lens vesicle that sits in the optic cup.
The lens vesicle gives rise to the solid lens of the eye.
Posterior cells of the lens vesicle form long slender
anteroposteriorly oriented primary lens fibers. Anterior cells
of the lens give rise to a simple epithelium covering the face
of the lens. This epithelium gives rise to the secondary lens
fibers, which make up most of the bulk of the mature lens.
Blood is supplied to the developing lens and retina by a
terminal branch of the ophthalmic artery called the hyaloid
artery. The artery gains access to the interior of the optic
globe via a groove called the choroidal fissure on the ventral
surface of the optic stalk. The portion of the artery that
traverses the vitreous body to reach the lens degenerates
during fetal life. As the lens matures the remainder of the
artery becomes the central artery of the retina.
The inner wall of the optic cup (the former optic disc) gives
rise to the neural retina whereas the outer wall gives rise to
the thin, melanin-containing pigment retina. Although the
intraretinal space separating these two layers is obliterated
as the retina develops, the two layers never fuse firmly. The
differentiation of the neural retina takes place between the
sixth week and the eighth month. Waves of cells are produced by
the outer proliferative layer next to the intraretinal space.
These cells migrate inwards to form the cell layers of the
mature retina. Axons from the neural retina grow through the
optic stalk to the brain, converting the optic stalk to the
optic nerve.
As the optic vesicle forms, it is enveloped by a sheath of mesenchyme that is derived in part from neural crest. This sheath differentiates to form the two coverings of the optic globe; the thin inner choroid and the fibrous outer sclera. This mesenchyme also grows to cover the anterior surface of the developing eye, including the lens. The mesenchyme overlying the developing lens splits into two layers which encloses a new space called the anterior chamber. The external wall of the anterior chamber is continuous with the sclera of the optic globe while the internal wall is continuous with the choroid of the optic globe. The external wall of the anterior chamber gives rise to the inner layers of the cornea whereas, the outer layer of the cornea is derived from the overlying surface ectoderm. The inner wall of the anterior chamber, overlying the lens, is called the pupillary membrane. Deep layers of this wall undergo vacuolization to create a new space, the posterior chamber, between the lens and the remaining thin pupillary membrane. Early in fetal life, the pupillary membrane breaks down completely to form the pupil.

The rim of the optic cup along with the overlying choroid differentiates to form the iris and the ciliary body. Mesoderm adjacent to the optic globe differentiates in the fifth and sixth week to form the extrinsic ocular muscles. The origin of this mesoderm is unclear; it is derived either from the paraxial mesoderm or from the prechordal plate. The connective tissue components of the extrinsic ocular muscles are derived from neural crest.

The eyelids arise as folds of surface ectoderm. The two eyelids remain fused from the eighth week to about the fifth month of gestation.
### Criteria for estimating gestational age during fetal period

**(Moore L. Keith 1993)**

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<thead>
<tr>
<th>Age (weeks)</th>
<th>CR Length (mm)</th>
<th>Foot Length (mm)</th>
<th>Fetal weight (gm)</th>
<th>Main external characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preivable fetuses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>7</td>
<td>8</td>
<td>Eyes closing or closed. Head large and more rounded. External genitalia still not distinguishable as male or female. Intestines in proximal part of umbilical cord. Ears low set.</td>
</tr>
<tr>
<td>12</td>
<td>87</td>
<td>14</td>
<td>45</td>
<td>Sex distinguishable externally, well-defined neck.</td>
</tr>
<tr>
<td>14</td>
<td>120</td>
<td>20</td>
<td>110</td>
<td>Head erect. Eyes face anteriorly. Ears are close to their definitive position. Lower limbs well-developed. Early toenail development.</td>
</tr>
<tr>
<td>16</td>
<td>140</td>
<td>27</td>
<td>200</td>
<td>External ears stand out from head.</td>
</tr>
<tr>
<td>18</td>
<td>160</td>
<td>33</td>
<td>320</td>
<td>Vernix caseosa covers skin. Quickening (signs of life) felt by mother.</td>
</tr>
<tr>
<td>20</td>
<td>190</td>
<td>39</td>
<td>460</td>
<td>Head and body hair (lanugo) visible.</td>
</tr>
<tr>
<td>Viable fetuses</td>
<td>22</td>
<td>210</td>
<td>45</td>
<td>630</td>
</tr>
<tr>
<td>----------------</td>
<td>----</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>24</td>
<td>230</td>
<td>50</td>
<td>820</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>250</td>
<td>55</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>270</td>
<td>59</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>280</td>
<td>63</td>
<td>1700</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>300</td>
<td>68</td>
<td>2100</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>360</td>
<td>83</td>
<td>3400</td>
<td></td>
</tr>
</tbody>
</table>

As per T.W.Sadler (T.W.Sadler 1995) fetal age can be estimated with the help of following features:

3rd month
- Eyes located on ventral aspect of the face
- Lower limbs little shorter and less developed than upper extremity
- Primary ossification centers are present in long bones and skull by 12th week
CONGENITAL CENTRAL NERVOUS SYSTEM MALFORMATIONS - A PROSPECTIVE STUDY

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4th &amp; 5th month</strong></td>
<td>• Lanugo hair present</td>
</tr>
<tr>
<td></td>
<td>• Eye brows and head hair visible</td>
</tr>
<tr>
<td><strong>6th month</strong></td>
<td>• Skin of fetus reddish and wrinkled</td>
</tr>
</tbody>
</table>

Socio-economic class


For January 2003, CPI was 320, Child is also taken as one capita

<table>
<thead>
<tr>
<th>Class</th>
<th>Rs./ Capita</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 1577</td>
</tr>
<tr>
<td>II</td>
<td>788-1576</td>
</tr>
<tr>
<td>III</td>
<td>473-787</td>
</tr>
<tr>
<td>IV</td>
<td>236-472</td>
</tr>
<tr>
<td>V</td>
<td>&lt; 236</td>
</tr>
</tbody>
</table>

Population of Anand, Ahmedabad and Panchmahal (Godhara) districts—(Census of India 2001<sup>13</sup>)

Anand district - 18,56,712
Ahmedabad district - 58,08,378
Panchmahal district - 20,24,883

K. Park (K. Park 2002<sup>13</sup>) has described the following in his text book:

INFANT MORTALITY RATES (IMR) - per 1000 births

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>National goal</td>
<td>60/1000 (2000)</td>
</tr>
<tr>
<td>India</td>
<td>68/1000</td>
</tr>
<tr>
<td>Gujarat</td>
<td>64/1000</td>
</tr>
<tr>
<td>Kerala</td>
<td>16/1000</td>
</tr>
<tr>
<td>Orissa</td>
<td>16/1000</td>
</tr>
</tbody>
</table>
Causes of IMR (INFANT MORTALITY RATE)

0-4 weeks of age - Neonatal mortality
- Low birth weight
- Birth injury and difficult labour
- Congenital anomalies
- Haemolytic disease of newborn
- Conditions of placenta and cord

1-12 months of age - Post neonatal mortality
- Diarrheal disease
- ARI
- Malnutrition

PERINATAL MORTALITY: It is defined as death from 28 weeks gestation to 7 days after birth (LATE FETAL DEATH, EARLY NEONATAL DEATH)

Current perinatal mortality rate is 42/1000 live births
- Rural is 43.3/1000
- Urban is 38.7/1000

Causes of perinatal mortality
- Prematurity
- Intrauterine and birth asphyxia
- Congenital anomalies (3rd most common cause of PMR)
- Low birth weight
- Birth trauma
- Intrauterine infection

Congenital malformations: Are defined as structural defects
Congenital anomaly: Are defined as biochemical, structural and functional disorders

Globally, the occurrence of congenital anomalies is estimated as 30-70/1000 live births

Congenital heart defects 6-8/1000 live births
CONGENITAL CENTRAL NERVOUS SYSTEM MALFORMATIONS - A PROSPECTIVE STUDY

Cleft lip/palate 0.5-2/1000 live births  
Spina bifida 0.5-4/1000 live births  
Anencephaly 0.5-4/1000 live births  
Others 10-12/1000 live births  
Congenital malformations in India - 17 to 30/1000 live births

In India 2.5% of newborns have birth defects and congenital malformations are the 3rd most common cause of perinatal mortality. In India (north) spina bifida is the most common neural tube defect. Rate of neural tube defects (congenital CNS malformations) in India as follows:

- Punjab 1 in 116 births  
- Rajasthan 1 in 145 births  
- Delhi 1 in 212 births  
- TN 1 in 330 births  
- Mumbai 1 in 450 births

No data is available for Gujarat

Guidelines for drinking water quality, WHO Geneva 1999, (Guidelines for drinking water quality 199924)

- Sodium
  - Most water supplies contain <20 mg/liter

- Zinc
  - Concentration is usually below 10 μg/liter (surface water)  
  - 10-40 μg/liter (ground water) (Zinc concentration may be high in tap water due to leaking of zinc from piping and fittings).

- Manganese
  - In lakes and rivers around world 0.001-0.6 mg/liter
In USA, public drinking water surveys shows mean manganese levels ranging from 0.004 to 0.03 mg / liter

In Germany, drinking water supplied to 90% of households contains <0.02 mg of manganese per liter.

- Iron

In rivers median iron concentration is 0.7 mg/liter

In sea water, it is 2700 mg/liter

In drinking water it is less than 0.3mg/liter

Sulphate

- Rain water contains 1.0-3.0mg/litre

- Sea water contains 2700mg/litre

- Fresh water contains 20mg/litre

Calcium 100mg/litre

Magnesium 10mg/litre

Health related chemical constituents

Inorganic

- Arsenic (From industrial effluents) Guideline 0.01 mg/liter

- Cadmium (From fertilizers, accumulated in Kidney) 0.003 μg/liter

- Chromium 0.05 mg/liter

- Cyanide (From industrial waste water affects Thyroid & CNS) 0.07 mg/liter
CONGENITAL CENTRAL NERVOUS SYSTEM MALFORMATIONS - A PROSPECTIVE STUDY

- **Fluoride**
  1.5 mg/liter
  Present in phosphate fertilizers (4%)
  Fish and tea (high exposure)
  Indoor air pollution
  Natural water: Raw < 1.5 mg/liter
  Groundwater 10 mg/liter
  High fluoride levels (> 5 mg/litre) are seen in China, India, Thailand. It leads to dental or skeletal fluorosis.

- **Lead** (from lead pipe)
  0.01 mg/liter
  - Placental transfer of lead in human (12 week of gestation)
  - Interferes with calcium metabolism both directly and indirectly
  - Toxic to CNS & PNS (subencephalopathic neurological, behavioral)
  - Associated with renal tumors

- **Mercury**
  0.001 mg/liter
  Affects mainly Kidney and CNS

- **Nitrate & nitrite**
  Nitrate 50 mg/liter,
  Nitrite 3 mg/liter
  (vegetables are main source)

- **Selenium**
  0.01 mg/liter