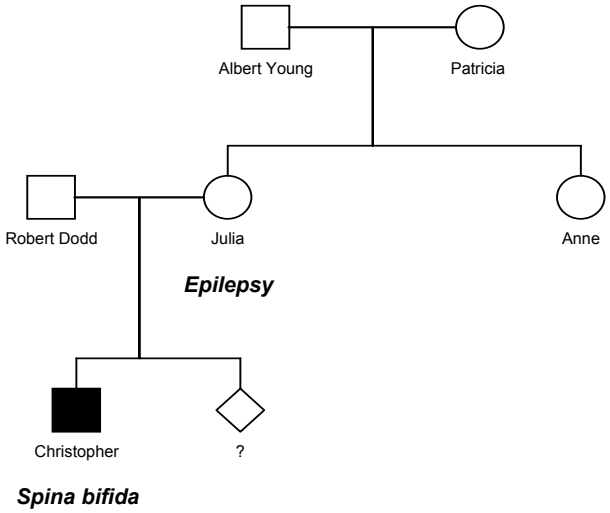
6. What is the chance that I will have another baby with a neural tube defect?

Christopher Dodd (III-1) has spina bifida as an isolated malformation . His mother Julia (II-2) is in early pregnancy. Christopher's father, Robert (II-1) thinks that he may have had a cousin with a neural tube defect but there is no further information available.



Q1 What is the mode of inheritance of neural tube defects?

(a) Neural tube defects include spina bifida and anencephaly. They result from defective closure of the developing neural tube during the first month of embryonic life. Large lumbo-sacral lesions usually cause partial or complete paralysis of the lower limbs with impaired continence. Anencephaly is incompatible with survival for more than a few hours after birth.

(b) The condition in this family is affecting just one person – a male. It could therefore be due to a new dominant mutation, an autosomal or X-linked recessive condition, a chromosome anomaly, a multifactorial condition or a teratogenic influence.

We know however from population and family studies that neural tube defects are usually multifactorial conditions.

When NTDs are found as part of chromosomal (particularly trisomies 13 and 18) and dysmorphic syndromes they are usually associated with other physical signs. As Christopher has no congenital anomalies apart from spina bifida, it is most likely that his condition is an example of multifactorial inheritance. Multifactorial conditions affect only one body system.

Q2 What features in the family might be particularly associated with Christopher having a neural tube defect?

Multifactorial conditions are considered to be determined by the summation of the effects of multiple genes at different loci resulting in a genetic susceptibility, together with environmental factors. Is there any evidence of either of these in Christopher's family?

Genetic susceptibility
It is likely that Christopher's increased genetic predisposition is due to combinations of genes he has inherited from both his parents. Christopher's father, Robert (II-1) thinks that he may have had a cousin with a neural tube defect, offering an unconfirmed glimpse of the familial susceptibility factors.

Environmental trigger factors
Christopher's mother, Julia, has epilepsy, treated by sodium valproate. This is a known enviromental factor in the aetiology of neural tube defects. There is a risk of about 2% of anencephaly or spina bifida in the offspring of a woman taking sodium valproate, associated with the teratogenic effects of the drug. Potential risks to the fetus have be weighed against the dangers of stopping drug treatment and risking fetal and maternal complications due to seizures during pregnancy. Drug therapy should be reviewed before pregnancy is contemplated. It is possible that the teratogenic effect is associated with alterations to folate metabolism.

Women in the UK who have had a child with a neural tube defect are recommended to take 4-5 mg folic acid daily before conception and during the first weeks of pregnancy, until the neural tube has closed. This has resulted in a reduction in recurrence risk by 70-75%. This is strong evidence that folate metabolism is an important environmental component of the multifactorial inheritance.

Q3 What is the probability of Julia having another baby with a neural tube defect?

The risk to Julia's next baby is found from population studies; the UK has a relatively high incidence of neural tube defects, although the incidence has been falling in recent years. The observed risk to 1st degree relatives of a person affected with a neural tube defect is

4% (1 in 25).

Note that this risk is considerably lower than those found in diseases due to Mendelian (single gene) inheritance (ie 1 in 2; 1 in 4).