AMELIA

(A case report with review of literature)

by

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Congenital malformations are commoner than is generally realised. Malpas (1937) found 2.1 per cent in 13,964 consecutive births in the Liverpool Maternity Hospital, of which, anencephaly, iniencephaly, spina bifida and hydrocephaly accounted for half the cases.

Congenital malformation involving both the limbs was a rather rare condition before the introduction of the Thalidomide group of drugs. In 1,500 congenital malformations, studied by the Perinatal Mortality Survey, before the introduction of thalidomide, there was only one case of bilateral phocomelia (Butler & Co. workers, 1962). Different parts of the limbs may be affected in this condition. Both arms and legs may be entirely absent — as in the present case, or almost entirely absent, when it is known as amelia, the proximal part of the limbs may be missing— phocomelia, or the distal parts may be missing — hemimelia.

There was a sudden increase in these congenital deformities in 1961 and 1962 after the use of thalidomide group of drugs, which were used as sedatives and tranquilisers. In Germany where the drug was sold without a prescription a total of 4,000 children are supposed to have been born with this type of deformity and two-thirds of these are expected to live (Taussig, 1962). Many of the babies have other associated congenital lesions present as well. A large number of papers were published in 1961 and 1962, showing definitely that most of these deformities of the limbs were due to the use of thalidomide, in the early stages of pregnancy. Lancet (1962) gives this information, gathered by the Ministry of Health from 1960 to August 1962, by which time all babies whose mothers had taken thalidomide were born, the drug being withdrawn from the European market by November 1961. A total of 805 returns were received of children with limb defects being born alive. Of these, 153 subsequently died, including 85 where the mother took thalidomide during pregnancy. Of the 652 living children, 244 mothers had definitely taken thalidomide; 146 of these children showed gross deformity of 2, 3 or 4 limbs, including 27 with additional deformities. In comparing the distribution of the type of deformity among these cases with those where the mother did not take thalidomide, it is seen that over half the children where the abnormality was associat-

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ed with thalidomide had gross deformities compared with about one-fifth among children regarding whose abnormality thalidomide could not be implicated. Of the 408 children whose mothers had not taken thalidomide, 86 had gross deformities, 85 had only one limb deformity and 237 had minor limb defects. Of the 146 gross limb deformities seen after the use of thalidomide, 36 had both arms absent, 3 had both legs absent and 12 had both arms and legs absent (Amelia). The others had either major defects of both arms or both legs or absence of one set of limbs with defective other set.

Case Report

Smt. T. R., 26 years, Hindu, was admitted to a Municipal Maternity Home, on 8-9-1965 at 6.20 A.M. for labour pains. Patient was gravida V with history of 3 full-term normal deliveries — living and healthy, and 1 full-term still-birth 2 years ago. There was no sign of any abnormality in any of the children. She had attended the antenatal clinic once before in the 7th month when abdominal examination showed vertex I, floating, and foetal heart sounds were heard. Haemoglobin was 65%, blood pressure 118/60 mm. of Hg. Albumin and sugar in urine were absent. On admission the patient was getting strong labour pains, the uterus appeared almost full-term, vertex was thought to be presenting, foetal heart sounds were heard. The membranes ruptured at about 7-15 A.M. and the presenting part seen at the vulva was a breech. No limbs could be seen and it was presumed to be a breech with extended legs. As there was delay in progress of the breech, a hand was introduced into the vagina, to give gentle groin traction on the breech, and it was realised that both the lower extremities were absent, hence no traction could be given and the delivery was allowed to progress on its own. Patient delivered a baby girl at 7.50 A.M. after a second stage of 35 minutes, during which time the foetal heart sounds disappeared. The placenta delivered normally 5 minutes later and was quite normal and healthy. The still-born weighed 4 lbs., and showed complete absence of both upper and lower extremities. One lower incisor tooth was present. No other congenital abnormality was seen. Unfortunately, a post-mortem examination could not be done, nor could a photographic picture of the foetus be taken, as the relatives were anxious to dispose of the body as soon as possible.

The patient gave a history of rat-bite in the second month of pregnancy for which she was given an injection by her family physician. After the injection, patient had slight bleeding per vaginam which lasted for a week. She was treated as a case of threatened abortion by 3 injections and some tablets by her doctor. Patient had no other trouble and had kept good health without any treatment during the rest of her pregnancy.

Comments and Discussion

A case of bilateral amelia is described. It is a rather rare anomaly and not many cases were reported before the use of the drug, thalidomide. It was only after the extensive use of the drug in England and Europe, especially West Germany, that congenital deformities of the limbs were recognised and a new clinical syndrome had appeared, the outstanding feature of which was phocomelia. As in most cases, the severity varied but the pattern was remarkably specific. The abnormality concerned the long bones of the extremities. The prehensible grasp was lost. The hand arose directly from the distal end of the affected bone. In severe cases, the radius, ulna and humerus were lacking and the hand buds arose from the shoulders. In extreme cases, as in the present one, both the arms and the legs were missing. A saddle nose was common and in some infants the internal organs were

affected, but most thalidomide children were normal mentally. In the present case there was no history of any special drug being taken, but there was a history of threatened abortion occurring in the second month of pregnancy. This is the critical age for the development of the extremities, and there may have been arrested growth at this stage. The only other obvious deformity was an erupted lower incisor tooth.

The other interesting feature of the case under consideration was the difficulty in diagnosing the presenting part during the antenatal period, as a limbless breech felt very much like a vertex on palpation. Also during extraction of the breech, there was difficulty, as groin traction could not be given and delivery of the breech was delayed due to lack of any grip on the presenting part.

Embryological Considerations

It is by the end of the 4th week of intra-uterine life, when the human embryo is 2.5 mm. in length, that indications of the limb rudiments may be present. The rudiments of the otic vesicles also appear as slight depressions at this stage. During the 5th week, the length of the embryo increases to 5 to 6 mm. and the rudiments of the limbs become quite distinct. By the end of the 6th week, the three segments of the upper limb become visible and the rudiments of the fingers appear. The lower limb is less advanced. It is by the 7th week that the thigh and the toes appear. In the 3rd month, the limbs begin to assume their proper proportions and nails appear on the fingers and toes. Hence these few weeks are crucial for the proper development of the extremities and any drug or disease, having an effect on the embryo during this stage, will lead to congenital defects of the limbs together with other congenital defects as have been noted in the thalidomide syndrome. The danger period is probably over by the tenth week of pregnancy. Stabler (1962) describes a case of phocomelia where the mother took 50 mg. of thalidomide a day from 5th to the 7th week of pregnancy. Lenz analysed 50 cases of phocomelia in full detail with date of conception and time of drug taken. Of 50 women, 45 had taken the drug between the 30th and 50th days, and five between the 50th and 60th days, after the last menstrual period. Among 21 instances, in which the date of conception was known, the mothers had taken the drug between the 28th and the 42nd days after conception.

Aetiological Considerations

The exact cause of congenital malformations cannot be defined, but several genetical and environmental factors play a part. (1) Genetical factor, as an important cause of congenital malformations, has been recognised. Penrose (1960) described various ways in which genetic factors may cause malformations. Some conditions are inherited direct from parent to child and are the result of genes in a heterozygous state inherited in a dominant manner, e.g. the mild skeletal deformities. The severe abnormalities, like achondroplasia and acrocephaly, are seen as the result of fresh mutations in parental germ cells, as these subjects

seldom become parents. Some congenital abnormalities are caused by specific genes in a homozygous state. Certain types of dextrocardia, amaurotic idiocy, infantile diplegia and osteogenesis imperfecta are examples of recessive inheritance in which there is an undue frequency of cousin marriages. In many other cases, the genetic complement may act merely as a disposition or susceptibility, as in harelip, cleft palate, congenital heart disease and anencephaly.

Murphy found that following the birth of a congenitally deformed baby, the chances of a woman having another defective child were 24 times greater. Certain congenital malformations are more common in one sex, harelip and cleft palate being more common in males, while anencephaly and spina bifida are more common in females. This again suggests that genetic factors may be responsible.

Some congenital abnormalities seem to be associated with increase in maternal or paternal age, causing an increase in unbalanced chromosome configuration. Most of the chromosome anomalies described in live-born individuals, have been found in sex chromosomes. Chromosome anomalies involving the autosomes are probably nearly always lethal, but may be found in 5-10% of abortions. According to Stevenson 20 in every 100 conceptions result in a congenitally malformed foetus, most of which are aborted. And of 1,000 live-born foetuses, 50 have disabling congenital defects, of which 25 have actual malformations.

(2) *Environmental factors:* Many different environmental agents have been used experimentally in animals to produce various anomalies in embryonic development. Such teratogenic agents, as x-rays and chromosal poisons may act on somatic cells by causing mutations besides affecting the cell metabolism. There are several similarities between the teratogenic effects of vitamin B deficiency, (viz. riboflavin deficiency) and drugs like thalidomide (Leck and Miller). Some patients receiving thalidomide in large doses develop glossitis and other oral lesions which respond to treatment with vitamin B Complex. These findings suggest that thalidomide may interfere with the metabolism of riboflavin or another vitamin B group. Similarly severe deficiency of vitamin B group may lead to thalidomide type of syndrome. Nelson, Baird, Wright and Evans (1956) found that if pregnant rats are given galactoflavine (a riboflavin antagonist) a more severe deficiency occurs and many of the off-spring exhibit hydrocephalus, microphthalmos ventricular septal defect, etc., as well as skeletal deformities. The response of the rodent embryo to riboflavin deficiency, therefore, appears to resemble that of the human to thalidomide, in respect of the type of malformations produced and the fact that the skeleton is more susceptible than the viscera.

The sedative drug thalidomide was first synthesized in Germany in 1954 and was marketed in U.K. in 1958, and by the end of 1961, when it was banned from use, it was estimated that about 4,000 congenitally deformed children had been caused by it in Germany and about 300 in Great Britain. The drug caused deformities,

is given and aetiological factors discussed.

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