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Drug-Induced (Thalidomide) Malformations

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ABSTRACT

Phocomelia (flipper-like limbs) has long been recognized as a rare malformation. Numerous cases of phocomelia and other congenital malformations have recently been reported in the United Kingdom, Australia, Europe and Canada in which the common factor appears to have been the administration of the hypnotic compound thalidomide during early pregnancy. Two additional cases of infants born with phocomelia, amelia and alimentary abnormalities are presented. In both of these cases the administration of thalidomide was initiated early during pregnancy (five to eight weeks after the last normal menstrual period) and maintained for several weeks. Thalidomide (alpha-phthalimido glutarimide) is related chemically to other glutarimides currently in clinical use. The possibility that these compounds and/or their metabolites may induce teratogenic effects warrants consideration. Emphasis is added to the view that caution should be exercised when prescribing new drugs.

WITHIN the past year an increasing incidence of disturbing and in some cases irreversible untoward reactions has been reported after the clinical use of some potent pharmacological agents, reactions which have necessitated the withdrawal from the market of a number of these therapeutically effective preparations.[1]

The concept of preventive medicine is receiving increasing emphasis in all areas of medical practice. In obstetrical practice it is generally recognized that adequate prenatal care is of paramount importance, not only in assisting the patient to meet the demands of pregnancy but also in anticipating and preventing possible complications.[2] However, despite this well-accepted view and the observations of conventional precautions, congenital anomalies and neonatal dysfunctions have been reported[3] after prenatal administration of a variety of pharmacological agents (tolbutamide, androgens, androgenic progestins, reserpine, hexamethonium, aminopterin, naphthoquinone, and antithyroid and iodine-containing compounds).

Since the latter part of 1961, numerous cases of congenital malformations (amelia, phocomelia, alimentary abnormalities) have been reported in the United Kingdom, Australia and Europe.[4] The common factor appears to have been the administration of thalidomide§ during early pregnancy. More recently, in Canada, a few cases of this nature have been described.[5, 6]

This communication presents two additional cases which lend support to the view[4] that there is a close association between certain types of congenital malformations of infants and the early prenatal administration of thalidomide.

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§This compound is known by the following trade-names: Kevadon, Thalimol, Contergan and Distaval.

Case Reports

Case 1.—The mother of this child was 30 years old and had two previous pregnancies, one 10 years ago, which resulted in premature and normally formed twins of whom one was stillborn, and the other eight years ago, which terminated in a full-term delivery. None of these children had any congenital abnormalities.

The date of the mother's last menstrual period was June 25, 1961. Very early (end of July) in her pregnancy she was given thalidomide (Kevadon), 50 mg. nightly. She took this medication each day until November 18, 1961, when it was discontinued because the possible dangers of this drug were realized. The patient was then switched to trifluoperazine (Stelazine) 2 mg. twice daily, on December 2, 1961. Her pregnancy con-

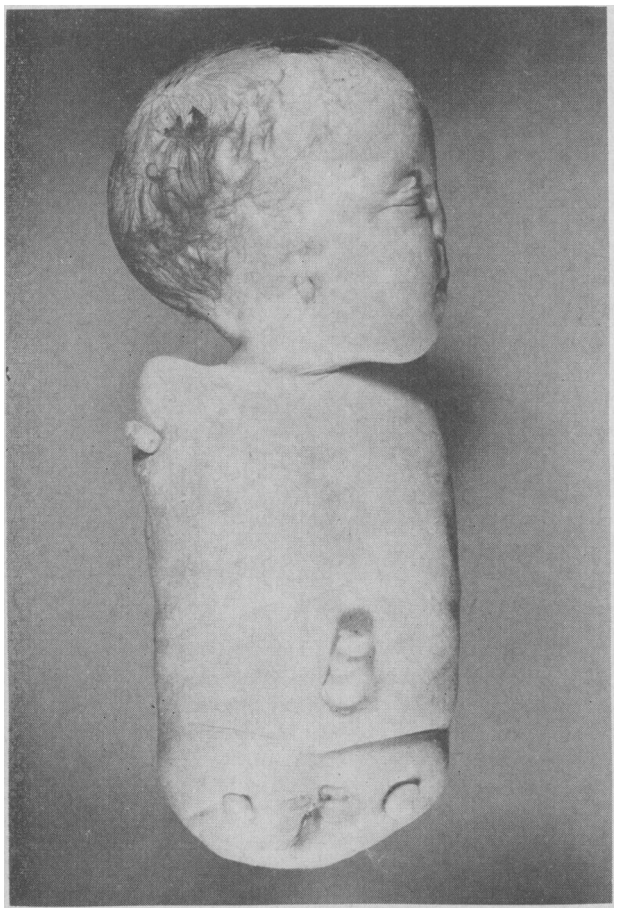

Fig. 1.—Shows the major external abnormalities.

tinued uneventfully. On March 25, 1962, she began to lose amniotic fluid. On April 25, three weeks after her expected date of confinement, x-ray pelvimetry was carried out. No extremities were demonstrable in the fetus. The mother returned in active labour three days later. A grossly deformed girl was delivered as a posterior breech. It was noted that the umbilical cord was very short. The child died during forceps extraction of the head.

Postmortem examination.—The major external abnormalities are readily visible from the photograph in Fig. 1. The legs and right arm were represented only by small tags, while the left arm was completely absent. The external ears were rudimentary. There was no gluteal fold and only a single cloacal cleft, lined by the labia majora.

The skeletal, cardiac, pulmonary, gastrointestinal and genitourinary systems were severely malformed. The skull, clavicles, ribs and upper spine, as demonstrated radiographically (Fig. 2), were normal. The lower spine ended at the second sacral vertebra. The scapulae were rudimentary, and the glenoid fossae and coracoid processes were absent. Of the pelvic girdle only the ilia had developed. A tiny bone formed the core of the left leg, while the other tags consisted only of skin-covered fat, in which, microscopically, nerve bundles and smooth muscle fibres were prominent.

The ventricles of the heart communicated through a high interventricular septal defect measuring 1 cm. in diameter, and the atria through a foramen ovale, measuring 1.5 cm. and only half covered by a thin

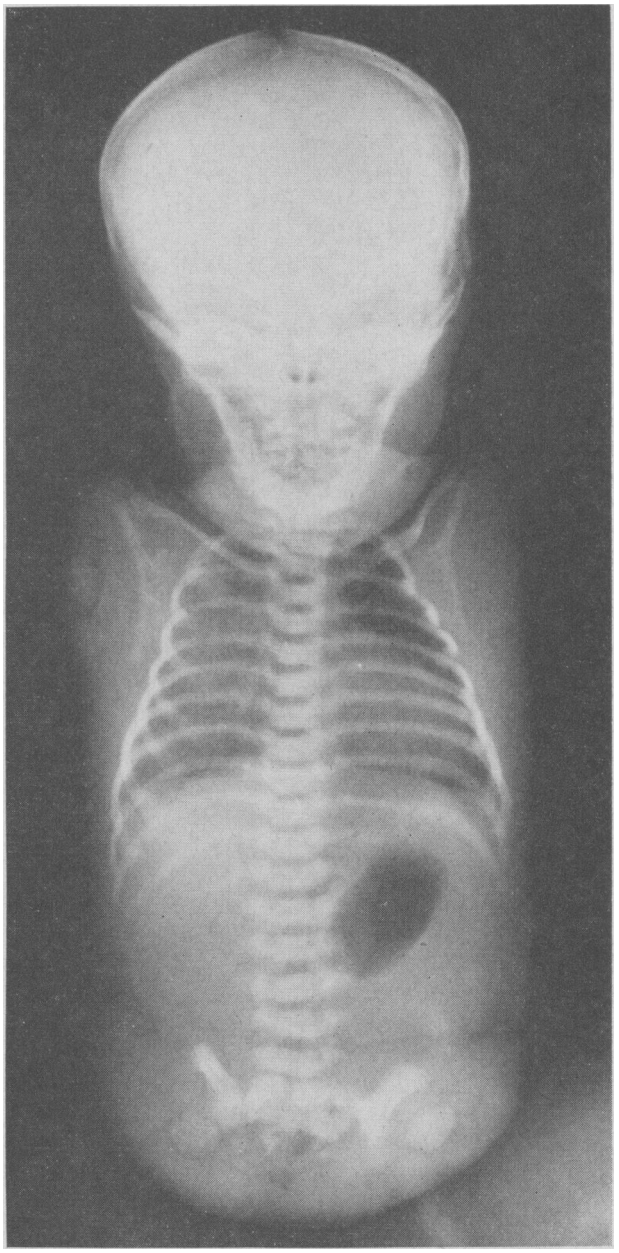

Fig. 2.—Radiograph demonstrates severely malformed skeletal, cardiac, pulmonary, gastrointestinal and genito-urinary systems.

membrane. From the left ventricle arose a truncus arteriosus which divided into aorta and pulmonary artery 6 mm. above the aortic valve. The pulmonary valve was absent, and the right ventricle emptied into the truncus through the interventricular septal defect. The aorta ended blindly, without dividing, at the usual site of bifurcation.

Both lungs were bi-lobed. There was a patchy bronchopneumonia, probably due to the premature rupture of the membranes.

The esophagus and stomach were normal. The second part of the duodenum was occluded by a complete atresia, 5 mm. in length. The ileum contained a Meckel's diverticulum. The ileocecal valve and cecum were poorly formed and lay high in the right upper quadrant. The appendix was absent. The mesentery of the colon was long, and the bulk of the large bowel lay in the left gutter. The rectum opened into the

cloacal cleft. The gallbladder was absent, resulting in poor demarcation of the quadrate lobe of the liver.

The right kidney lay in a somewhat lower position than normal but was otherwise unremarkable. The left kidney also had a normal structure but was situated in the centre of the pelvis. Both ureters drained into the bladder, which emptied into the cloaca. The ovaries and tubes were normal. The uterus was double and consisted of two muscular solid cords which ended blindly in the wall of the bladder. There was no cervix or vagina. The other organs appeared normal.

CASE 2.—The mother of this infant was 34 years of age and had two normal children, both females. The first child was born in 1956, the second was delivered in 1958, and they weighed respectively 7 lb. 9 oz. and 9 lb. 8 oz.

Her last normal menstrual period was June 9, 1961. On July 24, she was given meclizine HCl (Bonamine), 25 mg. twice daily for four days, to relieve her nausea. This medication proved ineffective. An antinauseant (Bendectin), consisting of three drugs, dicyclomine HCl (10 mg.), doxylamine succinate (10 mg.) and pyridoxine HCl (10 mg.), was then administered, with some measure of relief. On the first day of August 1961, she was given thalidomide (Kevadon), 50 mg. at bedtime, for insomnia, and during the next two months consumed a total dose of 2000 mg. of this compound. Soon after, she had fever, malaise, sore throat and vomiting which lasted for about two weeks.

The patient was followed up regularly from August 17, 1961, until delivery. She experienced no further distress, her blood pressure was normal throughout the pregnancy, and her laboratory findings were negative. She had a total weight gain of 27 lb.

Spontaneous labour began on March 18, 1962, and after four hours she was delivered of a female child weighing 9 lb. 7 oz. The newborn infant had typical phocomelia involving both arms, but no other abnormality was evident at that time. The child was breast-fed from birth, has been generally well, and on August 1, 1962, weighed 14 lb. The only difficulty noted by the mother is a tendency for this child to be colicky.

Because of clinical evidence of a club-foot, a radiographic survey of the infant's bone structure was carried out on July 15. In summary, the skeletal examination was normal except for the following: Both humeri were missing; the scapulae were malformed, and the glenoid fossae absent; bilaterally the radius and ulna were fused, there was no elbow, and no true wrist joints; the metacarpals and fingers were formed normally except for fusion of the middle and distal phalanges on the left fifth finger. Examination of the right foot showed metatarsus varus of mild degree, with an atavistic great toe. At present the foot is being treated by a Denis Browne splint.

DISCUSSION

These two cases lend support to the view that congenital amelia and phocomelia may be induced by the administration of thalidomide during the early months of pregnancy. Phocomelia has long been known as a rare malformation.[7] Although not a single phocomelic infant was born over a 10-year period (1951-1960) at one British hospital in which there were well over 20,000 confinements, there were four such births during the year 1961.[8]

In Europe as well as in Great Britain, a few cases of ectromelia were seen in 1959; this condition became increasingly more numerous in 1960, and within a small geographical area affected more than one per 1000 infants born in 1961.[7-9] Thalidomide (alpha-phthalimido-glutarimide) was first introduced in West Germany in 1958. Early suspicion of an association between the increased incidence of these malformations and the use of thalidomide has been strengthened by the well-planned retrospective investigations of Lenz,[10] Speirs[11] and Smithells.[9] Further, definitive proof that thalidomide does indeed cause ectromelia appears to be emerging from experiments in laboratory animals. Somers[12] has demonstrated that the oral administration of thalidomide in New Zealand white rabbits, from day 8 to day 16 of pregnancy, can induce teratogenic effects. Similar effects have also been obtained recently in the offspring of pregnant mice of strain C-57-BL/6.[13]

According to Taussig,[7] the crucial period for inducing such changes in the human is between the 28th and the 42nd day after the date of conception. It appears that as little as 400 mg. of thalidomide may be teratogenic if administered during this interval,[5] whereas if this drug is used only before conception, the risk of neonatal malformation seems negligible.[14]

Although it cannot be demonstrated unequivocally that thalidomide is directly responsible for the ectromelia in the present cases, the finding in Case 1 that the only drug administered from the 3rd to the 18th week of this pregnancy was thalidomide (50 mg. nightly, at bedtime) indicates that a causal relationship may exist between the administration of this compound and the observed malformations. In Case 2, an antiemetic agent consisting of three drugs, dicyclomine, doxylamine, and pyridoxine (Bendectin) was administered concomitantly with thalidomide. The possibility that the antinauseant *per se* may have contributed to these effects cannot be ruled out. However, one of the authors (J.B.) has used this antiemetic compound extensively, and no previous case of malformation is known to be associated with its use.

Thalidomide is a derivative of glutarimide. A number of other glutarimides are now currently in clinical use, e.g. glutethimide (Doriden), aminoglutethimide (Elipten) and bemegride (Megemide). The question arises whether similar anomalies might occur in comparable circumstances following the administration of these compounds. To the authors' knowledge, congenital anomalies have not been reported following the use of these other agents. Other drugs which are chemically related to thalidomide should be studied extensively for possible teratogenic properties in experimental animals. The metabolic fate of thalidomide and other glutarimides should be the subject of careful

investigation in order to determine whether or not metabolic derivatives of these compounds may, like thalidomide, be involved in the production of teratogenic effects.

Recent experiments by Runner,[15] on pregnant mice of known strain, have demonstrated that prolonged fasting or the administration of insulin, iodoacetate or alpha-methyl folic acid can independently result in similar fetal abnormalities of the precartilaginous mesenchyme. Runner has proposed a metabolic scheme which suggests that the mechanism common to all these teratogens is their ability to suppress substrate-coenzyme interactions that appear to be essential for supplying the energy demands of rapidly growing cells. Can a similar mechanism of action be assigned to the teratogenically induced effects of thalidomide? Can other central nervous system depressants which interfere with cellular respiratory mechanisms[16] induce comparable effects? Roux[17] has shown that some phenothiazines can produce teratogenic effects in experimental animals. These and related questions will undoubtedly stimulate studies of the possible teratogenic effects of many compounds used during pregnancy, and will once more emphasize the importance of critical and adequately controlled laboratory and clinical evaluations of drugs for clinical use.

Every potent pharmacological agent may produce some complication, and in every case the known risk involved in using the selected drug must be weighed against the expected benefit. The authors support the view that physicians should employ the greatest reserve in prescribing new drugs, particularly when the risk of unknown toxicity is not offset by proved or significant superiority over older and effective standard remedies.[18] Furthermore, during pregnancy, and in particular in the first trimester, drug therapy should be kept to a minimum. In those cases in which the indications for drug administration are unmistakably urgent, prime importance should be given to compounds whose usage over the years has provided evidence of an optimal balance between therapeutic effectiveness and the occurrence of side effects.

SUMMARY

Two cases are reported in which there appeared to be a close association between certain types of congenital malformation and the administration of thalidomide (alpha-phthalimido-glutarimide) early in pregnancy. The question is raised whether or not similar anomalies might occur in comparable circumstances after the administration of other glutarimides currently in clinical use. Drug therapy should be kept to a minimum in pregnancy, and in particular during the first trimester.

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