Congenital Phocomelia in Monozygotic Twins

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Phocomelia is the congenital absence of legs and arms, resulting in the hands and feet being in close proximity to the trunk. Occasionally deformed intermediate segments may be demonstrated radiologically (Carey, 1919), though the limb girdles and digital elements may appear normal.

In the past decade interest has been taken in abnormalities showing phocomelia as a result of thalidomide taken by the mother during pregnancy. It has been shown (Lenz and Knapp, 1962) that a critical period of sensitivity, 34 to 50 days after the last menstrual cycle or 20 to 36 days' ovulation age, exists in the human in those cases having thalidomide deformities. These results have recently been reproduced in mammals, including primates (Hendricks *et al.*, 1966).

Similar defects are known to have existed many years before the use of this drug. Two paintings, one entitled *Handschriften* depicting the armless town clerk of Nuremberg at the end of the sixteenth century (Oertel, 1962), and the other by Goya in the Louvre (Smithells, 1966), must surely refer to the same defect.

The case discussed below is unrelated to thalidomide therapy, though the deformity, particularly of the arms, resembles in many respects that seen after thalidomide therapy.

Case Report

A married woman aged 30 had a history of primary infertility of five years' standing and was found on examination to have an enlarged, blocked left uterine tube. Radiology was not undertaken during the pregnancy, and only routine investigations had been made previously.

History of Pregnancy.—Tubal insufflation was carried out three weeks after a normal menstrual period. No further vaginal loss occurred until the fourteenth week of her pregnancy, when she had a threatened miscarriage. She was found to be group O Rhesus-negative with no antibodies. A normal pregnancy persisted until 38 weeks, when mild pre-eclampsia developed, but still no antibodies were present. She was treated by bed rest, and was admitted to hospital in labour at 39 weeks. She had an assisted vaginal delivery of stillborn malformed "locked twins," sharing a single placenta.

Description of Twins (Fig. 1).—Both twins were male. Twin 1 showed a normal head and trunk. The hands were set directly into the shoulder region, both appearing like flippers with no division into fingers. The feet were appended to the lower end of the trunk and pointed laterally. The right and left feet had five toes each. Twin 2 had a normal head and trunk, but there was a complete absence of arms. The feet were attached directly on to the lower end of the trunk and showed division into toes: six on the right foot and only four on the left foot. *Radiologically* their appearance was stated as follows. *Twin 1* (Fig. 2): The skull, vertebrae, ribs, and pectoral girdle are normal. There is complete absence of any bone in the upper limbs apart from a metacarpal and phalanx representing one digit. The pelvic girdle is normal. The lower limb skeleton is represented only by a talus, a calcaneum, and metatarsals and phalanges of five digits on each foot. *Twin 2* (Fig. 3): Again the skull, vertebrae, and ribs are normal. The pectoral girdle is normal, with complete absence of any upper-limb skeleton. The pelvic girdle is normal. The lower limb shows only the presence of a talus, a calcaneum, and six metatarsals and phalanges on the right side, and a talus and four metatarsals and phalanges on the left side.

Development of Limbs.—Limb buds in the human make their appearance at about 30 to 32 days' estimated age, 28 to 30 somite stage, or 5 mm. crown–rump length, and the digits at a later stage (40 mm. crown–rump length) (Fig. 4). The arm buds appear opposite the fifth to seventh cervical somites at the level of the pericardial swelling and the leg buds appear some 48 hours later opposite the second lumbar to the third sacral segments and lie just caudal to the attachment of the umbilical cord. The first evidence of a limb bud is of a condensation of mesenchymal cells, showing frequent mitotic figures in the body wall, throwing up a slight

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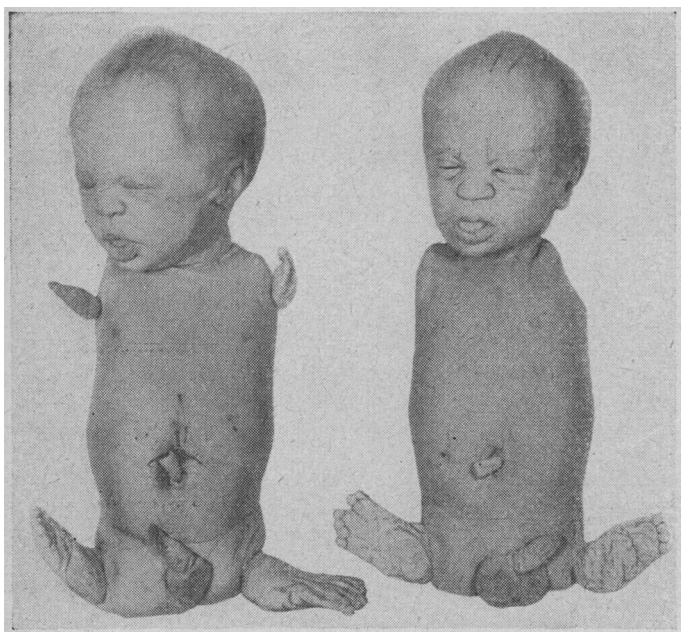

FIG. 1.—Twins 1 (left) and 2 (right) showing limb deformities.

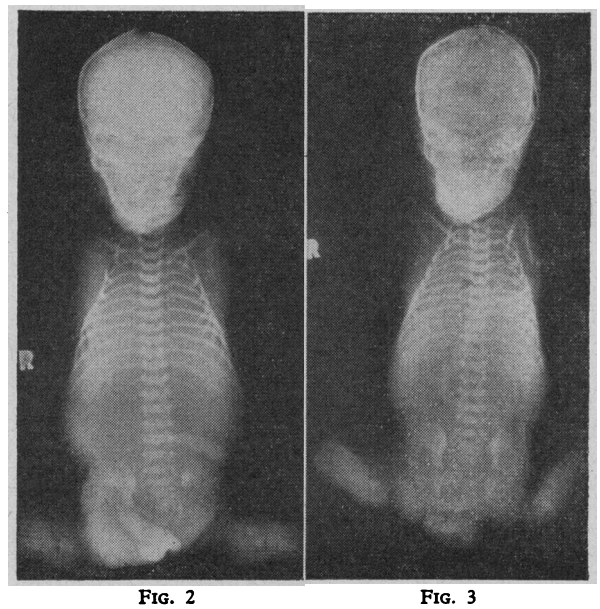

FIG. 2 FIG. 3

FIG. 2.—Radiograph of Twin 1, showing normal pectoral and pelvic (rotated) girdles. FIG. 3.—Radiograph of Twin 2.

longitudinal ridge on the surface of the embryo. At the apex of this condensation the ectoderm is thickened (Fig. 5)—the apical ectodermal ridge (Boyd, 1960). In the mesenchymal tissue vasculogenesis occurs, forming a fine-meshed plexus between the cells, tapping the segmental artery at the base of the limb bud and draining into a marginal vein. All the structures of the limb are derived from the ectodermal and mesenchymal cells of the limb bud except the nerves, pigment cells, and possibly the larger vessels. Except for these structures the limb is a "self-differentiating system."

The limb buds develop before there is any differentiation of anterior horn cells in the spinal cord, and in one case (Curtis and Helmholtz, 1911) there was no cervical enlargement and no lateral portion of the anterior horn cells.

Experimental Embryology

Most experimental work on limb development has been performed on amphibians and birds, though similar processes have been shown to exist in mammals (Milaire, 1965).

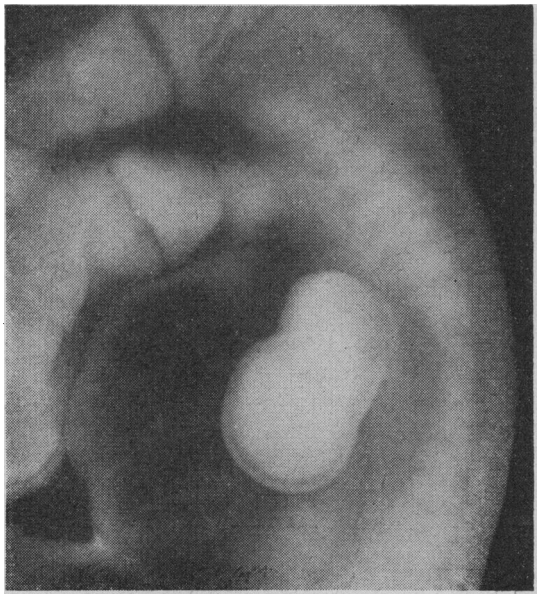

FIG. 4.—Photograph of a portion of a human embryo (10 mm. crown-rump length) to show the development of a limb bud. Note the peripheral sinus around the tip of the limb bud.

It would seem that for normal limb growth to occur both limb mesenchyme and an apical ectodermal ridge must be present, and the latter's persistence depends on a "maintenance factor" from the mesenchyme, distributed asymmetrically. Abnormal development may thus result from interference with this "inductive" mechanism either by loss of capacity for inducing or loss of response from the subjected tissue, or failure of the one from reaching and reacting with the other (Beck and Lloyd, 1966). Of the experiments leading to this conclusion one appears to be pertinent in the present context: if *non*-limb mesenchyme is covered with limb ectoderm, including the apical ridge, the structure so formed does not develop into a limb, but if a fragment of limb mesenchyme is introduced beneath the ectodermal jacket at the apical ridge the latter maintains its thickened structures and an elongated outgrowth forms (Zwilling, 1956). The mesenchyme acts, therefore, as an inductor force on only a limited area of the ectodermal ridge and is insufficient in capacity to cause the formation of a normal limb.

Normally development progresses in a proximo-distal differentiation, and in bilateral organs this differentiation may occur at slightly different times, giving a discrepancy in size between the two sides (Stockard, 1931).

Discussion

Much attention has been focused recently on the effect of drugs, particularly thalidomide, on limb skeletal abnormalities. The twins described were born after a pregnancy in which no drug therapy had been employed, no fever had interrupted, and only possible hypoxia as a result of insufflation and perhaps temporary disestablishment of implantation had resulted. Several cases have been mentioned, and six patients who have

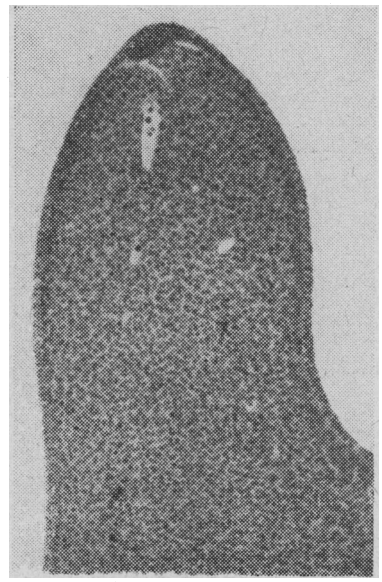

FIG. 5.—Photomicrograph of a longitudinal section of a human limb bud to show the apical ectodermal proliferation.

appeared since the withdrawal of thalidomide are at present alive and under treatment (E. P. Quibell, personal communication, 1966).

It is suggested that the formation of the deformity of phocomelia may result in one of two ways. (1) Some agent damages the proximal mesenchymal cells after they have been separated from the subapical mesenchymal cells, and that these latter, provided the damaging agent is no longer functional, may then give rise to normal distal limb elements. (2) It has been shown that mesenchymal cells destined to become thigh, if placed under the apical ridge, may form digits (Saunders *et al.*, 1957). It may be that the destructive agent damages the distal mesenchymal cells, and, by leaving the proximal mesenchymal tissue under the apical ectodermal ridge, these cells now differentiate into digits. Such a deleterious agent is thalidomide, and it has been shown (Lenz and Knapp, 1962) that there is only a limited period of development when such an agent may act to produce this effect.

It would seem that a number of teratogenic agents may exist, and that drug therapy, though bringing the subject to the forefront, is not the only cause for the development of such abnormalities.

Summary

The occurrence of phocomelia in monozygotic twins other than that resulting from thalidomide therapy is described. The exact way by which the anomalies are produced is not known, though two possible mechanisms are discussed in the light of experimental embryology and the development of the normal human limb bud.

The critical time in pregnancy for such defects to be produced varies for upper and lower limbs between narrow limits, and the rate of growth and the stage of development of one

of the twins described comparable to the other emphasize the variability of the abnormality.

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REFERENCES

Beck, F., and Lloyd, J. B. (1966). In *Advances in Teratology*, edited by D. H. M. Woollam, vol. 1, p. 131. London.
Boyd, J. D. (1960). *Med. Press*, **243**, 157.
Carey, E. J. (1919). *Anat. Rec.*, **16**, 45.
Curtis, A. H., and Helmholtz, H. F. (1911). *Trans. Chic. path. Soc.*, **8**, 127.
Hendrickx, A. G., Axelrod, L. R., and Clayborn, L. D. (1966). *Nature (Lond.)*, **210**, 958.
Lenz, W., and Knapp, K. (1962). *Arch. environm. Hlth*, **5**, 100.
Milaire, J (1965). In *Organogenesis*, edited by R. L. DeHaan and H. Ursprung, p. 283. New York.
Oertel, O. (1962). *Mschr. Kinderheilk.*, **110**, 481.
Saunders, J. W., jun., Cairns, J. M., and Gasseling, M. T. (1957). *J. Morph.*, **101**, 57.
Smithells, R. W. (1966). In *Advances in Teratology*, edited by D. H. M. Woollam, vol. 1, p. 251. London.
Stockard, C. R. (1931). *Physical Basis of Personality*. New York.
Zwilling, E. (1956). *Cold Spr. Harb. Symp. quant. Biol.*, **21**, 349.

ABO Blood Groups and Polyps of the Colon*

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Though it appears that a significant proportion of villous adenomas or papillomas of the large bowel develop malignant properties, the debate still continues on the importance of adenomatous polyps as the sources of large-bowel cancer. Evans (1966) feels that the associations between multiple cancers of the colon and adenomatous polyps, and multiple polyps and cancer of the bowel, do not necessarily indicate an orthogenetically determined polyp-carcinoma sequence. He favours the view that they represent varying degrees of genetically determined large-bowel proneness to both cancer and adenoma.

With the exception of polyposis coli, no genetic locus has been associated with cancer of the large bowel or polyp formation, though Veale (1965) has postulated an unfavourable allelic modifier of the polyposis gene which in double dose produces a few adenomas of the rectum or colon. The ABO locus which is implicated in the causation of cancer of the stomach (Aird *et al.*, 1953), multiple primary cancers (Fadhli and Dominguez, 1963; Tsudaka *et al.*, 1964), and possibly chronic lymphatic leukaemia or lymphoma and carcinoma of the colon (Hyman *et al.*, 1963), does not appear to be a factor in carcinoma of the colon.

This paper reports the ABO blood group distributions in 373 patients with polyps of the colon or rectum and an association between group O and papillary adenoma of the colon.

Materials and Methods

Case records of all patients seen at Columbia–Presbyterian Medical Center between 1948 and 1960; at Montefiore Hospital, Bronx, N.Y., between 1952 and 1959; and at the Bronx Veterans Hospital, Bronx, N.Y., between 1952 and 1959 who had the diagnosis of polyps of the colon or rectum were checked. Only Caucasian patients whose blood types were known and whose polyps were removed and examined histologically were selected, and any family history of polyps or of carcinoma was carefully noted. For all cases from this centre the ABO blood groups were determined in the Presbyterian Hospital Blood Bank and were done on admission before transfusion. The cases totalled 317 from Columbia–Presbyterian Medical Center, 22 from Montefiore Hospital, and 34 from the Veterans Hospital. Follow-up was not complete, but 90% (335) of the patients were examined by barium meal, proctoscopy, or both to determine whether carcinoma or additional polyps had developed. During a five-year follow-up 58% (217) of the patients were seen several times. Patients were assigned to groups depending on pathological diagnosis, the number of polyps, and the family history.

For the purposes of this study adenomatous polyps are defined as being composed of a rounded, lobulated compact mass of branching glandular tubules, lined by columnar epithelium and supported by branching connective tissue. They are usually pedunculated, with the pedicle covered by normal mucosa (Grinnell and Lane, 1958). Papillary adenomas are defined as sessile growths, composed of innumerable branching villi clothed in stratified or pseudostratified columnar epithelium and usually covered by a coating of mucus (Grinnell and Lane, 1958).

Case records of all patients seen at Columbia–Presbyterian Medical Center between 1930 and 1966 with the diagnosis of polyposis of the colon, defined as 10 or more polyps, were checked. Of the 18 cases found 12 were examples of intestinal polyposis and seven had a positive family history. All patients with polyposis coli had their colon removed surgically and were found to have large numbers (from hundreds to thousands) of adenomatous polyps. The six patients with as few as 10 polyps have been included in the multiple polyposis group because it is thought by some (Veale, 1965; McConnell, 1966) that these patients may have inherited a weakly expressed polyposis gene.

As most of the patients were treated at the Columbia–Presbyterian Medical Centre the control group was chosen from this hospital's blood bank records. Non-profit Caucasian donors at the Presbyterian Hospital Blood Bank for the year 1960 were decided to be the most appropriate control, since the few Negroes with polyps were excluded from the study. In spite of careful selection there was a higher incidence of group B and a lower incidence of group A in the Presbyterian Hospital series than in other control groups (see Table I). This

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