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Case Report

Intrauterine Wound Healing in a 20 Week Human Fetus

Ursula Rowlatt

Department of Pathology and the Center for Craniofacial Anomalies, Abraham Lincoln School of Medicine, University of Illinois at the Medical Center, Chicago, IL60612, USA

Summary. Limb amputations, probably caused by amniotic constriction bands, were examined histologically in a 20 week human fetus to assess the degree of intrauterine healing. No acute inflammatory process, no removal of necrotic material, and no granulation tissue formation were seen at any of the amputation sites. A recent ulcer, probably caused by friction of an exposed piece of bone in the stump of the right leg, also showed no inflammatory response. Healing was by coagulation of exposed tissue and by a minor degree of mesenchymal proliferation without repair. Similar changes have been described in experimental intrauterine wound healing in rats, lambs, opossums and baboons. Conversion from a non-specific to a classical postnatal inflammatory response occurs sometime before term. It is not known at what point this change takes place in man; examination of this infant suggests that it occurs after the twentieth week of gestation.

Key words: Intrauterine wound healing – Limb amputations – Amniotic bands.

Introduction

Very little is known about the ontogeny of various tissue reactions in the developing human fetus[1]. The birth of a preterm, stillborn infant with intrauterine injuries of all four limbs, presumably from strangulation by amniotic bands, presented an opportunity to examine the healing process before the middle of gestation.

[1] **Anmerkung der Schriftleitung**
Die „Pathologie der Lebensalter" wurde von Robert Rössle (1876 bis 1956) begründet. Der Keimling (die „Kyeme") reagiert mit den Mitteln seines Entwicklungsstadiums. Einzelheiten in Verh. dtsch. Ges. Path. 19. Tagg., S. 18 (1923): Zusammenfassende Darstellung durch W. Doerr in H. Hamperl „Robert Rössle in seinem letzten Lebensjahrzehnt". Berlin-Heidelberg-New York: Springer 1976, S. 76 und 77.

W. Doerr (Heidelberg)

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Clinical Findings

The infant's mother, a black primigravida aged 21 years, was first seen at the University of Illinois Hospital in the twentieth week of gestation, for investigation of mild vaginal hemorrhage and abdominal cramps. There was no history of trauma at any time during pregnancy. Sonography revealed a breech presentation and a posterior placenta previa. Spontaneous delivery of a stillborn male infant took place three days later.

Post-Mortem Examination

The body was that of a preterm male infant weighing 550.0 g and measuring 22.0 cm crown-rump (Fig. 1). There was overriding of the skull bones and marked edema of the head and face. The right nostril was abnormally wide and communicated with a cleft that extended through the lip, alveolar process, and hard and soft palates. The nasal septum was displaced toward the left, while the left lip, alveolar process, and anterior one-third of the hard palate were intact (Fig. 2). There was a cleft in the soft palate and in the posterior two-thirds of the hard palate so that the nasal septum was free except for the anterior attachment to the primary palate. The mandible was intact though small and displaced backward.

The distal one-third of the right leg was missing below the knee. Exposed bone protruded for about 0.2 cm beyond the rest of the stump, which was covered by dried tissue and not by skin. There was an elliptical, full-thickness ulcer measuring 2.0×1.7 cm with a well-demarcated edge on the medial aspect of the left knee. Muscle and cartilage were seen clearly in the floor of the ulcer, which was free from exudate. The distal phalanges of the left foot and left hand were missing as were the medial three fingers of the right hand. A small fragment of necrotic material was attached to the right hand in the position of the base of the fifth finger. A string of desiccated brown material was attached to the left hand and to the left foot at the point of extrinsic syndactyly of the left fingers and at the base of the middle toe (Figs. 3 and 4). There were no other external nor internal anomalies. The placenta weighed 215 g with a centrally inserted umbilical cord measuring 18.0 cm. At the point of insertion, there were two rolled up free-standing fibrous bands. Microscopy confirmed that there was no amnion overlying the chorion which was thickened and infiltrated with chronic inflammatory cells (Figs. 5 and 6).

Microscopy of Limb Lesion

Right Stump. Neither the bone, exposed soft tissue nor skin were undergoing repair (Fig. 7). Epithelial cells were piled up at the margin of the defect but lacked a proliferative basal layer or normal stratification. Necrotic soft tissue around the bone was mixed with mesenchymal cells and, near the tip, with collagen fibers. Several large vessels, in no way resembling the small vessels of healthy granulation tissue, were clustered near the compressed necrotic tissue of the stump (Fig. 8). There was no removal of dead tissue by phagocytosis.

Left Knee Ulcer. Flattened perichondrium and bare cartilage formed the base of the ulcer. Epithelial cells stopped abruptly at the margin of the defect, those nearest the edge being flattened and necrotic. There was no formation of granulation tissue and no phagocytosis of necrotic material.

Left Foot. The terminal phalanx of the great toe, part of the middle phalanx, and all of the terminal phalanx of the second toe, part of the terminal phalanx of the third and fourth toes, and all of the terminal phalanx of the fifth toe were missing. Epithelium was intact over the surface of all five digits but it was thinner and not keratinized over the great toe and to a lesser extent over the fourth toe. There was some disorganization of cartilage formation at the tip of the proximal phalanx of the great toe without tissue reaction here or elsewhere in the foot.

Left Hand. All or most of the distal phalanges of the third, fourth, and fifth digits were missing. Epithelium covered the digits except at the tip of the third finger where it was compressed and necrotic. At the tip of the fourth finger there was an epithelium-covered skin tag with a ring

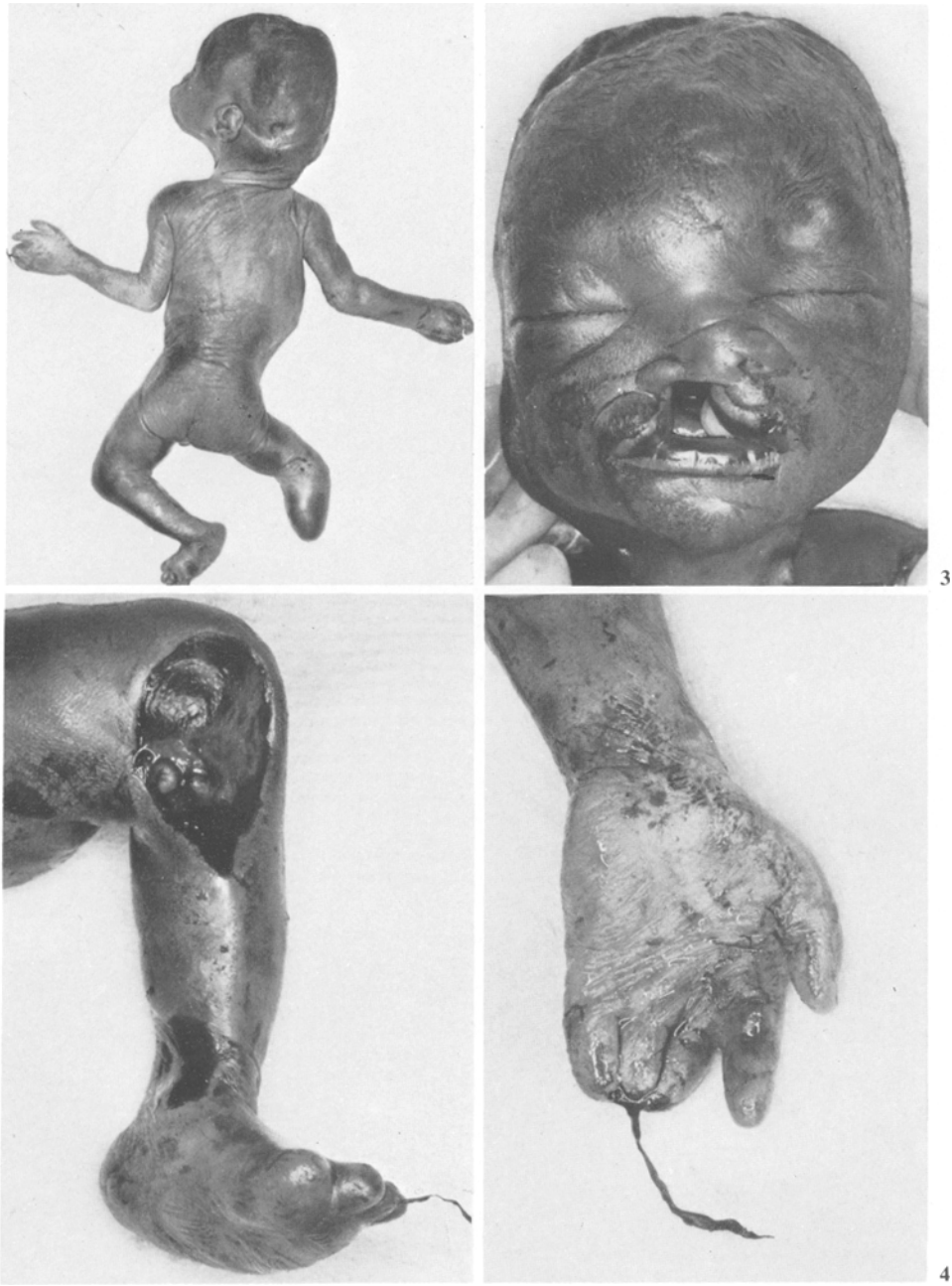

Fig. 1. (CCFA#4176) Posterior view of the infant to show amputation of the digits of both hands, a below-knee amputation of the right leg, and attachment of fibrous strings to the left hand and left foot

Fig. 2. Full face to show complete right unilateral cleft lip and palate. The left nostril is intact

Fig. 3. Left leg showing amputation of the distal phalanges and a recent ulcer on the medial aspect of the knee. A fibrous string is attached to the stump of the third toe

Fig. 4. Left hand showing amputation of the distal phalanges of the third, fourth and fifth digits

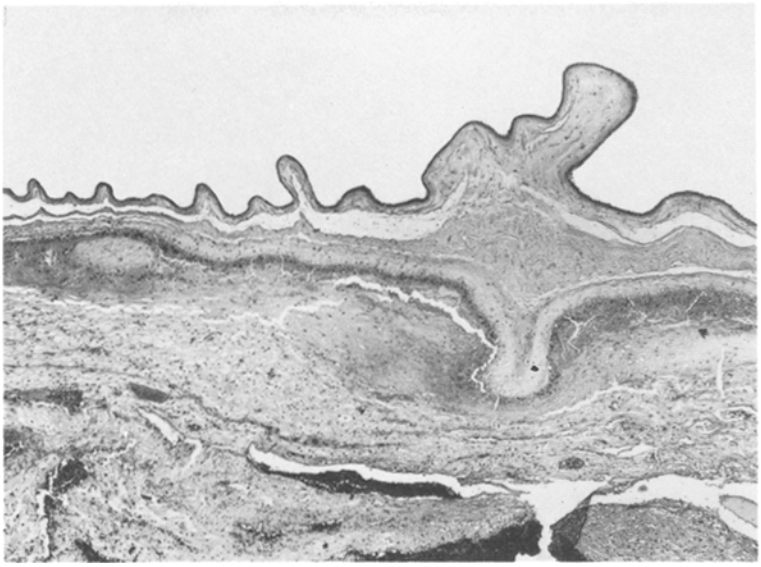

Fig. 5. Photomicrograph of a normal placenta to show the normal line of cleavage between amnion and chorion. Hematoxylin and eosin. ×40

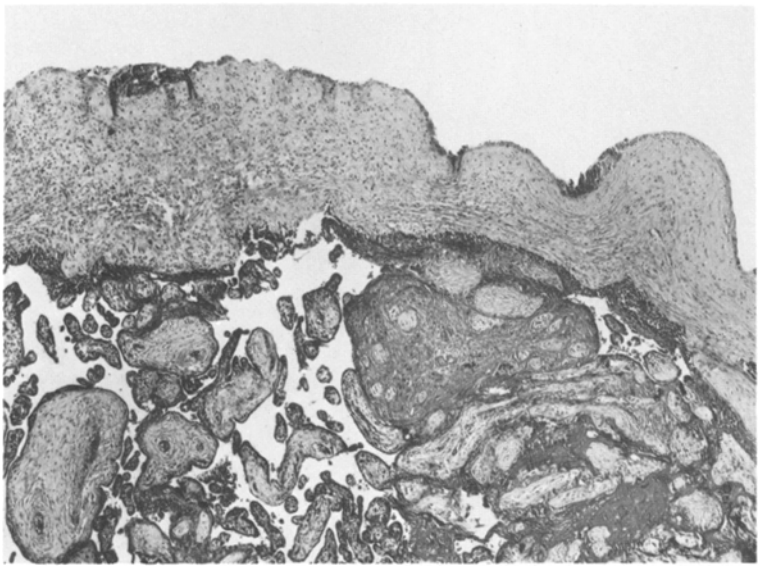

Fig. 6. Photomicrograph of the infant's placenta to show thickening and inflammatory cell infiltration of the chorion and absence of the amnion. Hematoxylin and eosin. ×40

of devitalized epithelium at its base (Fig. 9). There was some thickening of subcutaneous tissue in the region of extrinsic syndactyly but no vascular engorgement and no inflammatory cell infiltration.

Right Hand. All but the distal part of the proximal phalanges of third, fourth and fifth digits were missing. The stump of the proximal phalanx of the fourth finger extended slightly beyond the other stumps and was covered by a mass of amorphous necrotic tissue. Under this lesion,

Fig. 7. Longitudinal section of the right leg to show protrusion of the tibia and non-epithelialization of the stump. Elastic van Gieson stain. ×4

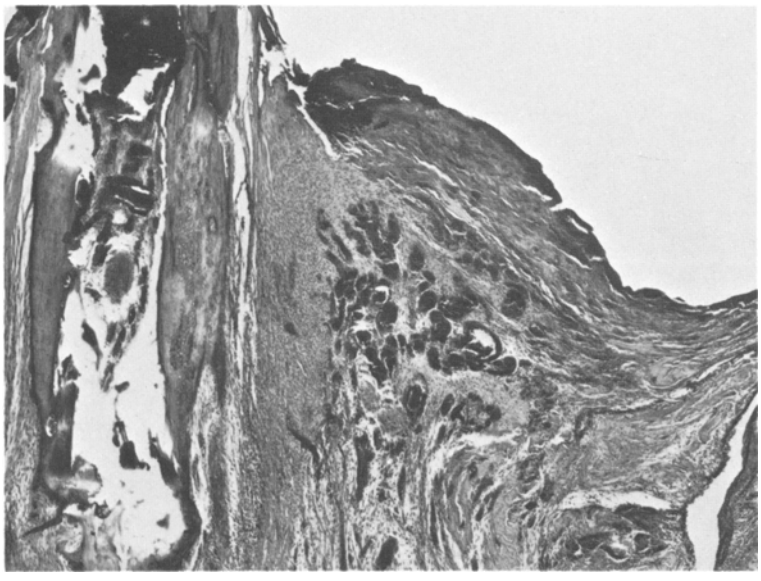

Fig. 8. Photomicrograph to show that the stump adjacent to the tibia is sealed by coagulation of necrotic tissue. Thick-walled blood vessels but no healthy granulation tissue are seen beneath the surface. Hematoxylin and eosin. ×40

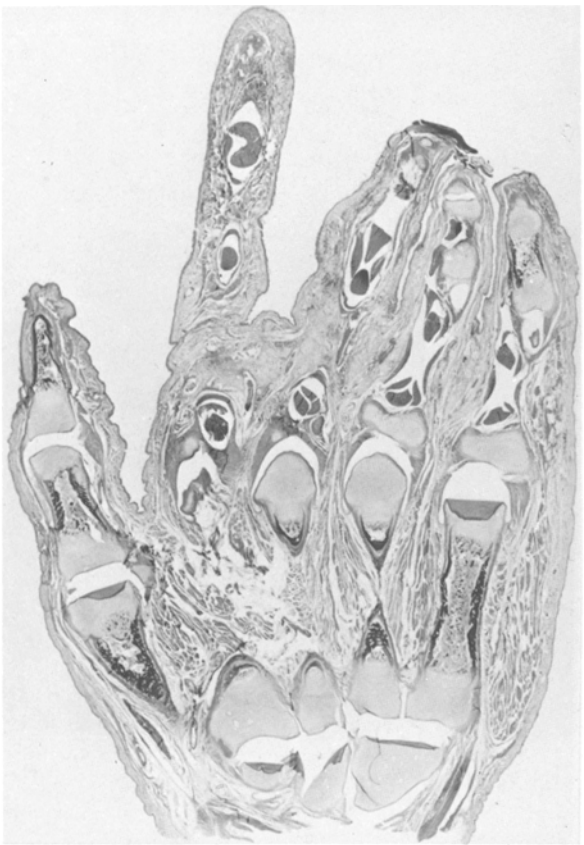

Fig. 9. Longitudinal section of the left hand to show extrinsic syndactyly of the third, fourth and fifth fingers. Development of the hand is normal. Elastic van Gieson. ×4

there was a nodule of cartilage separated from the shaft of the proximal phalanx by a band of fibrous tissue and proliferating periosteal cells. The distal part of the phalanx was ossified but the base was fragmented. Some of the fragments were surrounded by osteoclasts but in general there was little tissue reaction or repair.

Discussion

Intrauterine injuries in which amputation or constriction bands are associeted with fragments of amnion attached to the lesions have been grouped together as the amniotic band syndrome (Blanc, 1970; Chemke et al., 1973). The subject has been reviewed in a monograph by Torpin (1968) who described the following criteria for distinguishing between an amniotic and a genetic origin for the lesions: 1) those produced by bands are asymmetrical, 2) syndactyly is distal, the proximal parts of the digits being free, 3) there are no bony defects or growth retardation of the remaining parts as in genetically determined lesions, 4) fibrous bands apparently originating from a denuded chorion are often

attached to the limbs. Most dysmorphologists accept Torpin's suggestion that the amputations are a result of arterial occlusion by external pressure leading to ischemic necrosis. An earlier explanation put forward by Streeter (1930) and recently revived by McKenzie (1974) was that focal dysplasia and subsequent vascular occlusion was responsible for the lesions and that the bands were formed by organization of exudate that had floated out into the amniotic fluid.

The main weakness of the favored theory is that the cause of the amnion rupture is often unknown. Ossipoff and Hall (1977) reviewed the literature and analyzed 24 cases of their own in an attempt to discover etiologic factors. Only 23 percent of their cases gave a history of abdominal trauma during pregnancy. They concluded that amnion rupture may be an intrauterine phenomenon, unrelated to genetic or external events, occurring spontaneously in a certain number of otherwise normal pregnancies.

It is not possible to date the amputations in our infant in the absence of a history of trauma. However, the ulcer on the medial aspect of the left leg was fresh. Judging from its position, it was probably produced by constant rubbing by the sharp piece of bone protruding from the stump as in a similar case described by Kohler (1962). Neither in this nor in the older lesions was there any inflammatory response as would have occurred in post-natal life.

Experimental intrauterine wound healing has been studied in fetal rats (Dixon, 1960; Sopher, 1975; Goss, 1977), rabbits (Hess, 1954; Somasundaram and Prathap, 1970, 1972), lambs (Burrington, 1971), opossums (Block, 1960), and baboons (Sopher, 1975). Other studies involving experimental and spontaneous fetal responses to bacterial and non-bacterial irritating substances are outside the scope of this review.

Tissue responses were studied in the skin, with the exception of Hess's experiments in which the entire vertebral column and overlying tissues were severed, creating lesions that were not comparable with those of other workers. In all instances, intrauterine healing before term differed from postnatal healing. In prenatal healing, the wound was filled by local mesenchymal proliferation without elaboration of collagen. There was no capillary dilatation, and consequently no fibrinous exudate or scab formation, no polymorphonuclear leukocyte infiltration, and no formation of granulation tissue. Dixon showed that in rats, conversion from the fetal to the postnatal response took place just before term, on the 18th day of a gestational period of 22 days.

In contrast to the observed constant characteristics of intrauterine wound healing, the degree of epithelial regeneration over the site of wounding was different in different animals. In rats, Dixon, Sopher and Goss, working independently, agreed that epithelialization of the raw surface was rapid and complete. Block found the same to be true for pouch young opossums, Burrington for lambs, and Somasundaram and Prathap for rabbits, as long as the wound was protected from amniotic fluid. No migration of epithelium was observed in fetal rabbits when the wounds were exposed to amniotic fluid in the normal way nor in baboons nor in the present human instance. It is not clear why wounds that were covered by a silastic sheet became epithelialized but uncovered wounds under the same circumstances did not. It is generally accepted that one of the reasons for reepithelialization of skin wounds is the lack of contact

inhibition between cells, a situation that should be independent of the immediate environment under sterile conditions.

Various explanations have been proposed for the difference between fetal and neonatal healing, the latter being of the adult type. Dixon suggested that the essential difference was in the behavior of the blood vessels and correlated this difference with low levels of histamine in the skin of developing rats. Although well-documented, this explanation has attracted little attention by other workers in the field. Emphasis has been placed on the alleged low level of polymorphonuclear leukocytes in the body as a whole to explain their absence in the wound. However, the work of Playfair, Wolfendale and Kay (1963) has cast serious doubt on this interpretation in man. They studied the peripheral blood count of fetuses obtained by therapeutic or spontaneous abortion ranging in age from 8 to 27 weeks. At 16 weeks of gestation, an aborted fetus that had experienced labor and vaginal delivery was able to produce a neutrophil leukocytosis of 5,000/c.mm. The figures for blood cells of all sorts were lower in fetuses that were delivered by hysterotomy. They repeated the teleological argument of others that a fetus protected by the sterile intrauterine environment under most circumstances does not need an inflammatory response. However, they pointed out that tissue death is a normal component of development and towards the end of pregnancy dying cells in the degenerating placenta may act as a stimulus to the proliferation of scavengers.

Cleft lip and palate in the present case may be part of the amniotic band syndrome. Facial clefts together with micrognathia, intrauterine amputations, and clubfoot were produced in fetal rats by removal of amniotic fluid (Poswillo, 1966; Singh, Mathur and Singh, 1974; Kennedy and Persaud, 1977). Facial clefts were produced in mice by Trasler, Walker and Fraser (1956) and Walker (1959), who suggested that intrauterine compression following loss of amniotic fluid may have forced the lower jaw and tongue upward between the palatal shelves preventing fusion. In view of the possible damage to human embryos in women undergoing amniocentesis before palatal fusion at about the 47th day of gestation, Poswillo (1972) removed a small quantity of amniotic fluid from macaque monkeys in the first trimester. No lesions were produced and subsequent development was normal. Numerous large series of women who had had amniocentesis show that this procedure is not hazardous to the developing infants (for example, Vrettos, Koliopoulos and Panayotou, 1975). In our infant, it is possible that amniotic rupture and temporary loss of fluid occurred at the time of palatal fusion but was soon replaced allowing development to proceed without the other results of intrauterine compression caused by oligohydramnios (Thomas and Smith, 1974). A similar facial cleft was found in association with constriction bands of the right arm in case 10 described by Baker and Rudolph (1971). However, if facial clefts are part of the amniotic band syndrome, one would expect a higher incidence in the 500 cases reported in the literature than has been described (Rowlatt, 1978). Repair here, as in other congential anatomalies occurring in the first trimester, is by mesenchymal proliferation and not by fibrous tissue scar formation.

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