Most physiotherapists, in due course, are asked to take part in the management of a child with a congenital deformity. Involvement with such a child inevitably provokes the question “Why was this child born handicapped?” In other words, what went wrong in the embryo to result in this birth defect?

The question has puzzled mankind for many centuries, and still begs an answer. The unknown invites speculation, and history provides ample evidence of speculation on this particular question through the ages.

Supernatural interference has always been a favourite explanation, and is not without its adherents today. The Greeks and Romans believed that earthquakes, eclipse, comets and the like were responsible for deformities, and were an expression of the wrath of their gods. Aristotle, in the fourth century B.C., however, wrote that a monstrosity was a deviation from nature and was due to an inherent condition in the male and female elements of generation, although sperm and ovum were unknown at that time. He also stated an alternative cause as external pressure upon the baby in the womb, which could distort tissue growth. Thus, two thousand years ago, Aristotle was aware of the two major causes of congenital abnormality, heredity and environment.

For a thousand years, no advance was made in our knowledge. Supernatural influences reigned supreme, only adapting to suit prevailing fashions. In the middle ages, divine retribution for one’s sins, and acts of the devil were popular. Another prevalent theory was that of “maternal impression” (Dodds, 1961), where a bad fright or some shocking experience was believed to influence the course of pregnancy and produce a deformed child. This maternal impression theory also survives today.

Science revived in the seventeenth century and people started to wonder how “maternal impression” worked. How was the mother’s shock transmitted to the baby? Harvey, who first described the circulation of the blood, examined pregnant deer, and found that the blood stream of the foetus is entirely separate from that of the mother. He declared that there was no obvious link through the blood stream by which “maternal impressions” might pass. A century later, Haller drew similar conclusions regarding the nervous system, when he demonstrated that there is no continuity of nervous tissue between mother and foetus.

The eighteenth century saw increasing interest in the study of reproduction and antenatal physiology. Scientists became increasingly sceptical and critical of existing theories as they experimented and established more and more facts about life before birth. The microscope was invented, and thereafter embryology and histology blossomed into basic sciences.

In the nineteenth century, the science of genetics became established from the work of Mendel, an Austrian monk who observed and recorded the laws of inheritance in experiments with plants in the garden of his monastery. He produced evidence for the concept that characteristics can be transmitted from generation to generation through the original seed or pollen. This genetic concept explains familial diseases and inherited malformations, and has gained increasing popularity in the twentieth century. However, a great proportion of malformations occur in families where there is no previous history of deformity, so genetics does not explain all cases by any means.

_Aust.J.Physiother., XXI, 4, December, 1975_
In 1941, the Sydney ophthalmologist Gregg, observed the link between German measles in early pregnancy and congenital cataracts and heart disease in babies. Gregg's observations forced medical scientists to look again at environmental factors, for the defects he observed were clearly not caused by any inherited genetic abnormality, but by injury to a normal embryo through an outside agent, the rubella virus. The possibility that a virus infecting the mother can cross the placenta and infect and injure the embryo was a new and very important contribution to scientific knowledge.

From 1958 to 1961, there was an outbreak of exceedingly rare limb deformities in several countries, maximum in Germany where it reached epidemic proportions. Lenz, a paediatrician in Hamburg, had referred to him an increasing number of babies with severe reduction deformities of the limbs. On questioning the mothers, he found that they had taken the sedative Contergan (thalidomide) in early pregnancy. He presented his findings to a meeting of paediatricians in Dusseldorf in November 1961. The drug was withdrawn from sale in Germany a few days later. Nine months later, the epidemic ceased.

This was another big step forward in our understanding of deformities. It established that a drug taken by the mother can cross the placenta and injure the embryo.

In human terms, thalidomide was a large scale tragedy that is still being enacted today as the children reach adolescence. In scientific terms, thalidomide presents, with renewed force, the challenge of the old unanswered question "What went wrong in the embryo?" That the drug caused limb defects is well known, but it is not generally appreciated that thalidomide produced a wide range of internal malformations, such as congenital heart disease, ear and eye anomalies, cranial nerve palsies, spina bifida, cleft palate, atresias and stenosis of the gut, aplasia and hypoplasia of kidney, lung, spleen, etc. In fact, thalidomide can mimic a large range of genetic and sporadic deformities. It has been recognised by scientists that thalidomide provides a model for the study of congenital malformations in general. If we knew how and where thalidomide acted in the embryo, we would be close to answering the question of what goes wrong in many non-thalidomide cases.

Scientists set about studying animal models, using this drug. Thalidomide deformities have been produced in rabbits, mice, chickens, hamsters, cats, dogs, monkeys and apes. Much valuable knowledge has resulted from these experiments in spite of failure to answer the crucial question. A major difficulty has been that the drug acts on the embryo very early, when it is so tiny and delicate that normal methods of tissue sectioning are comparatively crude and difficult to apply.

When conventional methods fail, unconventional methods should be tried. Diagnostic radiology appeared to have been overlooked as a scientific method in this field. Yet, an X-ray picture is essentially a reflection of anatomy and pathology, and most diseases have characteristic X-ray changes from which a radiologist can deduce their cause. I wondered what the characteristics of these deformed bones and joints were. I wondered whether one could work backwards from the radiology of the thalidomide children to an understanding of what had occurred in the embryo. Nobody had approached the problem in this way in the past, so I decided to analyse the X-ray films and to define the nature of the process if I could.

After a detailed study of two series of cases (Australia and the United Kingdom, 1972), I became convinced of two outstanding features. The nature of the bone and joint changes was extraordinarily similar to that seen in adults with sensory peripheral neuropathy of longstanding. In other words, the children had congenital neuropathic bones and congenital Charcot's joints (McCredie, 1973). This meant that there had probably been a sensory peripheral neuropathy in the embryo. The other feature was that the distribution of this disease did not obey the laws of bone disease radiologically, but it did seem to fit the dermatome pattern of the limbs. For instance, the commonest upper limb defect was absent radius with absent, hypoplastic or tri-phalangeal thumb. The structures pruned out of the arm all lay beneath the sixth cer-
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tical dermatome. This suggested an injury to the developing sixth cervical sensory nerves (McCredie, 1975). Thus, both the nature and the distribution of the limb defects suggested that the pathology should be sought within the sensory nerves.

It seemed from the literature on animal experiments with thalidomide, that researchers had assumed that the drug acted on mesoderm, the middle of the three layers of the embryo from which bones, muscles and internal organs arise. My radiological study indicated that the drug injured the ectoderm, or outer embryonic layer, from which skin and nervous tissue are derived. In particular, I suspected that the drug attacked the neural crest, the part of the ectoderm from which peripheral sensory and autonomic nerves are derived.

This idea was scientific heresy, I knew, so I was careful to consolidate and test it as much as possible before exposing it in the scientific journals. In 1972, I was given study leave from Royal Prince Alfred Hospital, and I spent several weeks exploring the literature in the library of the Royal Society of Medicine in London. I was able to find a number of facts which supported my hypothesis. The most exciting article was about newts, which showed that the sensory nerve stimulates limb growth in these amphibia (Singer, 1943). This phenomenon is known as the trophic function of the sensory nerve. Translated to the human embryo, this biological principle supported my hypothesis that sensory nerve damage in the embryo resulted in defective growth of the related limb segments. Extrapolation of this biological principle to the embryo is supported by the knowledge that monsters are born without brain, heart or spinal cord, yet all these have had sensory ganglia recorded.

To test my hypothesis, I studied the dorsal root ganglia of newborn rabbits deformed by thalidomide. In the ganglia related to the deformities, we have found immature nerve cells (McCredie and McLeod, 1974). It seems that the drug can inhibit the normal maturation of the sensory neurons, and at the same time interfere with the neural trophic function, resulting in growth failure.

How can the internal deformities be explained? The answer is through the neural crest. That special section of embryonic ectoderm gives rise to the autonomic as well as the sensory nerves. Let us suppose that the autonomic nerves normally exert a trophic influence on the internal organs they supply. Then an insult to the neural crest might well cause impairment of trophic action of the autonomic nerves on the viscera, as well as that of the sensory nerves on the limbs. Atresia, stenosis and hypoplasia can thus be theoretically explained. Spina bifida, cleft palate, etc., represent impairment of growth towards the midline due to failure of trophic stimulus from their sensory nerves. The theory can be expanded to explain many other congenital malformations (McCredie, 1974). I believe it offers a rational alternative to the superstitious concepts of the past.

When you next treat a child crippled by some birth defect, you will perhaps reflect upon the possibility of embryonic neuropathy, and pause to wonder what physical or chemical agent has interfered with neural crest development in the embryo of this child.

REFERENCES