RES MEDICA
Journal of the Royal Medical Society

Aetiological Factors in Congenital Abnormalities

Alexander M. Davidson
B.Sc.

Abstract
The problem of congenital abnormalities has been with us for many years. The surviving records of some of the oldest civilisations depict cases of congenital malformations. Achondroplasia is found in Egyptian paintings over 5,000 years old and the god Phtah revered at Memphis, the ancient capital of Egypt, is without doubt one of these cases. Club foot and cleft palate have also been detected in records and mummies of the Egyptian era. In other ancient civilisations, abnormalities have also been recorded. Prehistoric Peruvian pottery has been found to depict hare-lip and other malformations. Greek mythology included many instances of monsters which presumably have their origin in abnormalities. However, not all references to monsters by the Greeks were confined to mythology. Aristotle describes a monstrosity as contrary to the most usual course of nature. This is probably the earliest reference to someone thinking that congenital abnormalities are due to the unusual development of a normal process.

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Autumn 1964, 4(3): 13-16
doi: 10.2218/resmedica.v4i3.427

AETIOLOGICAL FACTORS IN CONGENITAL ABNORMALITIES

By ALEXANDER M. DAVIDSON, B.Sc.

Based on a Dissertation read before the Royal Medical Society on Friday, February 14th, 1964

I. *INTRODUCTION*

The problem of congenital abnormalities has been with us for many years. The surviving records of some of the oldest civilisations depict cases of congenital malformations. Achondroplasia is found in Egyptian paintings over 5,000 years old and the god Phtah revered at Memphis, the ancient capital of Egypt, is without doubt one of these cases. Club foot and cleft palate have also been detected in records and mummies of the Egyptian era.

In other ancient civilisations, abnormalities have also been recorded. Prehistoric Peruvian pottery has been found to depict hare-lip and other malformations. Greek mythology included many instances of monsters which presumably have their origin in abnormalities. However, not all references to monsters by the Greeks were confined to mythology. Aristotle describes a monstrosity as contrary to the most usual course of nature. This is probably the earliest reference to someone thinking that congenital abnormalities are due to the unusual development of a normal process.

Although painting and sculptures of abnormalities exist from some of the earliest civilisations it is not until fairly recent times that any effort has been made to determine the aetiology of such defects. In the Middle Ages the birth of a congenitally defective child was viewed with superstition and fear. Even physicians were inclined to ascribe such events to the supernatural and mystical cause. The famous French surgeon Ambroise Paré tabulated the causes of monstrosity beginning with God and ending with the Devil. This list is far from being ridiculous, and many of his ideas have a firm foundation. The causes he gives fall into three large categories—religion and superstition; environmental factors; and hereditary. Although we would generally agree that God and the Devil have no direct intervention, the other two reasons still hold.

It was not until the 18th century that some of our present day ideas about malformations had their scientific foundations. There began the collection and examination of embryos. The normal development of embryo and foetus was investigated and the deviation from normal noted. From such studies Mickel was able to show that some abnormalities are not due to random growth but persistence of some stage of normal embryonic development. It was not long before many theories arose explaining all abnormalities on this basis. This prompted

investigations into factors which could influence the development of an embryo and thus the era of experimental embryology began. Since the early experiments, work has increased in amount and in variety.

II. *AETIOLOGY*

The causation of congenital malformations can fall into two main groups: Intrinsic factors and Extrinsic factors. The intrinsic factors are genetically determined anomalies either due to alteration of the gene or the chromosome. The extrinsic factors include all agents which can have an effect on the normally developing child. This list includes such factors as radiation, drugs, mechanical disorders of the womb producing pressure symptoms, infections, dietary deficiencies, hormonal imbalance and environmental factors. However, although this list is impressive by its length, it is important to realise that the actiology of most malformations is not clearly understood. Even in cases where a causal agent can be detected it is still obscure how many of these factors produce their effect.

INTRINSIC FACTORS

Genetic and Chromosomal

In the case of the chromosome there are two main types of aberrations, either anomalies of number or translocation of part of the chromosome. Probably the best known anomaly of number is trisomy 21 associated with mongalism. There is an interesting malformation of the hands in such patients -- a horizontal palmar crease and characteristic finger prints are seen. This was probably the first congenital condition connected to a chromosomal defect. Other trisomy conditions have since been recognised. In trisomy 17-18 there is a flexion deformity of the fingers, mental retardation, hypoplasia of the mandible, small mouth, low set ears and ventricular septal defect. Another recognised condition is trisomy 13-15 in which polydactyly —frequently quadrilateral, mental retardation and eye defects are seen. How the extra chromosome in such cases produces these manifestations is pure conjecture.

Alterations in the gene can lead to a wide variety of conditions. Hereditary malformations of the digits are fairly common and can in some cases be traced back through many generations. Phalangeal synostosis can be traced back for fifteen generations in the family tree of the Earl of Shrewsbury. In many instances a genetic defect may not produce such a simple picture. In arachnodactyly due to a dominant gene, there is a multitude of malformations both ectodermal and mesodermal. There are long hands with spidery fingers, spinal anomalies are common, including hemivertebrae, the eyes are often affected in numerous ways and heart anomalies are common. The fact that there are multiple anomalies, some of which may occur alone, lead many people to think that such a syndrome was due, not to one gene, but multiple gene abnormalities. The present day feeling is that the gene is no observer of germ layers and that there is almost no limit to the effects that they can produce. However, it may be that with further research a syndrome with multiple defects will be traced to a single enzyme defect in a similar way to the recent elucidation of phenylketonuria. Alternately the defect may be in an organiser which would be much more difficult to trace and characterise.

EXTRINSIC FACTORS

Radiation

At the present time there are three main means whereby we can be exposed to ionizing radiation; during therapy, from environmental background and by accidents.

Radiotherapy may play an important part in the treatment of disease. As it is normally administered by competent people, the hazard from this source is considerably reduced. In many cases, however, the difference between adequate and harmful dose is small and difficult to judge. Changing the dose of radiation by as little as 10% may render the dose lethal, a point seldom considered by people not used to dealing with therapeutic agents having this fine borderline between curvative and lethal doses.

The environmental radiation has always been present but recently due to such devices as diagnostic X-rays, the explosion of test nuclear bombs in the atmosphere, the development of peaceful uses of atomic energy and many other causes the background radiation has increased. This means that in his lifetime man is exposed to a higher level of whole body ionizing radiation. Besides this increase in background radiation there is an increase in the number of individuals employed in the manufacture and use of radioactive materials. The effect of such long-term low-level exposure is not known but the possibility of delayed effects appearing in later generations must be borne in mind.

The third means of exposure is due to an accident at some nuclear installation or during wartime. The effects of this vary from death to little or no detectable change. Accidental exposures of these kinds are rare and it is to be hoped that no further intentional high yield explosion will ever take place.

Radiation can produce cellular damage by different methods. It may, if strong enough, produce cell death in the intermitotic phase or in cells incapable of further division. It may delay or completely inhibit mitoses, or if mitoses takes place there may be chromosomal changes or alteration in genes. Mutations in chromosomes can be seen as visible breaks and structural rearrangement of the individual chromosomes. Gene mutations, on the other hand, are noticed only by the effect they produce. A gene is regarded as a small discreet part of a D.N.A. molecule and a mutation is caused by a change in its chemical composition or steric arrangement. Naturally occurring mutations may be the result of background radiation on the gene.

The amount of harm which a given dose of radiation will produce is impossible to estimate. If the gene is harmful, such as the one for haemophilia, then any increase in the mutation rate from normal to pathological will cause an increase in handicapped people. However, many genes are not capable of producing pathological alleles.

It is therefore necessary with regard to radiation to ensure that workers and patients receive only the minimum amount of radiation and that pregnant women receive radiation only after careful consideration.

Drug-induced

There is no doubt that drugs of various kind can produce malformations. This was brought out dramatically recently by the thalidomide disaster. It is now known that thalidomide taken any time between conception and three months is likely to produce an abnormality of the limbs. The type of malformation produced is variable. There is frequently a small haemangioma on the forehead, the bridge of the nose is depressed and small ears are not uncommon, phocomelia or seal-like limbs are usual quadrilateral and are the commonest limb deformity. However, in the limbs there may be all degrees of malformation, from complete absence of the long bones to absence of the thumbs only. Defective or absent radius with accompanying deviation of the hand is common. Single limb defects are rare although in a quadrilaterally affected child one limb may be more affected than the others. In some children mental retardation may be noticed but this is by no means common.

In discussing thalidomide it is as well to keep in mind the number of deformities it produced. Between 1960 and the end of August 1962 there were 805 live-born children with limb deformities in England and Wales. Of these 153 subsequently died leaving 652. Of this number only 244 were due to the mother having ingested thalidomide at some time during pregnancy. In Scotland the situation was a little better with only 51 of the 114 deformed babies being due to the ingestion of thalidomide.

Other drugs are also known to produce foetal malformations. Drugs which inhibit tumour growth do so in many cases because the tumour cells are divided more rapidly than the normal body cells. With this in mind it can clearly be seen that these drugs will exert some effect on the actively growing embryo. It is understandable that the embryo may experience a temporary inhibition of growth resulting in distortion. To a large extent it will depend upon time of administration and dosage of the drug whether a deformity or a stillbirth will follow. Many other types of drugs have been incriminated in congenital malformations but in many cases it is difficult to prove the relationship between the drug and the malformation produced. It is even more difficult to prove that a given drug will not produce abnormalities.

The important factor to bear in mind is that

in the majority of cases the malformations produced by drugs can be avoided. To achieve this a greater control over the prescribing of drugs linked with congenital malformations must be exercised. New drugs must be used with caution until they have been proved by time to be safe. While all species do not react in the same manner to drugs it would be advisable to test new drugs on pregnant animals of several species receiving variable doses of drugs at different stages of pregnancy. In this way some idea about the teratogenic actions of a drug may be revealed but it is by no means an absolute test.

Infections

Following the discovery of bacteria it was thought that congenital malformations were due to bacterial infection. It was known that syphilis would cause foetal death with subsequent abortion and so syphilis was named as the prime cause of malformations. However, with the introduction of therapy against syphilis and the subsequent fall in its incidence not followed by a corresponding fall in malformations investigations turned in other directions. As with so many other cases, investigators were looking for one cause of malformation. We now know that this concept is false and that bacteria and viruses do have a part to play in the aetiology of abnormalities.

It is well known that rubella in the first trimester of pregnancy may produce malformations. The mechanism whereby the rubella virus produces its lesion is unknown but it has been suggested that it is due to the localisation of the virus in the developing embryonic cells causing their death. Other theories are that the virus initiates a metabolic defect or that it constricts blood vessels producing anoxia. However, as with most conditions which have a multiplicity of theories as to aetiology little is really known as to the mode of action of the rubella virus.

Dietary Deficiencies

Although malformations can be produced in animals fed on diets lacking in some constituents these malformations are not found in humans. The only dietary factor of any proved significance is iodine. Endemic cretinism occurs in areas where endemic goitre is common. The child is born with an enlarged thyroid and shows a generalised lesion of bone, the growth of which is severely impaired. The bones are smaller and shorter than normal due to a defect in endochondral and intra-membranous ossification. An interesting feature is the presence of deaf mutism in many of the affected cases.

Hormones

Disturbances in hormones in the mother have been regarded as causes of congenital anomalies but this is not based on sound evidence. About the only defect due to this cause has been the appearance of masculinised genitalia of some female children born to mothers who received synthetic progesterones for threatened abortion.

III. *SUMMARY*

In this article only some of the known causes of congenital malformations are discussed. The aetiology of many conditions has still to be worked out and with further elucidation the door may be opened towards prevention of many of these crippling conditions.

REFERENCES

CARTER, C. O. (1963). *Practitioner, 191*, 129.
Ciba Foundation Symposium (1960). "Congenital Malformations."
British Medical Journal (1962). Editorial, *2*, 1176.
Fraser Roberts, J. A. (1959). "An Introduction to Medical Genetics", 2nd ed. London: Oxford University Press.
Harrison, C. V. (ed.) (1960). "Recent Advances in Pathology." London: J. & A. Churchill.
Ward, S. P. (1962). *Brit. med. J., 2*, 646.
Woollam, D. H. M. (1962). *Brit. med. J., 2*, 406.