Extrinsic factors in the genesis of congenital heart disease¹

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The extrinsic factors responsible for the production of congenital heart malformations both clinically and experimentally are reviewed.

The method to be followed in the investigation of extrinsic factors as teratogenic agents for the heart and the great vessels both clinically and experimentally is studied.

With Saxen and Rapola's work as a starting point, an hypothesis is proposed on the pathogenesis of congenital heart disease based on the alteration of the morphogenetic processes which normally participate in the development of the heart and the great vessels, such as the morphogenetic movements, growth, and degeneration, the disturbance of which originates those malformations.

The most common congenital cardiopathies are interpreted by combining this hypothesis with others previously proposed by one of us (de la Cruz and da Rocha, 1956; de la Cruz et al., 1959, 1964) on truncoconal malformations, and ventricular and atrial septal defects.

The main objectives to be attained in a programme of prevention of congenital heart disease caused by extrinsic factors are pointed out.

The evidence that rubella virus causes congenital heart disease (Gregg, 1941; Swan *et al.*, 1944; Swan and Tostevin, 1946; Michaels and Mellin, 1960); the discovery of the teratogenic action for the heart of the Coxsackie B virus (Brown, 1966, 1969); the discovery that sub-clinical forms of viral diseases are teratogenous (Evans and Brown, 1963; Brown, 1966); the advances in epidemiology and immunology which permit the prospective studies of the viral diseases by means of their early serological diagnosis (McIntosh *et al.*, 1954; McDonald, 1958; Brown, 1969); the recent development of the vaccine for rubella virus which provides preventive therapy (Marshall, Dudgeon, and Peckham, 1969); and the recent studies in genetics which point to the importance of multifactorial inheritance and its interrelation with the extrinsic factors in the genesis of some congenital heart disease (Nora, 1968), have led us to review extrinsic factors as teratogenous agents for the heart.

In this paper brief consideration is made of the extrinsic factors as aetiological agents in congenital heart disease, both in their clinical and experimental aspects, and the method to

be followed in studying them is examined. An hypothesis is also presented on the possible pathogenesis of congenital cardiopathies, which is valid for the extrinsic and intrinsic factors as causative agents. General outlines are given for the prevention of these diseases in the particular case of extrinsic factors.

Aetiological factors

The aetiological factors of congenital malformations are called teratogenous agents: these interfere with the normal development of the embryo, causing defects in it. In their study one must consider the extrinsic factors, the intrinsic factors, and the interrelation between both.

The extrinsic factors are physical, chemical, or biological agents different from the embryonic genoma, which may act on it or on the cytoplasm or on both, affecting the cells which are in the process of differentiation (Fig. 1).

The intrinsic factors are apparently spontaneous alterations in the desoxyribonucleic acid of the nucleus within the chromosomes. They are, therefore, of genetic origin. Their alterations may be quantitative, such as in

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FIG. 1 Diagram representing the action of extrinsic factors on the embryonic cells in the process of differentiation.

trisomy, translocations, and deletions, or qualitative, such as in dominant or recessive inheritance, linked to somatic or sexual chromosomes, and multifactorial inheritance.

The division of intrinsic and extrinsic factors is mostly conventional, since they are both intimately interrelated. For instance, it is a well-known fact that the effect of drugs with teratogenic action (extrinsic factor) depends on the species or the strain used, whose difference lies in their genotype. Both factors are present in the genesis of congenital malformations and the division into intrinsic and extrinsic is one of predominance and not of exclusiveness. The analysis of teratogenous agents will be considered from the clinical and experimental points of view.

Clinical studies The clinical studies have usually referred to viruses (Gregg, 1941; Brown, 1966; Manson, Logan, and Loy, 1960), hypoxia (Alzamora *et al.*, 1953; Espino-Vela, 1967), drugs (Lenz, 1962; Smithells, 1966), maternal hormones (Hoet, Gommers, and Hoet, 1960), and radiation (Hicks and D'Amato, 1966). The clinical in-

vestigations have proved that hypoxia (Alzamora *et al.*, 1953; Chávez *et al.*, 1953; Espino-Vela, 1967), rubella virus (Gregg, 1941; Michaels and Mellin, 1960), and Cocksackie B virus (Brown, 1966, 1969) are teratogenous for the heart.

Hypoxia

Statistical studies have proved that there is a higher incidence of congenital heart disease with arteriovenous shunt in children born in regions at an altitude of about 3000 metres and over above sea-level, as compared with populations at sea-level (shown by Alzamora *et al.*, 1953), comparing the cities of Junin and Lima in Peru and those of Chávez *et al.* (1953) and Espino-Vela (1967) at the altitude of the Mexican plateau. In Junin, ventricular and atrial septal defects are more common, and persistent ductus arteriosus is more common on the Mexican plateau. These clinical findings suggest that hypoxia is a possible causal factor, and this in turn is supported by the experimental work of Ingalls, Curley, and Prindle (1952) who proved its teratogenic effect in mice by producing interventricular septal defects.

The frequent occurrence of congenital heart disease has been pointed out in children born of mothers with congenital heart disease (Ingalls, 1960). This fact could be due to an intrinsic factor related to sex or to an extrinsic factor represented by hypoxia of maternal tissues. It seems as though this latter is the causal factor but a study in large populations is needed in order to reach some valid conclusion.

Virus

The rubella virus causes patency of the ductus arteriosus and ventricular septal defect with greater frequency, and less commonly tetrad of Fallot, transposition of the great vessels, and aortic coarctation (Ingalls, 1960). Recent studies have further clarified the pathogenesis of its action on the embryo. The virus penetrates the embryo through the blood stream, destroying the placental barrier where it becomes fixed in some of the embryo's organs, and causing cellular death and inhibition of cellular multiplication. When these disorders are severe, irreparable lesions are produced in certain organs, which are expressed as malformations. When they are slight, they cause a delay in the growth of organs (Töndury and Smith, 1966). It has also been pointed out that Cocksackie B virus causes cardiomyopathy in the foetus when the mother has been affected in the latter months of pregnancy (Kibrick

and Benirschke, 1956, 1958), and gives rise to congenital cardiopathies when the infection takes place during the first months of gestation (Brown, 1966, 1969).

Experimental studies The experimental study of extrinsic factors has proved that the following agents cause congenital cardiopathies: a diet deficient in vitamin A (Wilson and Warkany, 1950; Wilson, Roth, and Warkany, 1953b), a hypervitaminic A diet (Kalter and Warkany, 1961), a deficiency of pteroilglutamic acid (Nelson, 1960; Baird *et al.*, 1954), a deficiency of riboflavine (Kalter and Warkany, 1957; Nelson *et al.*, 1956), trypan blue (Fox and Goss, 1958; Wilson, 1955), hypoxia (Ingalls *et al.*, 1952), actinomycin D (Tuchmann-Duplessis and Mercier-Parot, 1960), experimental haemodynamic disturbances of the embryo (Rychter and Lemež, 1961), alantoid fluid (de la Cruz *et al.*, 1963), radiation (Wilson, Jordan, and Brent, 1953a; Le Douarin, 1963), and hypothermia during incubation of the chick embryo (de la Cruz, Campillo-Sainz, and Muñoz-Armas, 1966).

Methodology

Teratology is a branch of science which lacks a specific methodology and uses the methods of other disciplines such as epidemiology, genetics, and embryology. For this reason the efficacy of these is doubtful in the investigation of aetiology and pathogenesis of congenital defects. The selection of the method will depend fundamentally on the type of study to be undertaken, either clinical or experimental.

Clinical aspect The clinical method is statistical, with a limitation due to the fact that samples obtained are not a true representation of facts, since many of the embryos with malformations are absorbed *in utero* and aborted in very early stages of development. Another difficulty of the statistical methods in the clinical study of teratogenesis is the impossibility that all the factors remain constant, both for the group under study and for the control group. Some of the factors that may affect the action of the teratogen, either inhibiting it or favouring it, are socioeconomic, geographic, and racial conditions as well as maternal pathological antecedents. Statistical studies may be prospective or retrospective. Each one has precise indications. In the case of virus, though the first reports which began with the work of Gregg (1941) on rubella were retrospective, the dis-

covery of new teratogenous viruses for man, the advance of the techniques for detection of antibodies and, especially, the fact that sub-clinical infections are the ones that most commonly cause congenital malformations, have oriented the epidemiological investigations towards a prospective examination of pregnant women. This is done by means of serial serological measurements of viral antibody content in every woman immediately after the diagnosis of pregnancy is made (Brown, 1966, 1969). In addition, anatomical and histological examinations (Nishimura, 1969) and virus cultures of abortions should be made. Finally the clinical study of newborn children up to those of school age should be undertaken.

Despite the fact that prospective studies are better, retrospective studies should not be discontinued since they may provide the bases for the discovery of new teratogens, and because when one of them appears in man unexpectedly, it is the only method that can be applied.

In evaluating the results of prospective and retrospective studies in the specific example of congenital cardiac malformations, it must be kept in mind that some malformations are asymptomatic during the first years of extra-uterine life, as for instance peripheral stenosis of the pulmonary artery branches and atrial septal defect. Therefore, one must proceed with the observation of children up to school age. Other malformations are asymptomatic throughout the entire life span, such as mirror-image dextrocardia, ventricular inversion with transposition of the great vessels without associated malformations, and some anomalies of the aortic arches which can only be diagnosed by means of careful cardiological study. On the other hand, in the newborn there are functional heart murmurs which mimic congenital cardiopathies and only their course will allow us to discount heart disease.

Experimentation The methodology to be followed in investigating the role of teratogens in congenital heart disease is set out below.

Choice of animal model

The type of animal to be used in the investigation of the teratogenic action of extrinsic factors is that animal, the control group of which shows no spontaneous congenital cardiopathies, with significant statistical value. Such is the case with White Leghorn chickens which do not show spontaneous interventricular septal defects, while the S line of the Brown Leghorn strain, which has a high spontaneous

incidence of these malformations (Rychter, Lemež, and Siller, 1960), constitutes an inadequate animal model for the study of the action of extrinsic factors in teratogenesis of the heart. The choice of animal will also be conditioned by the possible teratogenous agent which will be subject to investigation. For instance, in the case of diets and drugs (Wilson and Fradkin, 1969), species will be selected according to the similarity of their metabolism to that of man, and in the case of the virus those species or races will be chosen which are susceptible to them.

The control group and that subjected to the action of the possible teratogen must be constituted by a population with a significant statistical value. Both groups must be subjected to the same conditions except the teratogen which is to be investigated in one of them. Conditions that must be maintained constant are: race, strain, diet, density of population, climatic conditions, immunization, and age of parents.

Age of embryo

According to concepts established by Wilson (1965), teratogenic agents produce their action during a certain period of development which is called the 'highly teratogenic stage' and is characterized by the maximal susceptibility of the embryo to the teratogen. The 'highly teratogenic stage' is preceded by an embryonic stage 'not susceptible to teratogenesis', in which the embryos do not have a teratogenic response or their response is lethal; it is followed by another stage, 'progressive resistance to teratogenesis', in which the embryo becomes more and more resistant to them until it loses its capacity to respond, and merely shows a delay in overall growth or a similar pathology to that observed in the postnatal period (Fig. 2).

The stage 'not susceptible to teratogenesis' corresponds to the blastular stage of the embryo, one in which the great majority of embryos resist teratogenic actions or die (Fig. 2). While the exact mechanism of the

FIG. 2 Diagrammatic representation of the three general periods of ontogenetic development of mammals. For each period the main events of development and their different susceptibility to the action of teratogens are indicated. (Based in part on the work of Wilson, 1965, p. 252.)

Pre - differentiation period	FERTILIZATION	BLASTULATION		Usually not susceptible to teratogenesis	
period of early differentiation	GASTRULATION Early Morphogenetic Movements Organ - Forming Areas Primary Induction		TUBULATION Late Morphogenetic Movements	Highly susceptible to teratogenesis	
Period of advanced organogenesis	Development of Kidney Secondary Induction	ORGANOGENESIS Development of Reproductive Organs Degeneration	Development of Intestine Differential Growth	Growth	Increasingly resistant to teratogenesis with increasing age

lack of teratogenic response is unknown, this could be explained, because in these developmental stages there are regulating mechanisms by means of which the damaged cells are replaced by other cells capable of substituting them in the morphogenetic processes. If cellular damage were extensive enough to destroy great populations of cells, the response would be lethal.

The maximal period of susceptibility or 'highly teratogenic period' begins with the establishment of the blastodermic layers, and it varies with the different species (Wilson, 1965); it starts on the 5th day after fecundation in the hamster and in the mouse, on the 8th day in the rat, on the 9th day in the rabbit, on the 10th day in the monkey, and from the 11th to the 12th day in man. In fowl, the susceptibility to teratogens takes place a few hours after the beginning of incubation, due to the fact that the pregastrulatory stages have taken place in the genital tract of the mother before laying the egg. During that stage a series of developmental processes takes place, which have an orderly and interrelated sequence. The action of the teratogen will depend on the process that has been altered and

on the disturbances that it in turn originates on the subsequent processes. This period starts with the gastrulatory morphogenetic movements by means of which the different presumptive organ-forming areas are placed in space in such a manner that they may interrelate in order to lead to the processes of primary induction. The organizing processes and primary induction processes take place simultaneously in an integrated fashion and they are of the utmost importance for the subsequent development of organs (Fig. 2). In this stage, teratogenic agents greatly affect the general morphogenesis of the embryo (Fig. 3).

At the end of the gastrulatory morphogenetic movements the presumptive organ-forming areas lose their capacity for regulation, the determination of them is produced and the primary induction systems are established, at which precise time, cellular differentiation at molecular level begins. It could be that, at this stage, extensive and severe malformations may be produced which affect numerous organs.

Once the establishment of the specific organ-forming areas has started, there begin

FIG. 3 Chick embryos after 4 days' incubation, stained with haematoxylin. (A) Embryo inoculated at 17 hours of incubation with active influenza A virus. Observe the great alteration of normal configuration. (B) Normal embryo.

the secondary morphogenetic movements, the processes of secondary induction, of degeneration, and of differential growth, all of which participate in the peculiar morphogenesis of each organ (Fig. 2 and 4).

Though the specific organ-forming areas are determined simultaneously, the morphological and physiological differentiation of the organs takes place usually in different stages of development, and there is a period of maximal differentiation for each one of them in particular. Furthermore, in the same developmental stage different organs are undergoing simultaneous maximal differentiation processes. These may be the reasons why the same teratogen acting on different stages of development produces different morphological alterations (Saxen and Rapola, 1969; Nelson *et al.*, 1956) (Fig. 5), and why different teratogenic agents acting at a certain stage produce characteristic syndromes (Runner, 1959). Besides, different teratogens acting at different stages of development, affecting a certain metabolic cycle, give rise to the same type of defect (Saxen and Rapola, 1969).

Choice of teratogen agent, dose, route of administration, and other modifying factors

The choice is conditioned by the object of the investigation.

The effective dose is that which modifies the normal development of the embryo without causing early death and without being lethal to the mother. Their range of action is narrow and is named 'teratogenic dose of the agent'. A smaller dose allows the normal development of the embryo (Wilson, 1965); therefore, not every dose of a teratogenic agent has a teratogenic action, and besides, in the case of certain drugs there is not a direct relation between the teratogenic and the therapeutic dose. A teratogenic dose is always inseparable from the age of the embryo and its genotype.

The total teratogenic dose may give rise to different malformations depending on whether it is given as a single dose or in several portions. Experimental data indicate that a single, acute, and short treatment is more effective in the production of malformations than a long treatment, because the embryo

FIG. 4 Diagrammatic representation of the two general periods of heart differentiation in birds and mammals. The principal morphogenetic phenomena and the corresponding susceptibility to the action of teratogenic agents in each one of them are shown.

Period of early differentiation	<p style="text-align: center;">GASTRULATION-TUBULATION</p> <div> </div> <p style="text-align: center;">Heart-Forming areas Morphogenetic movements of heart forming areas Fusion of primitive tubular heart Torsion of Cardiac tube</p>	Highly susceptible to teratogenesis
Period of advanced organogenesis	<p style="text-align: center;">THE PARTITIONING OF THE HEART</p> <div> </div> <p style="text-align: center;">Septal Growth Degeneration (Interatrial foramen secundum)</p>	Increasingly resistant to teratogenesis with increasing age

FIG. 5 Developmental periods of the internal ear, lens, and heart, sensitive to the teratogenic action of rubella. The numbers in the external circle indicate weeks of development. Notice that during the 7th week, the three structures are affected simultaneously. (After B. Mayes, Triangle, 3, 10, 1957.)

under the prolonged action of noxious agents usually dies (Fraser, 1964).

The route of administration of a teratogenic agent may cause the disappearance of its teratogenic action, or transform into a teratogen an agent that was not teratogen given by a different route (Fraser, 1964). These changes may depend on the absorption mechanism of the metabolic subproducts and on the duration of their action on the embryo.

The vehicle of the drugs and the means of suspension of the viruses may have in themselves a teratogenic action, and in the particular case of drugs if the vehicle combines with them forming a new compound, they may transform them into teratogens or neutralize their possible teratogenic action.

There are a number of environmental factors such as undernutrition, climate (Kalter, 1959), crowding, infections, and endocrine diseases in the mother, which may in themselves be teratogen or, without being so, may modify the action of the possible teratogen, either increasing it or inhibiting it.

Examination of results

The material obtained is divided for study into two groups: pre- and postnatal, since the method followed for the diagnosis of cardiovascular malformations is different in each one of them.

In the prenatal study the embryos and foetuses should be examined periodically; in the case of fowl, the embryos and foetuses that have died during incubation should be studied, and in mammals, besides the study of spontaneous abortions, it will be necessary to sacrifice periodically some pregnant females in order to analyse the dead embryos and foetuses that were not aborted and that would be absorbed *in utero*. The survivors of the same litter should likewise be examined. The embryos whose cardiac tube is in the stage of torsion should be stained and block-mounted. In later stages the heart will be examined by microdissection, and in certain cases, histological techniques should be used. First, the morphological age of the embryos should be determined and later the resulting cardiovascular morphologies must be compared with normal individuals of the same morphological age (de la Cruz, Muñoz-Armas, and Muñoz-Castellanos, 1969). Thus, the presence of a common truncus arteriosus in the chicken embryo of 4 days of age is normal, while it is pathological starting on the 5th day; an atrio-ventricular canal is normal on the 4th day and it is abnormal from the 6th day on (persistent common atrioventricular canal), which leads to the inference that it is necessary to know in detail the normal embryology of the animal selected for experiment.

In the case of viruses as teratogenic agents, it is necessary to show the multiplication of infecting particles in the embryonic tissues during the first hours after incubation (de la Cruz *et al.*, 1963).

In the postnatal study of animals, every newborn animal must be sacrificed in order to prove if the possible teratogen produced cardiovascular malformations. When certain cardiopathies are produced experimentally, the experiment must be repeated under the same conditions, but the adult animals should be sacrificed in order to learn the natural history of the malformations; for instance, if interventricular septal defects were produced it is necessary to know if pulmonary hypertension appeared, if a prolapse of the sigmoid aortic valve cusps took place, and also the evolution of the ventricular enlargements imposed by the haemodynamics. If the animals are sacrificed exclusively at an adult age, the statistical analysis of ventricular septal defect will not be true to fact, since many of the ventricular septal defects close spontaneously in the first days of postnatal life (Siller, 1958).

The method of study is micro- or macrodissection, depending on the size of the species and the age of the animal; in selected cases

this should be complemented with histological techniques and tissue culture techniques.

Hypothesis on pathogenesis

The morphogenetic movements,¹ induction,² growth,³ and degeneration,⁴ are the fundamental processes that determine the development of form, structure, and function of an organ. The intimate nature of these processes is unknown. In the development of a particular organ, one or more of these processes participate.

In normal organogenesis of the heart, morphogenetic movements, growth, and degeneration participate. It is unknown at the present time if there are induction processes. If we examine in a general way how these processes participate in the development of the heart, we find that morphogenetic movements determine the fusion of the two cardiac primordia (DeHaan, 1963a, b); growth processes are those that participate in the development of the interventricular septum (Streeter, 1948), of the septum separating the ascending portion of the arch of the aorta from the pulmonary artery trunk (Kramer, 1942), the valvular apparatus (Kramer, 1942), the cardiac chambers, and the interatrial septum in which there is also a degenerative process (Fig. 4). This latter factor is the reason for the normal disappearance of the aortic arches (Congdon, 1922).

Using the criterion established by Saxen and Rapola (1969) for the classification of congenital malformations according to the altered morphogenetic processes, we divide congenital cardiopathies into three large groups and their respective subgroups: those due to disorders in morphogenetic movements, in growth, or in degeneration (Fig. 6).

It is important to emphasize that the abnormal morphology of the heart is not determined only by the alteration of the processes mentioned, but also by the secondary malformations created by them and pre- and postnatal haemodynamics.

Disorders of morphogenetic movements (Fig. 6) This group comprises only cardia bifida which originates because of a failure of the two cardiac primordia to unite (DeHaan, 1963a).

Growth disorders (Fig. 6) These are divided into three subgroups: excessive growth, ectopic growth, and absence of growth.

Excessive growth

This group comprises aortic valvular and pulmonary stenosis, both of which are due to an excessive

¹ Morphogenetic movements are the oriented and irreversible displacements of a group of cells of the embryo which participate in the moulding of it and of its organs.

² Embryonic induction in general is the influence exerted by one embryonic structure on another one, determining their differentiation.

³ Growth is the increase in a cell population by multiplication of its elements.

⁴ Degeneration is the death of cellular groups, which normally takes place during embryonic development.

FIG. 6 Classification of the most common genital cardiopathies according to the type of alteration of morphogenetic processes.

growth of the primordia of the valves, which leads to a narrowing of the valvular orifice (de la Cruz and da Rocha, 1956).

Ectopic growth

In this group we find numerous congenital cardiopathies, among which are transposition of the great vessels, Eisenmenger's complex, Taussig-Bing complex, and tetrad of Fallot.

Transposition of great vessels It originates due to the ectopic growth of the truncocoanal ridges which develop in a straight fashion (de la Cruz and da Rocha, 1956) instead of having a normal rotation of 180 degrees.

Eisenmenger's complex This is due to an ectopic growth of truncocoanal ridges which develop with a rotation of less than 180 degrees and above 90 degrees, affecting exclusively the conal portion of the ridges. This leads to the anterior position of the pulmonary artery and the posterior position of the aorta, to the right of the pulmonary artery. In this malformation, the conoventricular flange is also involved, since its late disappearance causes the great vessels to arise from the right ventricle. Ventricular septal defect is due to the failure to align between the conal portion of the truncocoanal septum and the primitive interventricular septum. The dilatation of the right ventricle and of the pulmonary artery are due to haemodynamic disorders.

Taussig-Bing complex This malformation is caused by the same fundamental disorders which give rise to Eisenmenger's complex, though dextroposition of the truncus-conus of the embryonic heart is of lesser degree.

Tetrad of Fallot The typical form is due to the ectopic origin of the truncocoanal ridges which are

normally rotated 180 degrees. The development of these truncoconal ridges takes place within the territory of the truncus-conus, which normally belongs to the pulmonary artery (de la Cruz and da Rocha, 1956), and causes a mixed infundibulo-valvular stenosis and a diminished calibre of the pulmonary artery trunk. Ventricular septal defect is caused by the lack of alignment of the conal portion of the truncoconal septum with the primitive interventricular septum. Right ventricular hypertrophy is the result of haemodynamic disorders.

Absent growth

In this group the following malformations are included: foramen primum, common atrioventricular canal, ventricular septal defect, agenesis of aortic and pulmonary sigmoid valve cusps, and common trunk.

Foramen primum This malformation is caused by the lack of growth of the septum primum and the septum secundum at their caudal portion (Oliveira Solari *et al.*, 1962).

Common atrioventricular canal This cardiopathy originates as a result of the absence of growth of one or both the dorsal and the ventral atrioventricular canal cushions (de la Cruz *et al.*, 1964). Atrial and ventricular septal defects are secondary to the alterations of those cushions.

Ventricular septal defect The different types of isolated ventricular septal defect are due to the absence of growth of one or several of the embryological components which normally participate in the development of the ventricular septum (de la Cruz *et al.*, 1959).

Agenesis of aortic and pulmonary sigmoid valve cusps These are produced by the absence of growth of the primordia of the cusps (de la Cruz and da Rocha, 1956).

Common trunk This is caused by the lack of growth of the truncoconal septum (de la Cruz and da Rocha, 1956). Ventricular septal defect is secondary to the absence of this septum which participates in the normal formation of the interventricular septum.

Disorders of degeneration (Fig. 6) These are divided into three subgroups: excessive degeneration, ectopic degeneration, and absence of degeneration.

Excessive degeneration

This group includes some of the atrial septal defects of the foramen ovale type, due to an excessive, greater than normal degeneration of the area of the septum primum which appears within the annulus of the foramen ovale (Oliveira Solari *et al.*, 1962).

Ectopic degeneration

This group includes especially coarctation of the aorta, complete interruption of the isthmus of the

aorta, and atrial septal defect of the foramen ovale type.

Coarctation of the aorta This malformation is due to a process of incomplete degeneration of the left fourth aortic arch or left aortic dorsal root. These vessels do not undergo this process during normal development.

Complete interruption of the aortic isthmus It is a more severe degenerative process taking place at the isthmus of the aorta than that causing coarctation of the aorta.

Atrial septal defect of foramen ovale type malformation This defect is caused by an ectopic resorption of the septum primum, at the area limited by the annulus of the foramen ovale (Oliveira Solari *et al.*, 1962).

Absent degeneration

Numerous malformations of the aortic arches belong to this group, which are represented by persistence of some which should normally disappear. These include persistent ductus arteriosus, due to the lack of degeneration of the distal portion of the left sixth aortic arch.

Following these criteria the majority of cardiac and vascular malformations can be adequately interpreted. Only the most representative malformations have been analysed in order to illustrate the disorders of morphogenetic processes of the heart.

Prevention: general outline

The scarce information obtained from the studies undertaken on intrinsic factors in the genesis of the congenital cardiopathies, and the increase in the number of people with these malformations who have prolonged their life as a result of surgical treatment which allows their procreation, make it difficult to practise preventive medicine.

Prevention of congenital heart disease caused by extrinsic factors, on the contrary, has been enriched by the demonstration of the importance of extrinsic factors in the expression of multifactorial inheritance, a more common transmission mechanism of those malformations due to intrinsic factors; the creation of a vaccine for rubella virus which permits prevention of cardiopathies produced by this virus; serological tests of antibodies against numerous viruses, which make possible massive prospective studies in order to discover new teratogenic viruses for the heart; the more precise clinical diagnosis of congenital heart disease and the improved knowledge of the natural history of many of them, as well as the fact that a series of environmental factors such as undernutrition, hypoxia, crowding, endocrine disease of the

mother, and some infectious diseases may be teratogenic in themselves, or, without being so, may increase or enhance the action of known teratogens or may transform into teratogens some agents that normally were not so.

The previous considerations should serve as a basis for the elaboration of prevention programmes against congenital heart disease, in which vaccination against rubella, the systematic serological study of pregnant women, the early diagnosis of congenital heart disease, and the observation of children up to school age in any prospective study of a possible teratogen for the heart, together with the improvement of socio-economic conditions, are the important goals to be attained.

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