Congenital Malformations of the Heart and Great Vessels

Synopsis of Pathology, Embryology and Natural History

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Pathological Anatomy Institute
University of Vienna, Austria

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PREFACE

The history of the development of pathological anatomy at Vienna University is closely connected with progress in the theory of congenital malformations of the heart. Starting with descriptive case reports, the path led, via the beginnings of clinical correlation, to an early peak, the classical work by ROKITANSKY on "The Defects of the Cardiac Septa" (1874) ("Die Defekte der Scheidewände des Herzens"). EISENMENGER (1897, 1898), in discussing the so-called "Overriding Aorta," raised a problem that is still pertinent today. SPITZER's phylogenetic theory (1933) explained fundamental knowledge of the construction of the vertebrate heart and of new aspects of the origin of cardiac malformations. PERNKOPF and WIRTINGER (1933) worked on the embryological bases of cardiac development and created an ontogenetic theory explaining the malformations. Recently, the more than 150-year-old tradition of the Viennese anatomical and pathological school of intensive work on congenital malformations of the heart has been taken up and carried forward (BANKL, 1971).

The study of congenital malformations of the heart and the great vessels, now more than ever, requires a secure pathologic-anatomical basis. This is especially so because clinical diagnosis as well as surgical therapy of modern medicine have become so subtle and intricate that even rare variants or combined complexes of malformations have to be analyzed.

This book is intended as an introduction to the pathology of congenital cardiac malformations as well as a guide to practical diagnosis. It presents a morphological survey of the many types of cardiac malformations, a detailed description of their anatomical criteria, a short review of the embryological basis of the origin of special types of malformation, and, as a supplement, pointers to the natural history of each type of malformation.

A *general section*, Part I, describes the development of the cardiovascular system with respect to the origin of malformations.

In Part II, *Particular Malformations,* individual chapters are devoted to malformations of the heart and the great vessels of practical importance, conforming to an anatomical classification. The arrangement of the individual chapters follows, as far as is meaningful, this sequence:

Definition and classification of subtypes
Frequency and distribution by sex
Embryology
Pathological anatomy of the individual types of malformation
Hemodynamic consequences
Life expectancy and causes of death.

The findings presented in this book comprise the results of the pathologic-anatomical analyses of 1000 examinations of congenital malformations of the heart and blood vessels and a compilation of observations in the relevant literature. It has been a great honor for me to be able to build, especially, on the work of H. TAUSSIG, R.E.B. HUDSON, M. LEV, J.E. EDWARDS, J.K. PERLOFF and R. VAN PRAAGH.

The present work could not have been accomplished without the constant advice of my mentor in cardiopathology, Prof. Dr. L. KUCSKO. My special thanks are expressed to Prof. Dr. J.H. HOLZNER who, through his continuing interest, made it possible for me to complete this book. Finally, hearty thanks are due to the graphic artist, M. CECH for the styling of the drawings as well as to Ms. G. RAIDL for the painstaking production of the manuscript.

Vienna, 1977 *Hans Bankl*

CONTENTS

PART I. GENERAL

Development of the Cardiovascular System

The following description of the development of the heart and major blood vessels is based on the contributions to the embryology of the human cardiovascular system by HIS (1885), TANDLER (1911), WATERSTON (1918), DAVIS (1927), PERNKOPF and WIRTINGER (1933), KRAMER (1942), STREETER (1942, 1945, 1948, 1951), AUER (1948), LICATA (1954), LOS (1958, 1960, 1970, 1971), DE VRIES and SAUNDERS (1962), R. VAN PRAAGH (since 1964), BOYD (1965), LANGMAN and VAN MIEROP (1968), NETTER and VAN MIEROP (1969), ASAMI (1969, 1972), DE HAAN (1970), SISSMAN (1970), O'RAHILLY (1971), TUCHMANN-DUPLESSIS and HAEGEL (1972), CHUAQUI and BERSCH (1972).

General Considerations

The development of the heart has two aspects from the morphological point of view: The *development of the pathways of circulation* and the *construction and differentiation of the structural elements* toward their final form. These two processes are closely connected, because at each stage the shape of the developing heart determines the direction of the blood streams, and these, in their turn, influence the growth and structural development of the heart.

The formation of the structural elements of the heart is based on the sum and synthesis of three individual processes (163, 169): growth, differentiation and morphogenesis. *Growth*, the mitotic activity and multiplication of cells, conditions the increase in size of the organ. *Differentiation* leads to the appearance of new cell characteristics and, therefore, to new functional and structural properties. Finally, *morphogenesis* expresses the sum total of cell movements, their aggregation to tissue combinations, and changes in the configuration. All these processes relate to one another by precise regulation and balance. In this connection it is important to state clearly that the organization of the cardiac structures in space, i.e. their topogenesis, is the product of different kinds of growth and of different magnitudes and directions of cell multiplication of the individual components.

If a localized burst of mitotic activity occurs a little too soon or a little too late, if a group of cells develops differential adhesiveness to other cells of one type instead of another type, if a sheet of cells bulges in instead of out, the whole system may be disrupted, and an abnormal organ or congenital defect will result.

Two formal genetic principles are decisive for the realization of the normal as well as the abnormal form of the heart:

1. Septation:

Modern embryological research has recognized two fundamental pathways of septum formation in a hollow organ (168, 502).

Expansive space-occupying growth within the cardiac tube at both sides of a non-growing segment leads to passive erection and invagination of a partition. Such a septum can never become a complete separating wall, but will always show an aperture which has to be closed secondarily by tissues of adjacent structures. In the heart, this mechanism leads to the different development of the trabeculated and non-trabeculated sections of the primitive ventricles. The trabeculated parts show the maximum of cellular multiplications subepicardially, with outward-directed growth as a consequence; the non-trabeculated regions do the opposite. At first, such passively erected separations are strikingly thin compared to their height, as increase in thickness follows much more slowly.

A second mode of septation consists of a *localized proliferation and increase in mass, with final amalgamation* of opposite bulges in a hollow organ as it occurs through the *active* growth of the (mesenchymal) endocardial cushions. In this way primary, thick, plump separating walls are produced, which are later transformed into thin-walled septa.

Of the seven septa formed in the course of the development of the heart, three are erected passivly, namely by expansive growth of the surroundings (the septum secundum atriorum, the muscular interventricular septum and the septum aortico-pulmonale), three are formed actively (the intermediate septum of the AV canal, the bulbar and the truncal septum), and one, the septum primum atriorum, starts as a passive invagination and is completed by active growth (388, 502).

2. Curvature of loops and the so-called torsions of individual segments:

The loop formation of the primitive heart tube is caused neither by narrowness within the pericardial sac nor by hemodynamic pressures, but occurs simply because one side of the heart tube grows faster than the other (168, 653). Higher mitotic activity of the left parts of the heart tube and segmentally differentiated growth, favoring the large curvature, comprise the basic mechanism of the tubal looping.

The rotation of individual segments of the heart during certain steps of development, in their totality, follow a complicated course that will be discussed particularly in connection with the description of the torsions of the aorta and the pulmonary artery.

In order to clarify the much used term *"torsion or rotation"* it should be stated that this does not express actual movement in space but a change in the relative positions of cardiac segments lying next to each other, in accordance with the difference in their growth. If a lateral segment grows faster than the contralateral region the curved heart segment is bound to turn to the side of lesser growth. The rotations and changes of position should not be visualized as active migrations of cardiac segments, as they are caused less by genuine torsions than by being feigned by additional appositional growth (273, 274). As not all parts of

the myoepicardium grow at the same time, at the same speed, and with the same intensity, there exist centers of growth. These rotations are secondary manifestations of that growth.

This is valid particularly for the bulbus-truncus segment: the outflow route develops as a hollow cord (70) which is directed frontally in the proximal bulbus, more sagitally in its cranial course, and further distal again frontally. The entire hollow cord is not mainly rotated by 180 degrees, as was thought until now (177), but rather is flattened differently at various sites (Fig. 1.4). The whole outflow tract adapts itself *in situ* to the growth processes in its surroundings and thereby is locally placed sometimes more frontally, sometimes more sagittally. The different flattenings slide into one another without any demonstrably strong torsion. This would really be most unlikely, for as a result of each torsion there would be tensions in the wall, which would have to be evened out by additional growth during development. The same applies to the torsion of the septa. The bulbus-truncus septum does not "rotate" due to its own growth tendencies, but adapts itself in accordance with the higher mitotic activity on the left side of the bulbus (653, 672) to the development and displacement of the bulbus.

Summing up, the realization of the two formal genetic principles of cardiac development—septation and curving or rotation, respectively—is achieved by

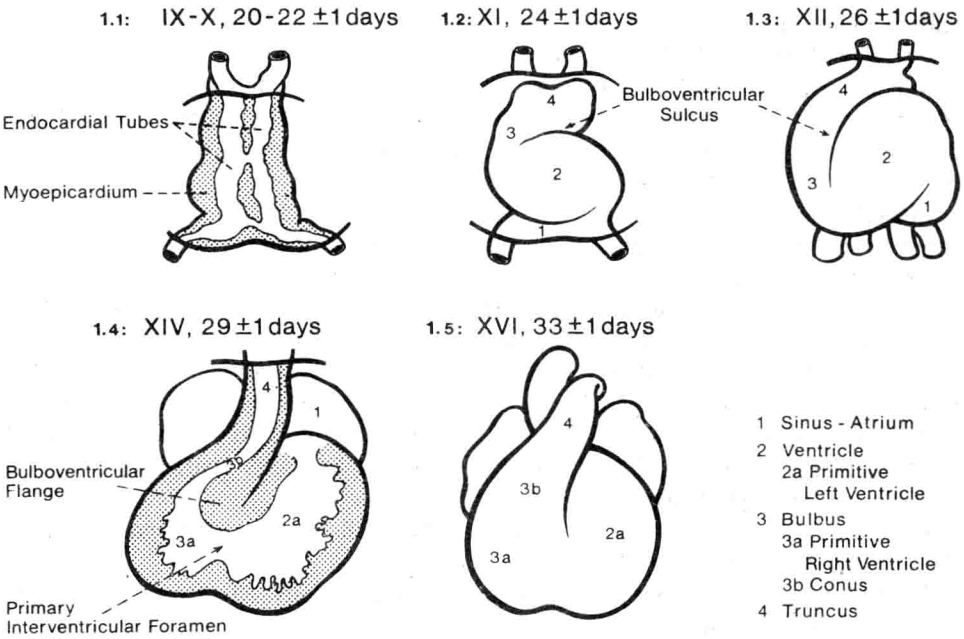

Fig. 1. Formation of the heart loop (d-looping). Note the medial-shifting of the bulbotruncus during horizon XIV. Schematic drawings of ventral views of human embryonic hearts in 1.2, 1.3, and 1.5; frontal sections in 1.1 and 1.4.

different growth tendencies. External and internal construction comes about through different, although predetermined, proliferation. Any disturbance of normal conditions of growth leads to the emergence of variants. Reversal of growth tendencies produces formations contrary to the norm, such as, e.g. a loop curvature directed inversely toward the left, or displacements of the bulbus-truncus-segment arising from the contralateral side.

Before concluding these general morphogenetic considerations, the question of the role of the blood stream as a formative factor in the shaping of the heart has still to be discussed (55, 56, 84, 85, 271, 272, 273, 598). The opinion that the blood stream governs septum formation and that partitions only develop as dependent formations between two cords of blood-flow in so-called "zones free from lateral pressures" could not be confirmed.

BREMER (85) described an embryonal chick heart that received inflow only from the right truncus vitello-umbilicalis; therefore, it presented only one line of blood flow, but it still showed regular spiral bulbar ledges. RYCHTER and LEMEZ (611) excluded the vitelline veins unilaterally, resulting in one undivided bloodstream but still achieving a completely normal development of both halves of the heart and of the great arteries. These results do not correspond to the hypothesis of the morphogenetic significance of the double bloodstreams in the embryonic heart.

We now know that the bloodflow exerts less influence on the morphogenesis than on the structural development, i.e., on the differentiation of endocardium and myocardium (524). We also recognize its significance for trabecularization (70). The shape of the heart tube determines the direction and position of the bloodstreams, and these, in turn, provide stimulation for differentiation of those segments of the ventricular walls that are under pressure. The course of the bloodflow and the formation of septal ledges are equally dependent on the shape (of the heart) and are not causally related to one another.

SPITZER (667, 668, 669) worked out three basic characteristics of normal heart development: development of metameres, development of antimeres, and cross-over exchange of major and minor circulation with parallel courses of bloodflow. Starting with the assumption that during phylogenesis of the heart pulmonary respiration and septation of the heart are in close mutual relationship, he arrived at the formulation that "the development of external respiration is the cause, the forming of a parallel and exchange circulation is the goal, and the formation of a septum rotated by 180 degrees at a certain site in the heart is the means for mechanical realization of this task." This idea has been designated by DOERR (180) as a basic phylogenetic principle.

Following the phylogenetic outlook of SPITZER we can distinguish among three basic types of heart (476):

1. Hearts in which the phylogenetic principle is fully effective (the normal mammalian heart).
2. Hearts in which this principle has been completely abolished and in which pulmonary and general circulation run side by side without any exchange (complete transposition).

3. Hearts in which the basic principle has been only partially realized and in which communications exist between the two circulations (formation of defects, with possibilities of shunt).

This classification should be used for a general understanding of the possible main types of human heart formation.

Early Cardiac Morphogenesis

The blood and the cardiovascular system are derived from the mesoderm. They develop at the same time, beginning about the middle of the third week.

It should be noted that the first blood and vascular elements appear at the exterior of the embryo, in the mesenchyme covering the yolk sac (the vitelline vessels) and in that of the chorion and connecting stalk (the umbilical vessels). However, this extraembryonic network rapidly blends with the intraembryonic circulation.

The presomite human embryo (STREETER's horizon VIII to IX; approximately 1.0-1.5 mm; approximately 18±1 days) may be characterized as a roughly flat plate of cells in which the three germ layers are clearly delimited, with the precardiac material located anteriorly in the "wings" of the lateral plate mesoderm. The lateral mesoderm splits to form two layers, the somatic and splanchnic mesoderm. The somatic mesoderm subsequently thickens and gives rise to a second generation of mesenchymal cells which are the precursors of limb muscle. The precardiac splanchnic mesoderm, on the other hand, remains epithelial throughout the formation of the tubular heart (445). In this position cells of the splanchnic mesoderm layer proliferate into the so-called *angiogenetic cell clusters.*

Continued cardiogenesis depends upon a complex of four types of morphogenetic movement, occurring simultaneously (170): (1) folding movements of the entoderm to form the crescentic pouch of the anterior intestinal portal and early shallow foregut; (2) formation of the intraembryonic coelom, of which the early pericardial cavity is a part; (3) rapid anteromedian migration of splanchnic precardiac mesenchym; and (4) ventral migration of cells from the splanchnic mesenchym to form the angiogenetic cell clusters.

After migration from the primitive streak to the pharyngeal membrane, the angiogenetic cell layer unites with its pair from the opposite side to form the *horseshoe-shaped cardiac primordium.*

As the next step of development (horizon IX; approximately 1.5-2.0 mm; approximately 20±1 days) the angiogenetic cell clusters rapidly increase in number and size, acquire a lumen, unite and form a plexus of vessels. From this plexus, which is obviously also horseshoe-shaped, the *two endocardial tubes* develop (Fig. 1.1 and 2.1, 2.2). The lateral portions of the plexus become simplified by coalescence into single endothelial tubes; the central part of the plexus retains its plexiform condition. In addition to this plexus, other clusters of angiogenetic cells appear bilaterally-parallel, acquire a lumen and form a pair of longitudinal vessels, the dorsal aortas (Fig. 2.1, 2.2). These vessels attain a connection with the dorsocranial aspect of the endothelial heart tubes, thus establish-

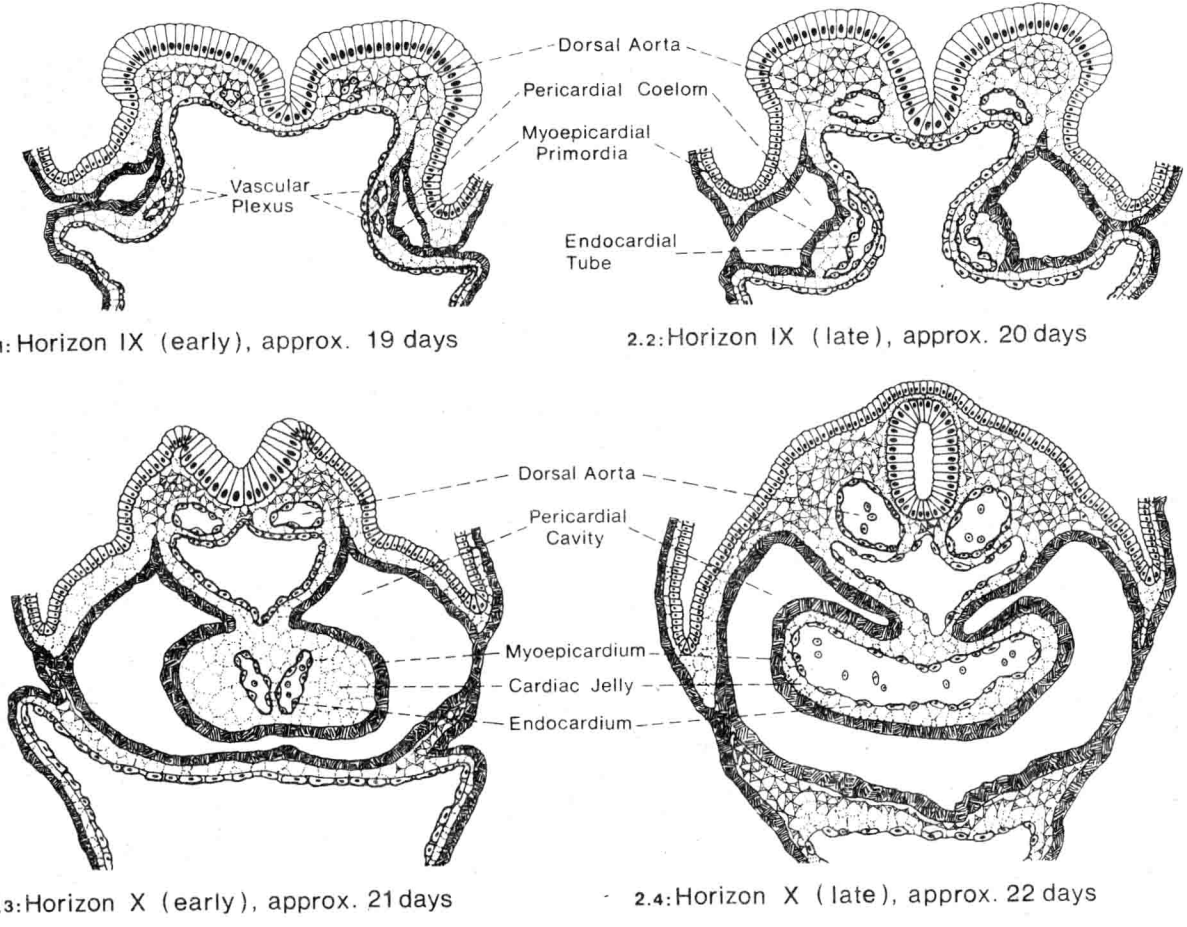

Fig. 2. Schematic representation of transverse sections through embryos at different stages of development, showing the formation of the single heart tube from paired primordia. (Adapted from several sources.)

ing the arterial pole of the developing heart. The caudal ends of the lateral endothelial heart tubes make contact with vessels arising in the yolk-sac mesenchym (-vitelline veins) and, somewhat later, with the developing umbilical veins, too. Thus, the venous pole of the heart, still paired, is determined. While the primitive bilaterally symmetrical cardiovascular system makes its appearance, growth processes elsewhere profoundly influence the relative position of the cardiac portion of this system. The central nervous system grows in the cranial direction, so that it extends over the cardiogenic area and the future pericardial cavity. During this growth the rapidly expanding brain pulls the prochordal plate (future buccopharyngeal membrane) and the central portion of the cardiogenic plate forward. This results in rotation of the buccopharyngeal membrane and the cardiogenic plate, including the pericardial portion of the coelomic cavity, along a transverse axis over approximately 180 degrees. Hence the central portion of the cardiogenic plate and pericardial cavity, initially located cranially to the buccopharyngeal membrane, are now located ventrally and caudally to these structures.

The consequence of this growth process is that the dorsal aortas, leaving the endocardial tubes at a now-cranial aspect, describe an arc along either side of the cranial end of the foregut. Thus, the *first pair of aortic arches* makes its appearance.

Simultaneously, the originally flat embryonic shield curves in both an anteroposterior (craniocaudal) and a transverse direction. Its dorsal (ectodermal) surface becomes increasingly convex and its ventral (entodermal) surface concave. As a result of these foldings, the two lateral endocardial (endothelial) heart tubes come closer to each other (Fig. 2.2, 2.3). The plexiform, median portion of the original horseshoe, still separating the left and right heart tubes from each other, gradually disappears, resulting in a fusion of the heart tubes in a craniocaudal direction.

It should be pointed out that in man there exists a plexiform phase of the development of the endocardium with anastomosis between the right and left vessel-plexus (524). ALLEN (1962/63) not only confirms this fact, but "believes that the bulboventricular part of the heart, rather than being formed by fusion of paired primordia, arises *in situ* from an elaboration of the mesoderm bridging the anterior of the embryonic disc."

In spite of the vagueness of our knowledge about this period of morphogenesis, it is a fact: *in horizon X (2.0-2.5 mm; 22±1 days) a single endocardial tube is formed* (Fig. 2.4).

The developing heart tube, located in the splanchnic mesodermal tissue, bulges gradually more and more into the pericardial cavity. This invagination continues until the heart tube with its investing layer lies completely within the pericardial cavity. The tube remains attached temporarily to the dorsal side of the pericardial cavity by a fold of mesodermal tissue, the *dorsal mesocardium*. A ventral mesocardium is never formed.

The developing myocardium is continuous with the splanchnic mesoderm through the dorsal mesocardium. Radioactive marking experiments have clearly shown (600, 672) that splanchnic mesoderm continues to migrate medially, passing through the dorsal mesocardium to become part of the definitive myocardium.

This occurs on both right and left sides. Both splanchnic mesoderm and developing myocardium are true epithelia, with distinct apical and basal surfaces. The apical surface is free, but the basal surface is in contact with extracellular matrix. This extracellular matrix of the heart proper is called *cardiac jelly*. It lies as elastic semisolid material between the relatively thick developing epimyocardium and the thin endocardium. Cardiac jelly is continuous with the matrix interposed between the inward-migrating splanchnic mesoderm and the ventral foregut entoderm (448). (For the histogenesis of the embryonic myocardium and the formation of the epicardium, see MANASEK 1968, 1969, 1970).

The mesodermal tissue surrounding the endocardial (endothelial) heart tube differentiates into three layers (Fig. 2.4):

1. The *endocardium* (endothelial lining);
2. The *myoepicardium* consisting of densely arranged myeloblasts and a layer of flat mesothelial cells;
3. A basic amorphous substance rich in mucoproteins and mucopolysaccharides which lies between the endothelium and the myoepicardium of the cardiac tube in its bulboventricular section. Cells of the adjacent layers enter this basic substance and form a loose reticulum of star-shaped ramifying cells (540) which is called gelatinous reticulum or *cardiac jelly* (158). But this entry of cells occurs only at stage XIII (4.0-50 mm; 28±1 days).

These concentrations of mesenchymal cells enlarge rapidly and soon cause the endocardium under which they lie to bulge into the lumen of the heart. Such internal bulges, irrespective of where they appear in the heart, are known as *endocardial cushions*.

The time between the first appearance of the intraembryonic vessels and the formation of the heart tube is about 4 days. By this time the heart begins to beat.

Formation of the Heart Loop

The term "looping" refers to the overall change in morphology of the developing heart as it assumes a characteristic "convoluted" configuration.

Until very recently, the primitive heart was always considered to be a straight heart tube in which curving and loop formation then begins. This is not correct, as at no stage of development can a straight extended cardiac tube be demonstrated (524). The heart is the first embryonic structure to exhibit a marked deviation from bilateral symmetry (672).

Even at the stage of the paired plexus, there are not only indentations on the surface of the myoepicardial area which point to future metameral organization, but the arrangement is already asymmetrical (Fig. 1.1), an indication that looping and curving has already begun. When the fused tubular heart has just been established, there are already a bulge on the right side of the later bulbus-ventricle and a tilt to the entry of the omphalomesenteric veins (169, 674).

The classical opinion that the cause of curving and loop formation is to be found in the faster growth of the tube within the more slowly expanding pericardial cavity (534) can no longer be accepted. It is not a general increase in