Familial Heart Disease

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Heart disease affecting more than one member of a family is an important clue in diagnosis besides being a prime factor in genetic counselling. The subject is somewhat diffuse and untidy, but from personal observation and from a survey of earlier publications (Hudson, 1965, 1969), it is possible to distinguish the following 10 groups of familial disorders in which the heart may be involved.

1: FAMILIAL CORONARY ARTERY DISEASE

Most physicians know of families with a bad history of atheromatous coronary artery disease leading to cardiac pain and infarction at a youngish age. This unhappy event is more likely to occur in a patient whose parents both have ischaemic heart disease; it is also inevitable if there is inherited hyperlipoproteinaemia, with very high levels of blood cholesterol and "galloping" atheroma. The writer has witnessed fatal cardiac infarction from coronary artery occlusion in such a case, a woman of 24, who also had skin xanthomata and extensive severe atheromatous plaque formation in the aorta and its main branches. The aortic valve was involved in the thickening; it was stenosed and possibly rheumatic too. Such severe arterial disease is rare in a young woman, and the occurrence provides good evidence for the cholesterol theory of atheroma in humans.

2: FAMILIAL IDIOPATHIC CARDIOMYOPATHY

By convention, this title refers to a non-coronary disorder of the myocardium, usually with replacement fibrosis, which may occur in families, and which is not part of a generalized disease. The heart is usually dilated and hypertrophied and the left ventricle especially may show endocardial thickening, mural thrombosis, and myocardial scarring.

The writer has encountered several examples. One was a youth of 18 years who was the last survivor of 5 brothers, all of whom died at a youngish age, 2 at least from heart failure. The heart showed much residual replacement fibrosis and also mural thrombosis in the left ventricle.

In another family, severe myocardial scarring was found at necropsy in a father aged 32, his son aged 12, and in his daughter aged 10 years. A third example concerned a woman of 28 years who died of puerperal heart failure after the birth of her second child. A few years later, her first child, a daughter, died at the age of 7 years, and at necropsy her heart resembled the mother's; both hearts were dilated and showed hypertrophy and mural thrombosis in the left ventricle. It is possible that both patients were victims of unrecognized myocardial infection, such as that caused by Coxsackie B virus, and that the appearances found were the end result of this.

Included in this group is hypertrophic obstructive cardiomyopathy, which has become widely publicized since the classical necropsy account of 8 cases, all young adults, by Teare (1958), who called the condition asymmetrical hypertrophy because the massive hypertrophy of the left ventricle dominated in the interventricular septum at the base of the heart. This hypertrophy may narrow the outflow of both ventricles and it may also compress the tricuspid valve causing the Bernheim syndrome of functional tricuspid stenosis; it may also hinder mitral valve closure. Many cases are familial and sudden death is not uncommon in younger victims. The writer has studied many examples, the youngest being from a baby boy of 3 months; this supports the view that the abnormality is congenital. Electron microscopy of biopsy material has revealed disorganized sarcomeres, some with their Z-bands pulled wide apart and others with these structures squashed together. Earlier reports of excessive noradrenaline in the myocardium as a specific feature are now doubted.

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3: FAMILIAL MUSCULAR DYSTROPHIES

These diseases may involve the heart, which shows changes similar to those in skeletal muscle. The best known type is the pseudohypertrophic dystrophy of Duchenne; most cases are inherited as a sex-linked recessive, but milder cases may result from autosomal recessive inheritance.

Dystrophia myotonica may also be considered in this group; the cardinal feature is slowing of contraction and relaxation of skeletal muscle, and in the later stages the heart may be involved.

4: FAMILIAL ATAXIAS

The ataxias of Friedreich and Refsum commonly involve the heart. In Friedreich's ataxia, there is replacement fibrosis of the myocardium; heart failure is common and sudden death not unknown. Stenotic lesions of small coronary arteries have been described by some workers, notably James and Fisch (1963), but the significance of these lesions is uncertain. By contrast, Refsum's disease has proved to be a recessively inherited lipid storage disorder involving phytanic acid, which appears in the blood and which is deposited in the heart, nerves, and other tissues (Klenk and Kahlke, 1963). This disease provides a link to the next group, the storage diseases.

5: FAMILIAL STORAGE DISEASES

The stored material may be lipid, glycogen, mucus, mucopolysaccharide, or iron.

(a) *Lipid storage* of the heart occurs in the diseases of Niemann-Pick, Hand-Schüller-Christian, and Refsum. In Fabry-Anderson disease, lipid accumulates in the media of arteries, including the coronary arteries, as well as in all other tissues of the body. In Gaucher's disease, lipid may accumulate in the lungs and pulmonary hypertension may result.

(b) *Glycogen storage* predominates in the heart in the Pompe's type of glycogen storage. The glycogen is normal, but it accumulates because of the congenital absence of the enzyme α -1, 4-glucosidase. Inheritance is autosomal recessive. The enlarged, thickened left ventricle may also show endocardial thickening.

(c) *Mucus*. In fibrocystic disease of the pancreas (mucoviscidosis) mucus accumulates in the intestine, and also in the pancreas and bronchi, leading to fibrosis at both the latter sites; there is also a high concentration of salt in the serous secretions of

the sweat and salivary glands and in the nails. The disease is inherited by a recessive gene, with a risk to sibs of 1 in 4 and to offspring of 1 in 50. Its most serious effect is the chronic lung infection leading to bronchiectasis, cor pulmonale, and right heart failure. The serum contains a substance which interferes with the ciliary action of mucosal cells.

(d) *Mucopolysaccharidoses*. Several types are distinguished according to the nature of the stored material, which may be chondroitin sulphate B, heparitin sulphate, or keratosulphate, or mixtures of these substances. The types are named after Hurler, Hunter, Sanfillipo, Morquio-Ullrich, or Scheie. Inheritance is recessive, usually sex-linked in Hunter's type and autosomal in the others. Common features include corneal clouding, and mucopolysaccharide deposition in the heart valves and in the intima of the coronary arteries, aorta, and pulmonary arteries. The urine may contain an excess of the mucopolysaccharide material, which stains metachromatically with toluidine blue.

(e) *Iron*. Familial incidence of haemochromatosis is known; also, other relatives may have raised serum iron. Low levels of gastroferritin, a protein which binds iron and prevents excessive absorption, have been described in some cases. There is evidence that the excess of iron in the myocardial cells inhibits aminolaevulinic acid (ALA) dehydrase, the enzyme necessary for the condensation of this acid to form porphobilinogen on the pathway to myoglobin synthesis. Cardiac complications include pericarditis, arrhythmias, and congestive heart failure.

6: FAMILIAL CONNECTIVE TISSUE DISORDERS

Several connective tissue diseases may involve the heart. Perhaps the commonest are rheumatic fever and rheumatoid arthritis, both of which may be familial.

Marfan's disease may cause aortic aneurysm, often with aortic valve disease; aortic dissection is common. Some patients also have homocystinuria, due to abnormal methionine metabolism and inherited as an autosomal recessive; such people may suffer arterial thromboses and fatty liver in addition to the stigmata of Marfan's disease.

Pseudoxanthoma elasticum is a rare, recessive, partly sex-linked disease of elastic tissue, causing inelasticity of the skin, mucosal bleeding such as haematemesis, coronary and peripheral arterial occlusion, angioid streaks in the retina, and, occasionally, endocardial lesions involving the heart valves.

Ehlers-Danlos syndrome, with hyperextensibility of the skin and joints, and a tendency to bruising, may be associated with Fallot's tetrad, atrial septal defect, varicose veins, arterial and arteriovenous aneurysms, and ruptured arteries. Inheritance is by autosomal dominance.

Osteogenesis imperfecta—defective collagen maturation leads to multiple fractures, hyperextensibility of joints, a tendency to hernias and to blue sclerotics; cardiovascular lesions include ruptured arteries and aortic aneurysm with valve regurgitation.

Holt-Oram syndrome of atrial septal defect with radial anomalies of the forearm and hand may be familial. The writer has seen a variation in a baby who had atrial septal defect, aortic coarctation, a right thumb attached to the hand merely by a skin pedicle, and a fourth right toe situated above the cleft between the middle and little toes.

Ellis-van Creveld syndrome of polydactyly and ectodermal dysplasia is commonly associated with single atrium.

7: FAMILIAL ENDOCRINE DISORDERS

Those affecting the heart include phaeochromocytoma, thyrotoxicosis affecting mother and baby, and Werner's syndrome of premature ageing and vascular degeneration.

8: FAMILIAL CHROMOSOMAL ABNORMALITIES

Down's syndrome (trisomy-21), especially the type in which the extra chromosome is "translocated" to another chromosome, may be familial. The classical cardiac malformation is atrioventricularis communis, but almost any cardiovascular anomaly may occur.

Trisomy-18 may be associated with double-outlet right ventricle, i.e. the aorta and pulmonary trunk both arise from the right ventricle.

Turner's XO syndrome may be complicated by aortic valve disease or coarctation, or both. The writer has seen a bicuspid, stenosed aortic valve replaced successfully at operation in a girl of 14

years who also had coarctation. Ullrich's syndrome has some of the clinical features of Turner's syndrome, including heart involvement, but the sex chromosomes are normal.

9: FAMILIAL CONGENITAL HEART DISEASE

Several congenital cardiovascular lesions tend to run in families. Examples include situs inversus, dextrocardia, persistent ductus arteriosus, endocardial fibro-elastosis, supra-valvar aortic stenosis, and atrial septal defect. The writer found an ostium secundum atrial septal defect in the heart of a dead unborn 5-month-old foetus at necropsy of the mother who died at 31 years from pulmonary hypertension complicating a similar defect in her heart.

10: MISCELLANEOUS FAMILIAL CONDITIONS

Familial deafness with cardiac arrhythmia is now established as an entity. Familial cor pulmonale may be due to primary pulmonary hypertension.

The above account is by no means exhaustive but most of the important familial conditions involving the cardiovascular system have been included. Such information is of great value in the genetic counselling of parents anxious about their family planning.

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