Quebec Cooperative Study of
Friedreich's Ataxia

# Cardiac Pharmacology and Cardiomyopathy in Friedreich's Ataxia

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SUMMARY: *Friedreich's ataxia is almost always associated with a cardiomyopathy. The cardiomyopathy and its attendant cardiopulmonary sequelae is the usual cause of death in this disease. The author reviews the known pharmacology of the heart, particularly as it applies to hypertrophic cardiomyopathy. The important role played by calcium and the possible role of taurine is stressed. Therapeutic possibilities are mentioned.*

RÉSUMÉ: *L'Ataxie de Friedreich s'accompagne le plus souvent d'une cardiomyopathie. Cette entité, et ses séquelles cardiopulmonaires, sont la cause habituelle du décès dans cette maladie. L'Auteur présente une revue de la pharmacologie connue du coeur, particulièrement dans ses relations à la cardiomyopathie hypertrophique. Il insiste sur le rôle important joué par le calcium et le rôle possible de la taurine. De ces considérations découlent quelques possibilités thérapeutiques.*

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## INTRODUCTION

Friedreich's ataxia is one of the commonest genetic ataxias and, in human terms, one of the costliest. It is usually detected in childhood and follows a course of increasing functional impairment terminated by death between 26 to 31 years (Andermann et al., 1976). Associated with the ataxia is a progressive cardiomyopathy and it is this, or the complications arising from it, which is responsible for the mortality. The cardiomyopathy therefore deserves the emphasis of the investigation. To date, this has not been done. Some detailed electrocardiographic studies have been performed, but in terms of the cellular or metabolic changes accompanying or causing the heart problems, we only have the occasional fact.

It is hoped that this review will aid in the definition of the therapeutic and scientific problems associated with Friedreich's cardiomyopathy. This article will have fulfilled its purpose if it is useful in any way to physicians and scientists concerned with Friedreich's ataxia, or if it encourages experimental work on the cardiac problems associated with this entity.

## PATHOLOGY

Although not pathognomonic for Friedreich's ataxia, cardiac changes are virtually always present (Hewer, 1968). Electrocardiographic (ECG) signs of disease may be present in over 90% of patients (Thoren, 1064). Nearly all patients die of either diabetes or the cardiac complications. As early as 1887, heart disease was recognized as a cause of death in Friedreich's ataxia (Pitt, 1887); in a study published in 1905, 20 out of 20 patients had heart disease (Saury, quoted in Thoren 1964). In the most recent study, of 14 fatalities, 12 patients had cardiomyopathy and this was given as the cause of death in five (Andermann et al., 1976). Heart problems, therefore, are an important determinant in the mortality of Friedreich's ataxia.

ECG changes are the commonest sign of abnormality in the heart. Reported percentages range from 30 (Evans and Wright, 1942) or 60 (Boyer et al., 1962) to in excess of 90 (Thoren, 1964). Electrical abnormalities often take the form of atrial tachyarrhythmias or sinus tachycardias. The most marked change in the ECG is an inversion of the T wave which may become normal during work (Thoren, 1964). This implies a defect in either potassium or calcium movements during repolarization.

ECG abnormalities often exist without clinical symptoms. The most frequent gross abnormality is ventricular hypertrophy (Coté et al., 1976; Malo et al., 1976; Gach et al., 1971). A finding of some interest in other studies is the high incidence of right ventricular hypertrophy. This is rare in other cardiomyopathies. Thoren (1964) reported right ventricular hypertrophy a common finding in his cases of Friedreich's ataxia. In the Quebec cooperative study, right ventricular hypertrophy was found in 23 of 35 cases. Biventricular hypertrophy was present in one case and left ventricular hypertrophy in two (Malo et al., 1976). Right ventricular hypertrophy was often found in association with septal hypertrophy (Gach et al., 1971).

The hypertrophy is associated with a diffuse fibrosis, and appears



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to be of the obstructive kind. Gross abnormalities in cardiac structures, such as valve defects, are rare, as are obstructive lesions of the larger coronary arteries or coarctation of the aorta. Obstruction is due to small vessel disease, involving primarily the arterioles. The vessels involved are mostly in the 100 to 300 micron range (James and Fisch, 1963). Larger arteries are normal on gross and microscopic examination. The luminal and medial hyperplasia may lead to complete obliteration of the vessel. In 25 autopsies diffuse fibrosis and medial thickening of cardiac arterioles was found in association with thrombi formation (Soulié et al., 1965). Typically, the medial hypertrophy is associated with arteritis and endothelial proliferation. It has been suggested that small vessel occlusion is an etiological factor in the development of the cardiomyopathy of Friedreich's ataxia (Krongrad and Joos, 1972). The arteries and arterioles of other organs, apart from the lung and heart, are normal. However, Thoren (1964) has pointed out that subintimal hyperplasia is not found in other myocardial degenerations and probably does not cause it.

Arterial changes observed in the lungs, such as endothelial proliferation and medial degeneration of the elastic lamina, have been interpreted as suggesting severe and long standing pulmonary hypertension (James and Fisch, 1963). Right heart catheterization studies of Friedreich's ataxia patients are rare. However, there is some evidence that pulmonary hypertension is common (Lorenz et al., 1950). Many of the above changes are strongly reminiscent of those observed in pyrrolizidine poisoning in experimental animals (McLean, 1970; Huxtable et al., 1977). It has been suggested that the cardiomyopathy may have an infectious or toxic origin (Ivemark and Thoren, 1964).

Changes in the cardiopulmonary system become manifest as dynamic alterations. Typically, patients have normal blood pressures but high heart rates (Coté et al., 1976), the pulse rate increasing with the severity of disease (Thoren, 1964). Heart rate also tends to increase very rapidly on light stress (Malo et al., 1976). This may indicate an increased sensitivity of the $\beta$-adrenergic system to epinephrine.

The cardiac output is high in one-third of the cases (Thoren, 1964; Coté et al., 1976), but is often low and may be normal. This range of findings may reflect individual combinations of hyperkinetic left ventricle and increased lung capillary resistance. An increase in the resistance of the pulmonary vascular bed will lead to decreased filling pressures of the left heart and eventually decreased cardiac output. Elevation in right ventricular end diastolic pressures (rvedp) is a common finding in Friedreich's ataxia. (Thoren, 1964; Soulié et al., 1965; Ruschhaupt et al., 1972; Coté et al., 1976). Elevations in left ventricular end diastolic pressure also occur, but the magnitude of change is less.

## MODIFYING FACTORS

### *Neurological Impairment*

In Friedreich's ataxia the association between ataxia and cardiomyopathy is striking in the majority of cases. Despite the association, ataxic and cardiac changes do not occur in parallel (Perloff, 1972). The ataxia usually precedes the heart disease, but the reverse occurs. Some evidence suggests that cardiac changes identical to those of Friedreich's ataxia may appear in neurologically normal siblings of Friedreich's patients (Thoren, 1964). Familial cardiomyopathy with histological features identical to (Roth, 1948) or similar to (Evans, 1949) Friedreich's ataxia cardiomyopathy has been shown in relatives of patients who never developed ataxia.

Sympathetic hyperactivity has been suggested as contributing to the development of the cardiomyopathy. There is little evidence of this. No increase in urinary catecholamine excretion can be detected and ganglionic blockade does not affect the ECG abnormalities (Thoren, 1964).

The heart problems are not secondary to the ataxia. Cardiomyopathy is an independent expression of genetic defect or defects.

### *Scoliosis*

Marked scoliosis puts an extra stress on the cardio-pulmonary system which may eventually result in functional impairment. However, in Friedreich's ataxia, scoliosis does not appear to contribute to the cardiomyopathy (Bureau et al., 1976). The signs of heart disease frequently precede scoliosis (Boyer et al., 1962) and eight patients without scoliosis developed cardiomyopathy (Thoren, 1964). Deformity of the chest does not produce the myocardial fibrosis which is a feature of Friedreich's ataxia. The right ventricular hypertrophy and right heart failure of Friedreich's ataxia is rarely seen in scoliosis where congenital heart disease is absent (Godfrey, 1970). Scoliosis is an aggravation, but is not the cause of the cardiac impairment.

### *The Lungs*

The cardiomyopathy is marked by right ventricular hypertrophy rarely seen in most cardiomyopathies (Malo et al., 1976). There is an obliterative vasculitis starting with the smallest vessels and progressing to the larger ones. This is accomplished by medial hypertrophy, endothelial hyperplasia and arteritis. The pathological findings are those typical of severe pulmonary hypertension (James and Fisch, 1963). High arterial pressure due to hypoxic vasoconstriction is possible, as blood oxygenation is about 10% below normal (Bureau et al., 1976). Any increase in arterial pressure would tend to be magnified by the myogenic response, regardless of what initiated it. Increased arterial pressure means an increased workload for the right heart and if the process continues long enough right ventricular hypertrophy and failure will be the result.

The evidence suggests that the lungs may be involved in the development of the right heart disease found in a large number of patients. A genetic defect in the heart, combined with an additional insult to the right side, could account for the



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asymmetrically developing hypertrophy.

*A Toxic Response?*

A toxic basis to Friedreich's cardiomyopathy has been suggested (Ivemark and Thoren, 1964). A defect in hepatic cell function is one of the four primary dysfunctions in Friedreich's ataxia (Barbeau, 1976) and the possibility of an impaired liver influencing the cardiopulmonary system is worth exploring. In one series of patients approximately one-third showed abnormally high bilirubin levels (Barbeau et al., 1976). This may indicate a deficiency in the hepatic conjugation mechanism. The typical process by which xenobiotics are handled in the liver involve an oxidation step by the microsomal P450 system followed by conjugation and excretion. The oxidation step tends to convert a substance into a more polar, more water-soluble and more chemically reactive form. If conjugation does not occur, one can conceive of toxic substances accumulating in the liver and being released into the blood stream. There are a number of examples of this type of situation. Acetaminophen can overwhelm the conjugative mechanism of the liver and produce severe damage.

The pyrrolizidines are hepatotoxic substances. In animals they produce a type of cardiopulmonary damage similar to that seen in Friedreich's ataxia. Microthrombi are formed in the lung capillary bed and damage to the endothelium results, leading to endothelial proliferation and obliteration of small vessels (McLean, 1970; Lalich et al., 1977). In the arterioles and arteries, medial hypertrophy reduces the luminal size and necrotizing arteritis is produced if the dose of alkaloid is high enough. These changes in the lung vasculature have a profound effect on the right side of the heart. Massive right ventricular hypertrophy is produced, associated with marked pulmonary arterial hypertension (Huxtable et al., 1977; Chesney and Allen, 1973).

It is not suggested that pyrrolizidine alkaloids are involved in the development of the cardiomyopathy of Friedreich's ataxia. However, in appropriate animal models the effects of the pyrrolizidine alkaloids are very similar to the alterations found in the myocardiopathy. Furthermore, pyrrolizidine-induced damage may be a valuable model in the elucidation of pathogenic mechanisms involved in Friedreich's ataxia. The mechanisms whereby the liver modifies a wide range of substances are similar in each case. A similar mechanism holds for such diverse substances as acetaminophen, bromobenzene and other aromatic compounds and halogenated hydrocarbons such as chloroform. The carcinogenic, mutagenic or lethal effects of these compounds are due to their conversion to entities capable of covalent bond formation at appropraite nucleophilic sites.

The pyrrolizidines are representative of a small but growing class of substances known to cause pulmonary hypertension and other manifestations of lung toxicity following dietary intake. There is recent realization that the lung is peculiarly exposed to the toxic actions of ingested substances (Fishman, 1974). After absorption and passage through the liver, any toxin ingested reaches the lung in a comparatively high concentration where it comes into intimate contact with the pulmonary vascular bed. The entire cardiac output must pass through the lung capillaries optimizing the opportunity for blood-borne toxins to cause damage.

The possibility must be considered that a toxin, endogenous or exogenous in origin, causes microthrombi formation and vascular damage in the lung circulation, affecting the right heart and modifying the course of the cardiomyopathy.

## BIOCHEMICAL DISTURBANCES

A constellation of biochemical disturbances have been found in Friedreich's ataxia which are probably interrelated. None of these disturbances is well established. There may be a dysfunction in the calcium regulation of the heart, which may be responsible for the high resting heart rate and its rapid increase on light exercise. Other cardiac findings can be rationalized in terms of an increased flux of calcium across the cell membrane. In the Quebec cooperative study, the one heart available for autopsy showed severe and diffuse intercellular fibrosis, with areas of intracellular calcifications (Sanchez-Casis et al., 1976). These calcified areas were particularly abundant in the septum and close to the conduction system. Increased transport of calcium across the cell membrane could be due to a number of possible mechanisms. Hartman and Booth (1960) suggested that the pathogenic mechanism of the myocardial damage was a result of sympathetic overactivity secondary to lesions of the vagal nuclei. In such a case, the cardiac muscle is abnormally sensitive to adrenergic stimulation. Such stimulation normally results in increased flux of calcium across the membrane, thereby mediating the normal chronotropic and inotropic responses to adrenergic agonists. If the muscle were overly sensitive, this response would be exaggerated. This mechanism in arterial smooth muscle has been suggested as a cause of arterial hypertension (Sivertsson and Olander, 1968). Other causes of abnormally high calcium flux through the membrane could be an intrinsic high permeability to calcium. High calcium flux may also be related to a defect in taurine transport discussed below.

Whatever the case, calcium overload has a number of important consequences. High fluxes of calcium in the cells comprising the sinoatrial node and conducting tissue have a chronotropic effect, which could account for the high heart rate observed in most Friedreich's ataxia patients. In addition, high calcium flux in myocytes has a marked inotropic action, causing a high cardiac output. A prolonged stimulation of cardiac contractility, particularly when combined with low filling pressures as a result of pulmonary obstruction, would induce ventricular hypertrophy. In addition, cell calcium levels are the most important determinant of energy consump-



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tion by the heart. The basis for the importance ascribed to alterations in calcium fluxes lies in the central role this ion plays in excitation — contraction coupling. A summary of its function in this process is available from many sources including Langer (1973, 1976).

Another possible biochemical abnormality is an impairment of oxygen transportation or utilization (Malo et al., 1976). Myocardial metabolism is sometimes anerobic (Thoren, 1964) and ischemia is occasionally detected (Hartman and Booth, 1960). Blood oxygenation levels are low, both absolutely and in comparison to patients suffering idiopathic scoliosis (Bureau et al., 1976). An intrinsic impairment of oxygen availability to the cell would have a synergistic effect on calcium overload.

A recent finding in Friedreich's ataxia is the presence of a possible defect in tubular resorption of taurine by the kidney (Lemieux et al., 1976). Although serum levels of this amino acid were normal, urine levels were twice normal and the clearance rate was markedly elevated. The average clearance of 12 patients examined was 58.9 ml/min/1.73 meter$^2$. Normal values depend on whose figures are accepted, but reported clearances of taurine range between 2 to 20 ml/min/1.73 meters$^2$. Taurine (2-aminoethansulfonic acid) is a $\beta$-amino acid and is transported in the brain, heart, platelets and kidney by a system specific for $\beta$-amino acids. It shares this system with $\beta$-alanine.

The relevance of this observation to the heart is that taurine is the most abundant amino acid present in this organ, comprising in excess of 50 percent of the total free amino acid pool. Its function in the heart awaits definition, but it has been shown to have a modifying influence on calcium kinetics (Huxtable, 1976). It increases the retention of calcium by the heart. The extra calcium is held in a bound form — i.e., it is not part of the free calcium pool in the cell — that can interchange with the free calcium so that there is an increase in the calcium that may be effluxed from this pool (Dolara et al., 1973). As taurine concentrations in the heart are several hundred times higher than in the serum, its transport into the heart is energy dependent.

It has been shown that $\beta$-adrenergic stimulation of the heart leads to stimulation in taurine influx (Huxtable and Chubb, 1977). This observation is important in linking two previously unconnected mechanisms for modifying cell calcium concentrations. Adrenergic stimulation leads to increased calcium flux through the cell. Although the stability constant for complex formation between calcium and taurine is low, it has been calculated that about eight percent of the free cell calcium in the heart cell is present as a taurine complex (Dolara et al., in press). This is a consequence of the high intercellular taurine concentrations (5mM in the human) (Huxtable and Bressler, 1974a,b) compared to calcium. Furthermore, it appears that taurine causes an increase in the affinity of calcium for various intracellular structures (Huxtable and Bressler, 1973). The pathological effects of high cellular calcium concentrations are due to the free ion and hence taurine, paradoxically, protects against energy depletion and calcified deposits even though total cell calcium is increased (Huxtable and Bressler, 1973; Dolara et al., 1973).

Taurine is found in muscle of all animals, and any carnivore or omnivore receives a considerable quantity in the diet. In some carnivores it has been shown to be an essential dietary constituent, the animal not having the capacity to synthesize it. The cat, for example, suffers retinal degeneration leading to blindness when maintained on a taurine-free diet (Schmidt et al., 1976). Addition of taurine reverses the blindness (Berson et al., 1976). It is probably that taurine is an essential amino acid for the human (Sturman et al., in press).

Unfortunately, no data are available as to taurine levels in the hearts of Friedreich's ataxia patients. However, if the body is normally in taurine equilibrium the greatly increased excretion of taurine found in Friedreich's ataxia would indicate a negative taurine balance. If taurine excretion in Friedreich's ataxia is consistently greater than intake, it seems at least probable that taurine content of the heart should be gradually depleted. Taurine may therefore be closely involved in the pathogenesis of the heart problems associated with Friedreich's ataxia.

## CARDIAC PHARMACOLOGY OF CALCIUM

Although our knowledge of the biochemical changes in the heart is slight, calcium is clearly involved in the development of Friedreich's and other cardiomyopathies. The consistent T wave alterations point to disturbances of calcium and potassium fluxes involved in repolarization. The high heart rate commonly observed in Friedreich's ataxia patients, in the absence of any evidence of an overactive sympathetic system points toward some disturbances in calcium. The physiology of calcium in the heart has been referred to above. The drugs that modify calcium movements in the heart are briefly reviewed, as a basis for developing rational pharmacological treatment.

The effects of adrenergic stimulation on the various areas of the heart are summarized in Table 1.

There are a number of points in this sequence at which pharmacological intervention is possible, as indicated in Figures 1, 2. As the net effect of stimulation is increased contractility, agents which intensify the adrenergic response are positively inotropic, whereas agents which attenuate the response are negatively inotropic. A number of agents act directly at the $\beta$-receptor. Adrenergic agonists, for example mimic the action of endogenous catecholamines. The prime example is isoproterenol. This has a greater adrenergic potency than either epinephrine or norepinephrine. Agents are also available which block the receptor. These are the $\beta$-antagonists or, as they are sometimes known,



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TABLE I
*β RESPONSES IN THE HEART*

| | |
|---|---|
| Sinoatrial node | Increased rate |
| Ventricles | Increased contractility |
| Atria | Increased contractility<br>Increased conduction velocity |
| Atrioventricular node | ↑ Conduction velocity<br>↓ Refractory period |
| His-Purkinje fibers | Increased automaticity |
| Coronary blood vessels | Vasodilatations |
| Metabolism | ↑ Glycogenolysis<br>↑ Lipolysis |

the β-blockers. For a physiological or pharmacological response to be produced at a receptor, two steps are necessary; first, receptor occupancy must occur, and secondly, occupation of the receptor must lead to an event; in this case, activation of adenylate cyclase. These two steps may be differentiated. Blockers bind competitively to the receptor, thereby denying access to the endogenous ligand, but do not produce the normal physiological response. As most blockers used pharmacologically are competitive inhibitors, i.e., the blockade can be overcome by excess of an agonist, the concept of complete blockade has no meaning. The degree of receptor blockade is a function not only of antagonist concentration and binding affinity, but of the agonist concentration present. Propranolol is an example of a widely used β-antagonist.

Yet another class of compounds acting at the adrenergic receptor are the partial agonists, such as dichloroisoproterenol and alprenolol. These agents bind to the receptor, eliciting an agonistic effect, but then are not readily displaced. Access to the receptor is blocked, leading to partial adrenergic blockade.

Pharmacological agonistic reactions at the β-receptor may also be produced indirectly (Fig. 1). Physiologically, norepinephrine is released from peripheral storage sites by sympathetic stimulation. Drugs are available which potentiate the release of norepinephrine from these storage sites. AMP and tyramine are examples of such drugs. Other drugs have mixed actions, having direct effects at the β-receptor and also indirect effects. Examples of this class are ephedrine, phenylpropanolamine, and dopamine. The two types of actions may be differentiated by use of reserpine. Reserpine causes a chronic depletion of peripheral storage sites, and if an indirect agonist is given subsequently, no adrenergic effect is produced and there is no additional catecholamine to be released. Direct and indirect acting sympathomimetics may also be differentiated on the basis of structure. Direct acting agents are either catecholamines or contain a metaphenol β-hydroxy grouping.

One other drug which may be mentioned here is cocaine. Cocaine has a potentiating adrenergic effect due to its action in blocking reuptake of norepinephrine at the peripheral storage sites. The action of norepinephrine is thereby prolonged.

Drugs are also available which modify adrenergic responses intracellularly (Fig. 2). The actions of cyclic AMP are potentiated if phosphodiesterase is inhibited. One class of drugs inhibiting phosphodiesterase are the methylxanthines, such as theophylline. Structural analogs of cyclic AMP are also used to mimic this action; tubercidin cyclic phosphate being one. The net effect is that direct or indirect acting adrenergic agonists and xanthines increase cyclic AMP concentrations within the cell, whereas β-antagonists decrease concentration.

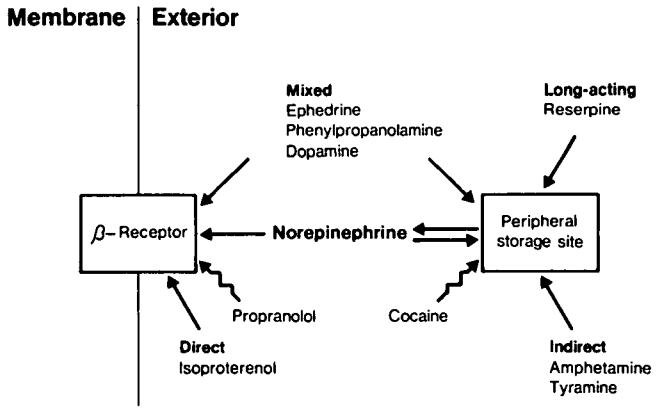


*Figure 1*—Drugs affecting β-adrenergic receptor responses. Norepinephrine is the endogenous agonist ⟶ drugs mimicking or potentiating the action of norepinephrine. ⟶ drugs having inhibitory effects.

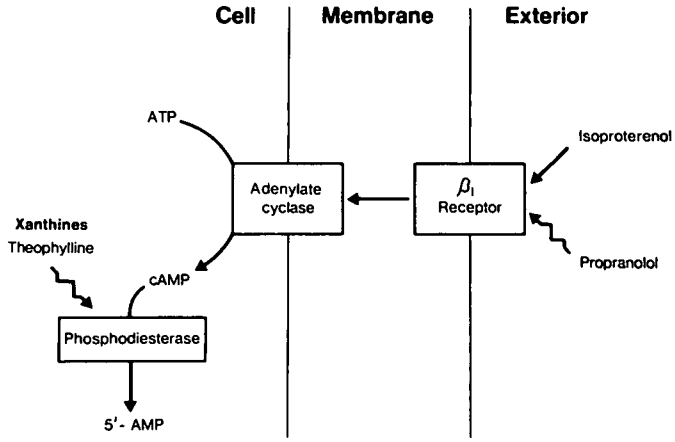


*Figure 2*—Production and breakdown of cAMP within the cell. Stimulatory and inhibitory effects indicated as in Fig. 1.



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Propranolol decreases calcium flux into the cell by β-receptor blockade. However, in addition to this, propranolol has a direct calcium antagonistic effect at the cell surface (Fig. 3). Clinically, propranolol is used as a mixture of the stereoisomeric D and L forms (or to use modern nomenclature, R and S forms). Only the L form has adrenergic antagonistic activity, but both forms have membrane stabilizing and direct calcium antagonistic effects. Other agents are available which are efficient direct antagonists of calcium entry, but which have no adrenergic activity. Nifedipine is an example, one molecule blocking the entry of several thousand calcium ions. Verapamil is another (Fleckenstein et al., 1975).

Mention may be made of another agent having inotropic and chronotropic effects on the heart, mediated via cyclic AMP. This is the polypeptide glucagon. Although this compound mimics the effect of adrenergic agents, it has no affinity for the β-receptor. As one would expect, its actions are not antagonized by β-blockade.

Another clinically important class of drugs affecting calcium entry independently of the adrenergic system are the cardiac glycosides, or digitalis glycosides. At therapeutic levels, they have an inotropic action, and at toxic levels they are arrhythmogenic. It is likely that the first action is caused by increased calcium flux into the cell, and the second by increased potassium loss from the cell. A confusing number of different glycosides are available. The mechanism of action is identical and the differences between them are mainly in the rates of absorption, distribution, metabolism and excretion. Although glycosides have been used for 200 years and have been intensely studied, their mechanism of action is still widely debated. However, the major biochemical action which correlates with the pharmacological response is that of sodium potassium ATPase inhibition, and the majority of scientists think the effects of the drug are a consequence of the inhibition of this enzyme (Fig. 4).

One other class of agents increasing calcium flux through the cell is the calcium ionophores. Ionophores are lipo-soluble compounds containing a hydrophilic region capable of binding cations. By virtue of these two properties, these compounds may act as carriers, shuttling ions from one side of a membrane to another. By appropriate chemical modification of the hydrophilic region, these compounds may be made more or less specific for various ions. One point that is often overlooked in discussions of ionophores is that ions may only be transported down a concentration gradient. All the presence of the ionophore does is to create a pathway whereby ions may move passively from a region of high to a region of low concentration, and when equal concentrations are achieved on either side of a membrane, net movement of ions will cease. Two ionophores that show a specificity for calcium are

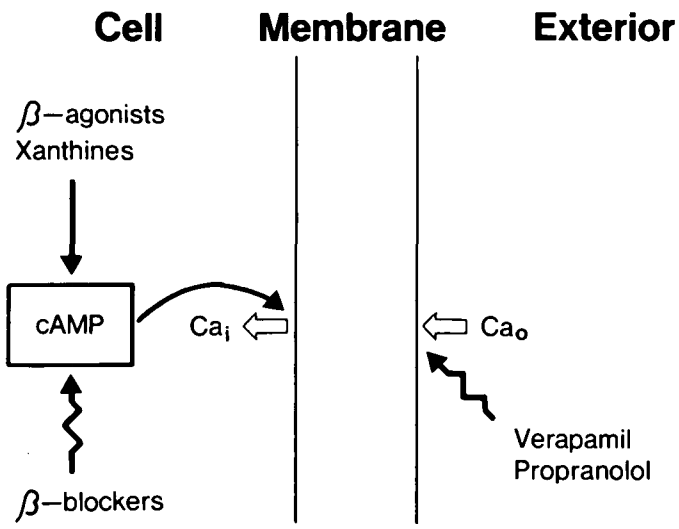


*Figure 3*—Agents influencing calcium flux across the cell membrane. Symbols as in Fig. 1.

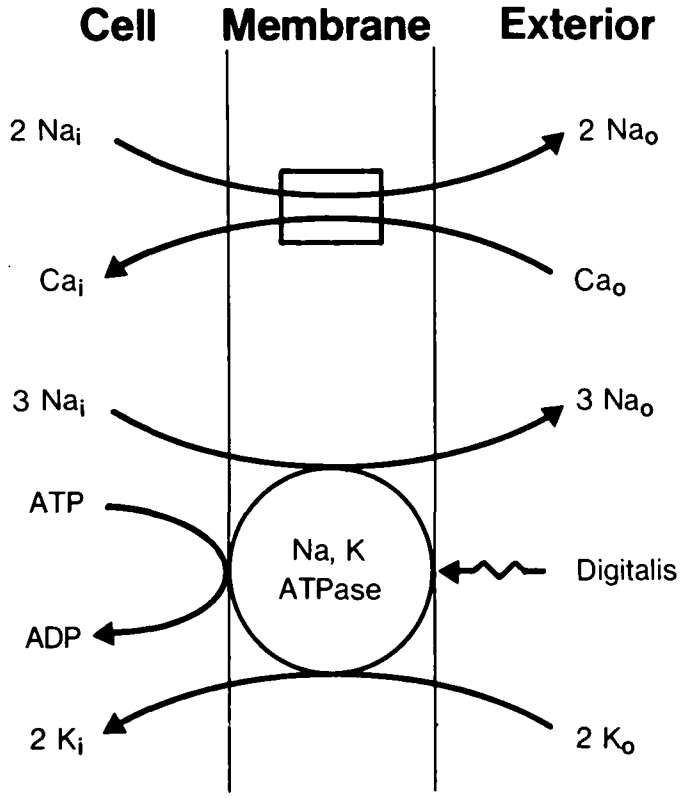


*Figure 4*—The interaction of cardiac glycosides with ion movements across the cell.



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X-537A and A-23187. These modify calcium flux across the membrane in a manner that is not affected by calcium antagonists such as verapamil or $\beta$-blockers. However, the effects of these agents are complicated by their additional ability to transport norepinephrine. They are extremely useful research chemicals and compounds of this class may have eventual clinical application.

The above discussion can be summarized in the statement that agents which increase the flux of calcium through the heart cell are positively inotropic (and usually chronotropic), whereas agents which decrease the flux of calcium are negatively inotropic. The high energy cost of calcium movement into and out of the heart has been discussed in a previous section. Furthermore, calcium is a key substance in excitation contraction coupling. The energy for contraction-relaxation is provided by myosin ATPase activity, and this enzyme is calcium-dependent. Apart from the direct cost of moving calcium, therefore, this ion is responsible, by virtue of its stimulatory effect on myosin ATPase, for a major fraction of the energy consumption of the cell. Oxygen consumption and the consumption of high energy phosphates are critically dependent on the free calcium concentration within the cell. Where conditions of calcium overload prevail, a dangerous fall in high energy phosphate concentrations occur, and myocardial fibrosis and hypertrophy result. These conditions may be achieved by chronic exposure to high levels of adrenergic agonists. Isoproterenol-induced cardiac hypertrophy has been a widely used experimental model (Huxtable and Chubb, 1976). This is associated with necrotic lesions, intracellular calcium deposits and damage to the microcirculation (Stanton et al., 1969). Deficiencies in high energy phosphates also result from exposure to metabolic uncouplers such as fluoroacetate, cyanide, dinitrophenol, or anoxia.

The effects of calcium overload are antagonized by $\beta$-blockers. A pharmacologically more specific effect can be obtained by the use of calcium antagonists. Verapamil, like the $\beta$-blocker propranolol, reduces heart rate, myocardial oxygen demand, and increases cardiac efficiency (Fleckenstein et al., 1975). It does not abolish exercise-induced tachycardia. Unlike propranolol, it has no membrane stabilizing or local anesthetic effects. The pharmacological action of verapamil is highly specific, being limited to reduction of cell membrane bound to calcium, and blockade of calcium entry to the cell. As a result of these actions, it is an uncoupler of excitation-contraction coupling. This in turn leads to a loss of contractility caused by interference with calcium dependent hydrolysis of ATP. Cell ATP and phosphocreatine content rise. This contrasts with the loss of contractility produced by metabolic inhibitors such as fluoroacetate, in which there is a sharp fall in ATP levels. The effects of verapamil are summarized as: a) inhibition of contractility without impairment of action potential, b) a decrease in oxygen demand per beat, c) a higher than normal high energy phosphate content, d) a fall in the velocity of tension development, with a fall in the stroke volume and cardiac output, e) the above effects are reversed by calcium chloride, or calcium promoters such as $\beta$-adrenergic agonists or cardiac glycosides.

## THERAPEUTICS AGENTS

The lack of detailed information regarding the etiology makes certainty impossible, but some suggestions may be made regarding pharmacological treatment. There may be an imbalance in the whole body regulation of taurine in Friedreich's ataxia. Taurine is a normal dietary constituent and has not been shown to have deleterious effects in clinical trials at high doses (Bergamini et al., 1974; Van Gelder et al., 1975; Takahashi and Nakani, in press). As the urinary excretion of taurine is high in Friedreich's ataxia patients it is quite possible that cardiac levels are being slowly depleted. Oral therapy with taurine would thus be indicated. Normally, excess levels of taurine are rapidly excreted through the kidney. Friedreich's ataxia, however, may be a special situation requiring continual large intake of taurine due to the deficiency in renal resorption of this amino acid.

There is incomplete evidence that there may be an actual or relative calcium overload in Friedreich's ataxia hearts. This is suggested by the apparent sympathetic overstimulation (high heart rate), anoxia, and calcium overload in Friedreich's ataxia heart.

These conditions should be ameliorated by verapamil as suggested by Barbeau (1976). Such an agent is preferable to a $\beta$-blocker because of the specificity of its effect.

As a corollary to the use of verapamil, caution should be exercised in the use of positively inotropic agents, which would place an additional energy demand on the heart.

## FURTHER INVESTIGATIONS

Definitive objectives are missing in the treatment of this cardiomyopathy because of the basic deficiency in our knowledge. Some suggestions are made below as to how we can increase our basic knowledge.

Clinical material has numerous and obvious limitations and therefore research of this and other cardiomyopathies has to be done on appropriate model systems. For a model system to be experimentally useful it does not have to mimic all aspects of the human disease.

The cardiomyopathic Syrian hamster is one model that appears to be appropriate. This animal suffers a genetic cardiomyopathy that gets progressively worse over its life. The cardiomyopathy is associated with the deposition of calcium within the myocardial cell and the sarcoplasmic reticulum shows a markedly decreased ability to bind calcium. The primary defect is thought to reside in a modification of the cell plasma membrane which renders it more permeable to calcium (Jasmin et al., 1975). The incidence and sev-



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erity of the cardiac lesions are decreased if the animals are kept on a calcium-deficient diet or if they are treated with verapamil.

Another model of experimental utility is the progressive right ventricular hypertrophy produced by chronic administration of pyrrolizidine alkaloids (Huxtable et al., 1977). Right ventricular hypertrophy begins to develop after two weeks of exposure to pyrrolizidines. This makes it possible to study biochemical changes which precede hypertrophy, as well as those accompanying it. For example, alterations in the permeability to calcium or variations in influx of taurine can be determined at different stages of hypertrophy. In this model, concommitant administration of propranolol has been shown to reduce the severity of the hypertrophy.

A third model that may be considered is isoproterenol-induced cardiac hypertrophy (Stanton et al., 1969). A dose and time dependent hypertrophy is produced by chronic adrenergic stimulation. Essentially, the hypertrophy is a result of calcium overload on the myocardial cell. The model has been used extensively for certain types of study, and also has application in the study of calcium overload on cellular metabolism.

There are numerous animal models available for various types of cardiac dysfunction, and the above suggests some of the advantages of three.

Another need is to increase the data base available on Friedreich's ataxia cardiomyopathy. A major problem is the difficulty in obtaining material for study. Both metabolic and structural information would be valuable. One question is whether organ taurine concentrations are lowered in Friedreich's ataxia patients. If they are, replacement thereapy is called for as an experimental procedure. It would be valuable to have information as to whether there is a defect in calcium permeability in the heart, or whether calcium fluxes are over-responsive to sympathetic stimulation. Possibly these questions could be studied on smooth muscle fibers.

Further information is needed as to the ultrastructural changes that accompany the cardiomyopathy.

The different patterns of left versus right ventricular hypertrophy seen in different studies suggest that external influences may be modifying the response of the heart. One approach would be a study of the diet of Friedreich's ataxia patients and their families. Are they being exposed to abnormal concentrations of hepatotoxins, heavy metals, aflatoxins or industrial chemicals? There is evidence that a subgroup of Friedreich's ataxia patients have impaired liver function. Does this affect the further development of an underlying cardiac defect?

## CONCLUSION

Friedreich's ataxia is almost always associated with a cardiomyopathy. The cardiomyopathy and its attendant cardiopulmonary sequelae are the usual causes of death, occurring at 29-30 years on average. If remission of the cardiac problems could be attained, the life expectancy of those suffering from this disease would be extended, preserving a group of people who have a valuable contribution to make to society. One only has to read the story of Claude St. Jean, the founder of L'Association Canadienne de l'Ataxie de Friedreich, to appreciate the social costs of this disease to all of us.

Despite the major place of cardiac problems in this disease, no direct or consistent treatment — pharmacological or otherwise — has been used. As outlined above, I believe there is sufficient rationale for more aggressive pharmacological treatment. However, the data base is insufficient for a vigorous and effective therapeutic solution of this problem. Further information, particularly at the biochemical level, is essential before major progress may be made.

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