Editorial

Thyroid heart disease

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The concept of thyrocardiac disease was introduced by Samuel Levine (Levine and Sturgis, 1924) who described atrial arrhythmias, congestive cardiac failure, and cardiac enlargement in hyperthyroidism occurring even in the absence of overt evidence of thyroid disorder. His clinical descriptions are as pertinent today as when they were written but it has always been a matter for conjecture whether thyroid disease in any of its forms can produce either specific pathological changes in the heart or an identifiable cardiac syndrome. The consensus from published work indicates that thyrocardiac disease as such is a clinical entity (Sandler and Wilson, 1959a; Staffurth and Morrison, 1968). Probably too much emphasis has been given to alterations in cardiac rhythm, a phenomenon symptomatic of associated muscle excitability. This survey discusses some of the experimental and clinical aspects of thyrocardiac disease and shows that a spectrum of response exists which may have a bearing on the nature of cardiomyopathy itself.

Action of thyroid hormones

The precise mode of action of thyroid hormones, thyroxine and tri-iodothyronine, is uncertain but contemporary view accepts that they have a direct inotropic and chronotropic effect on the heart. Much data have come from experimentally produced thyrotoxicosis and caution should be exercised in relating the results of animal experiments to the clinical situation in man, especially as the level of thyroxine dosage employed may exert effects at pharmacological and not physiological levels (Bernal and Refetoff, 1977). DeGroot (1972) has summarised the various ways the heart may be affected by thyroid hormones; the effects may be secondary to an increased cardiac output from a raised total body oxygen consumption, in turn the result of a

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direct action of thyroxine on mitochondrial oxidative phosphorylation, protein, and ribonucleic acid synthesis. Additionally adenylate cyclase activity may be altered and there may be an augmented response to catecholamines. There is now good evidence that the earliest action of thyroid hormones is to accelerate the basal respiratory rate of mitochondria (Hoch, 1967; Cohen, 1974). Experimentally, Zaimis *et al.* (1969) and Page and McCallister (1973) have shown that thyroxine greatly increases the number of mitochondria in the heart muscle cell and this change occurs before muscle hypertrophy. Hypertrophy has been described both in animals given thyroid hormones (Sandler and Wilson, 1959b; Cohen *et al.*, 1966) and in hyperthyroidism in man (Sandler and Wilson, 1959a).

Cellular activity is activated by adenylate cyclase which catalyses the production of cyclic $3'5'$ AMP from ATP. Until recently it was thought that the positive inotropic and chronotropic effects on the heart produced by thyroid hormones were mediated in part by the action of catecholamines on the adenylate cyclase system. It now seems possible that there are separate adenylate cyclase systems for thyroid hormones and catecholamines (Levey and Epstein, 1969). Though it is accepted that in hyperthyroidism there is a normal sensitivity to circulating catecholamines, and plasma catecholamine levels are not increased (Stoffer *et al.*, 1973), the clinical picture presents as a summation effect of augmented adrenergic and thyroid responses. Buccino *et al.* (1967) have shown experimentally, in the isolated cat papillary muscle preparation, that the level of thyroid activity profoundly affects the intrinsic contractile state of cardiac muscle, independent of both noradrenaline stores and alterations in high energy phosphates. Beta-blockade reduces tachycardia and improves the general well-being of the hyperthyroid patient but does not reduce the excessive oxygen consumption (Howitt and Rowlands, 1967), return the heart rate to normal, or affect the underlying pre-ejection phase of cardiac contraction and duration of left ventricular

systole (Pietras *et al.*, 1972). The role of calcium may be important, for the intrasarcomeric movement of this ion is intimately related to excitation-contraction coupling in cardiac muscle (Langer, 1968). Liu and Overman (1964) have shown that thyroxine increases the accumulation of intracellular calcium, and Nayler *et al.* (1971) showed that microsomes, prepared from the heart muscle of animals rendered hyperthyroid, accumulate and exchange calcium more readily than microsomes from euthyroid heart muscle.

Clinical thyrocardiac disease

The prime haemodynamic change in hyperthyroidism is an increase in cardiac output, more so than is actually required to accommodate the rise in oxygen consumption (Kroetz *et al.*, 1962). The reason for the increased flow is obscure, but it is relevant that the heart has excessive work to perform arising from both increased preload caused by augmented peripheral flow, and by afterload resulting from the drive of thyroid hormones on the myocardial cell itself. The opposite prevails in hypothyroidism where even the low cardiac output is sufficient for the depressed metabolic requirements of the body. Essentially, thyroid hormones cause an unremitting positive inotropic and chronotropic effect on the heart in hyperthyroidism. In this respect, the circulatory changes arising in thyroid disease provide us with a useful model to indicate how any heart would respond over a prolonged time to near-maximal preload and afterload stimulation. We should be able to find examples of many forms of rhythm and heart muscle disorder arising from this form of stress and this appears to be the case. This hypothesis helps explain both the hyperkinetic circulatory response and the physical signs in the cardiovascular system, though persistent damage to the heart in any form of thyroid disorder can only be truly assessed when the endocrine condition has been fully treated. It also becomes simple to understand why, if some additional burden is present, as in mitral disease if a patient becomes hyperthyroid, severe circulatory changes manifest very quickly.

Clinically, the effects of thyroid hormones will be to produce changes in cardiac rhythmicity or of heart muscle function, or of both. There is little doubt that until recently, because of the dramatic effects on cardiac rhythm, the equally important underlying muscle changes have received insufficient attention. In hyperthyroidism, sinus tachycardia, ventricular ectopic beats (unifocal or multifocal), either singly or in salvoes, paroxysmal and then persistent atrial fibrillation, are common. There may

be a specific predisposition to changes in atrial rhythm in thyroid disease. Five per cent of all clinically euthyroid patients with paroxysmal or permanent atrial arrhythmias were found to have underlying hyperthyroidism, as disclosed by routine laboratory screening procedures (Symons *et al.*, 1978). Wan *et al.* (1972) have described a high incidence of thyroid disorder in patients with sinuatrial disease. Instances of prolongation of the PR interval have been described (Hoffman and Lowrey, 1960) and the Wolff-Parkinson-White syndrome has been reported in thyrotoxicosis, with reversion to normal conduction after treatment of the thyroid condition (Strong, 1949; Sanghvi and Banerjee, 1961). Transitory and frequently florid inversion of T waves are commonly present in severe hyperthyroidism in younger patients and in the more acutely ill subject (Hoffman and Lowrey, 1960).

Most of the physical signs in hyperthyroidism other than those resulting from arrhythmias can be explained by the high output circulatory state. Vasodilatation and increased peripheral flow are manifest by warm extremities, a bounding pulse, and an easily visible jugular venous pulsation. Biventricular cardiac enlargement may be present, there is a snapping first heart sound, an apical third sound (or mid-diastolic flow murmur), or a basal systolic bruit, classically scratchy in character. An apical early peaking systolic murmur is occationally audible (Ueda *et al.*, 1963) and is probably the result of a muscle sound produced during the phase of powerful isovolumic contraction. In the older patient, signs may be minimal despite the increased cardiac output and the accent is more on chronic rhythm disturbance, that is atrial fibrillation. Cardiac failure, unusual today because of earlier diagnosis and an increased index of suspicion in unexplained cardiac disease, may be insidious in onset and high-output congestive in type, and is almost invariably accompanied by rapid atrial fibrillation. It is in these cases particularly that an underlying muscle problem must be sought, but both modern haemodynamic data and endomyocardial biopsy material are lacking in this form of thyrocardiac disease. Non-invasive techniques such as the estimation of systolic time intervals and left ventricular ejection times appear promising in the assessment of myocardial performance in thyroid disease (Parisi *et al.*, 1974; Burckhardt *et al.*, 1978).

Bradycardia with low voltage T waves in the electrocardiogram is common in hypothyroidism but occasionally the rate may be normal, and instances of arrhythmias which resolve, somewhat paradoxically, by treatment with thyroxine, have been reported (Ohler and Abramson, 1934; Hansen, 1961). Paroxysmal rapid arrhythmias also

occur in patients with autoimmune thyroid disease, impaired thyroid reserve but normal serum levels of thyroxine (Symons *et al.*, 1978). Cardiac enlargement is usually the result of increased diastolic filling from bradycardia and, infrequently, caused by a large pericardial effusion. Minor degrees of effusion are common but are only detectable by echocardiography (Kerber and Sherman, 1975). Graettinger *et al.* (1958) found no haemodynamic evidence of cardiac failure in this condition and this accords with the rarity of failure and the generally complete resolution of physical signs on adequate treatment with thyroxine. Much debated is the role of atherosclerosis in hypothyroidism. Steinberg (1968) in a necropsy study of myxoedema found that coronary disease was more obvious only when hypertension had been present in life. Vanhaelst *et al.* (1967) failed to observe any increased frequency of occurrence of myocardial infarction in untreated or in inadequately treated patients with thyroid failure, though they reported an increase in incidence in coronary artery disease in these cases. The association of a raised serum cholesterol level in patients who are euthyroid but who have positive thyroid antibodies has been described by Bastenie *et al.* (1967) and Fowler and Swale (1967). It is claimed that recognition and treatment with thyroxine of this form of subclinical hypothyroidism or 'premyxoedema' may prevent progression to atherosclerotic disease (Fowler *et al.*, 1970). This is still a contentious matter, for thyroid disease is predominantly a disorder affecting women while coronary heart disease is much more common in men. Tunbridge *et al.* (1977) in an extensive survey of a mixed urban and rural population concluded that there was no association between cholesterol or triglyceride levels and thyroid antibodies or thyroid stimulating hormone (TSH) and that any relation between ischaemic heart disease and minor degrees of thyroid failure was unlikely to be mediated by lipid abnormalities. Symons *et al.* (1978) have not recorded a raised cholesterol or a propensity to coronary artery disease in patients with subclinical hypothyroidism, and they suggest either a cardiomyopathic response resulting from autoimmune disease or adverse effects on the myocardium of circulating analogues of thyroid hormones.

Cardiomyopathy and thyroid disease

Considerable clinical variation exists in the manner in which thyroid hormones affect the heart and circulation. Generally the non-cardiac element of the endocrine disorder will overshadow symptoms and signs, and little notice is (or need be) taken of the cardiovascular status, which will return to normal once treatment of the thyroid condition is effected. An entirely different situation is extant in the older subject who is less likely to show evidence of thyroid disease though the underlying metabolic disturbance is still pronounced. Thyroid disease as the precipitating cause of arrhythmias, cardiac failure, and even angina pectoris may go unrecognised for many years before hyperthyroidism is diagnosed (Somerville and Levine, 1950), and it is this form of hidden thyroid disorder, both under- and over-activity, which may be responsible for prolonged cardiac invalidism. Appropriate treatment then clearly indicates the endocrine basis of the hitherto idiopathic nature of the cardiac condition. Occasionally with the return of the euthyroid state it is evident that some form of heart muscle disease is present, especially if atrial fibrillation remains or recurs after DC reversion. Congestive cardiomyopathy caused by previous thyroid disease becomes the only possible diagnosis. An indication that cardiomyopathy may be allied to metabolic disorder is suggested from the work of Resnekov and Falicov (1977) who described patients with hyperthyroidism and lactate-producing angina pectoris but with normal coronary vessels as assessed by cineangiography. The clinical findings related to the experimental findings become even more complex and concern the role of analogues of tri-iodothyronine and thyroxine, triac and tetrac, respectively. These substances appear to have a direct action on heart muscle by increasing cellular respiration with only a marginal increase in the overall metabolic rate (Barker and Lewis, 1956; Lerman, 1961). In 1971, Symons *et al.* reported the presence of circulating triac and tetrac in a euthyroid patient with heart disease who later became hyperthyroid. Because of this and because longstanding thyroid disease had been reported in patients with hypertrophic cardiomyopathy (Symons *et al.*, 1974), a series of experiments was designed using carefully titrated doses of thyroid hormones to simulate longstanding covert hyperthyroidism and to study the effect on the myocardium. In the first experiment (Symons *et al.*, 1975) hypertrophy was produced in the heart of young adult rats, more so by triac than by thyroxine; in the second study gross changes of muscle fibre disarray at subcellular level, comparable with that seen in hypertrophic cardiomyopathy in man, were produced in the fetal but not the maternal heart when triac was given to pregnant rats (Olsen *et al.*, 1977). Propranolol prevented the production of disarray but not the changes of simple hypertrophy (Olsen *et al.*, 1978), and this finding may again revive earlier hypotheses that the circulatory manifestations of hyperthyroidism are mediated through the sympatho-adreno-

medullary system (Brewster *et al.*, 1956). Equally interesting possibilities merit consideration. Is hypertrophic cardiomyopathy an endocrine disorder, possibly caused or accentuated in fetal life by some alteration in thyroid metabolism? This is of particular interest, for experimentally the placenta is relatively impermeable to thyroxine, tri-iodothyronine, and TSH (Fisher, 1975). Does a hyperkinetic or hypertrophic circulatory state precede obstructive hypertrophic changes as Perloff (1971) and Williams *et al.* (1973) have suggested? Is this change initiated in fetal life during rapid development when the heart muscle may be vulnerable to any physiological or pathological stimuli having inotropic and chronotropic effects? Bulkley *et al.* (1977) have shown that disarray of myocardial fibres is relatively common in some forms of congenital heart disease. Another possibility is that analogues of thyroxine and tri-iodothyronine are present in the circulation in adult life and, because of minimal evidence of overall metabolic disturbance, are able to cause underlying heart muscle disease. Further work is required to determine the respective role of catecholamines and thyroid hormones in producing hypertrophic cardiomyopathy and the related changes of gross muscle disarray. Clinically, in patients with heart disease, a reliable method of estimation of circulating analogues of thyroid hormones is needed.

Treatment

It is not the purpose of this review to discuss in detail the modes of clinical presentation of thyroid heart disease. Unexplained cardiac symptoms or signs in any patient with or without heart disease should lead to a request for laboratory assessment of thyroid status, especially a serum thyroxine estimation, thyroid antibodies, and ideally TSH levels after thyrotrophin-releasing hormone stimulation. A biochemical diagnosis of hyper- or hypothyroidism, despite the absence of clinical evidence of thyroid disease, should lead to effective treatment and may result in impressive recovery, especially in the older subject who has suffered prolonged cardiac ill health. Indeed there is much to commend a serum thyroxine estimation as a routine screening procedure in all patients in the latter half of life with cardiac disability.

Knowing the excessive systemic overload caused by hyperthyroidism on the one hand and cellular depression produced by hypothyroidism on the other, the various forms of treatment that are available can be rationalised. A remarkable advance in the treatment of hyperthyroidism occurred with the advent of beta-blocking drugs which competitively

inhibit the action of catecholamines at the beta-adrenergic receptor sites. Propranolol is still the best of these compounds and has immediate effect in reducing anxiety, tremor, and tachycardia, and does much to bring the acute manifestations of thyrotoxicosis under control. Nevertheless it does not alter the underlying thyrotoxic disorder, and carbimazole, thyroid surgery, or radioiodine treatment will still be required as definitive treatment in the majority of cases. Too large a dose of propranolol in the acute state is unnecessary and can occasionally be harmful since the metabolic action of thyroxine is unaffected and the negative inotropic and chronotropic effects of beta-blockers on the heart could compromise myocardial function. Digoxin and diuretic treatment is indicated in the high output cardiac failure state with atrial fibrillation caused by hyperthyroidism. The serum levels of digoxin are low in thyroid overactivity, principally because of increased renal excretion (Croxson and Ibbertson, 1975), and larger doses than usual are required which should be given after estimating serum levels. It is important to realise that cardiac glycosides will still augment contractility of cardiac muscle to the same maximum as that observed in the euthyroid state (Buccino *et al.*, 1967). Occasionally propranolol is indicated with digoxin and diuretics, even in the presence of cardiac failure, to combat otherwise uncontrollable atrial fibrillation. In younger patients atrial fibrillation will usually revert to sinus rhythm when the euthyroid rate is attained, but in the older subject this may not be the case and DC reversion is indicated. Most are reverted and remain in sinus rhythm, but if the arrhythmia persists or returns then it is possible that cardiomyopathy is present. Congestive cardiomyopathy is treated in the usual way with digoxin and diuretics, as antithyroid treatment has already been used. Staffurth *et al.* (1977) have reported frequent episodes of arterial embolism in their patients with thyrotoxicosis and atrial fibrillation, and for whom they recommend anticoagulation if under the age of 65 years. Hypertrophic cardiomyopathy can only be regarded at present as an incidental and additional form of cardiac disorder occasionally occurring with hyperthyroidism, though Bell *et al.* (1978) report a high incidence of hyperthyroidism in patients with hypertrophic disease. Propranolol is still the best form of treatment for this condition.

In myxoedema the cautious institution of thyroxine therapy is essential for, though failure is rarely present in the florid state, the capacity of the heart to respond to increased peripheral demand is limited and left ventricular failure may be precipitated. Pericardial effusion as shown by echocardiography may take some time to disappear but it is only

infrequently of clinical significance. It is not yet known whether treatment for premyxoedema will prevent overt disease or if it delays progression of atherosclerosis.

To think of thyroid disorder as a possible cause of illness in a patient with heart disease, be it an unexplained arrhythmia or some form of cardiomyopathy, is to request a laboratory profile of thyroid function tests. The measure of improvement that can be obtained by appropriate treatment is satisfactory not only to the patient but to the cardiologist who realises that covert thyroid disease is often clinically undiagnosable. It is salutary to reflect that in 1936 Levine wrote of thyroid heart disease as, 'probably the most important aspect of all heart disease for it comprises the one large group of cases in which the difference between accurate and inaccurate diagnosis and treatment is the difference between chronic invalidism or death and restoration of health and life'. Methods of diagnosis and treatment have improved almost beyond measure since this statement was made, but awareness that thyroid disease may be present as an associated cause of cardiac ill health is still not fully recognised.

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