Leading Article

Drug and non-thyroid induced changes in thyroid function tests

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The basis of good medicine is a careful history and a thorough examination, supplemented by a minimum of tests to confirm the diagnosis. There is, however, an increasing tendency to perform screening tests just in case (Bahemuka & Hodkinson, 1975; Hodkinson & Denham, 1977). Screening tests for thyroid disease are particularly fraught with difficulty, since there are at least 11 different tests available, each of them capable of being carried out by several different techniques and the results of each of them can be subject to alteration in one direction or another by non-thyroidal disease or by drug therapy, as illustrated by an article in this issue (Wilkins *et al.*, 1985).

Thyroxine (T_4) is the main hormone secreted by the thyroid gland. Once in the circulation most of it is bound to thyroxine-binding globulin (TBG), a lesser amount of thyroxine-binding pre-albumin (TBPA) and albumin and a small fraction (0.05%) remains in the free form. Peripherally 25% of the T_4 is mono-deiodinated to form the more active hormone triiodothyronine (T_3), though a small amount of T_3 is also secreted directly by the thyroid gland. T_3 , like T_4 , is bound to the above mentioned proteins, though less so than T_4 . The main effects of non-thyroid illness and of drugs are on the binding proteins, the degree of binding and on the conversion of T_4 to T_3 . Changes in any of these may alter thyroid function tests and lead to misleading diagnoses of either hyper- or hypothyroidism.

The most commonly seen abnormality in clinical practice is the rise in total T_4 and T_3 in women who are pregnant or who are on oral contraceptives; this is caused by an oestrogen-dependent rise in TBG and thus in total hormone bound to it. A measurement of the free thyroxine index (FT_4I) or of free thyroxine (FT_4) measured by equilibrium dialysis will be normal in euthyroid patients on oral contraceptives, but it should be noted that in pregnant patients, particularly in the third trimester, the FT_4I may be slightly elevated (Ramsay, 1984) and the FT_4 and FT_3 may be below the

normal non-pregnant range (Ramsay, 1984). Drugs other than oestrogens which may cause rises in T_4 and T_3 due to increased binding include clofibrate, 5-fluorouracil, heroin and methadone (Wenzel, 1981). A small number of patients may have an increased amount of TBG due to porphyria (Kaplan, 1984) or as an inherited familial disorder (Jones & Seal, 1967).

Reduced amounts of T_4 and T_3 in the blood may be due to a low level of TBG. This may be either familial or due to diseases such as Cushing's syndrome, acromegaly and nephrotic syndrome (Kaplan, 1984). A drug-induced reduction in the binding proteins may also occur; the drugs responsible are androgens, anabolic steroids and danazol (Graham & Gambrell, 1980; Wenzel, 1981), but the commonest cause is a drug-induced inhibition of binding, most often due to fenclofenac (Ratcliffe *et al.*, 1980), though this drug has now been withdrawn from the UK market. Other drugs which can produce the same phenomenon are diazepam, heparin, phenylbutazone, salicylates, sulphonylureas (Wenzel, 1981), halofenate and o-p' DDD (Kaplan, 1984).

Another mechanism by which levels of T_4 and T_3 may be reduced by drugs is by enzyme induction in the liver. The drugs involved are those used in the treatment of epilepsy and include carbamazepine, phenobarbitone, phenytoin and primidone (Larsen *et al.*, 1970; Heyma *et al.*, 1977; Wenzel, 1981).

Both iodide and lithium inhibit the release of thyroid hormones from the thyroid and may lead to low levels of T_4 and actual clinical hypothyroidism, particularly in those who are genetically susceptible to thyroid autoimmune disease (Braverman *et al.*, 1971; Spaulding *et al.*, 1977). Amiodarone, which contains large amounts of iodine, can do the same thing or conversely may cause an iodide-induced thyrotoxicosis in a patient who is predisposed to Graves' disease or who has an autonomously functioning multinodular goitre (McKenna *et al.*, 1983). Other effects of amiodarone are discussed below. Sodium nitroprusside and co-trimoxazole have a slight thyroid inhibiting effect and may cause lowered T_4 levels (Wenzel, 1981). Somatostatin has a similar effect,

though via inhibition of TSH release by the pituitary (Wenzel, 1981).

Although T_4 levels are sometimes reduced in euthyroid hospital in-patients (Gooch *et al.*, 1982), because of low levels of binding proteins, it is more common to find increased T_4 in this population (Mankikar and Clark, 1981; Gooch *et al.*, 1982). The cause is either a high TBG which is familial or due to pregnancy, oestrogens, chronic active hepatitis (Schussler *et al.*, 1978), primary biliary cirrhosis (Schussler *et al.*, 1978) and acute intermittent porphyria or to collagen disease and myeloma (Kaplan, 1984).

In many acutely or chronically ill euthyroid patients a slight rise in T_4 is due to inhibition of the peripheral conversion of T_4 to T_3 . There are reduced T_3 levels (Bermudez *et al.*, 1975; Gooch *et al.*, 1982) and an increase in the inactive hormone reverse T_3 (rT_3). These changes are seen in febrile states, renal failure, anorexia nervosa, cirrhosis, disseminated malignancy and following surgery (Cavalieri & Rapoport, 1977). However, it is important to note that T_3 levels are normally lower in old age than in the young (Cavalieri & Rapoport, 1977). Similar slight rises in T_4 with reduction in T_3 and an increase in rT_3 may be found with amiodarone (Burger *et al.*, 1976), sodium iopodate for oral cholecystography (Bürge *et al.*, 1976; Wu *et al.*, 1978; Beng *et al.*, 1980), propranolol and certain other β -adrenergic receptor blockers (Kristensen & Weeke, 1977; Cooper *et al.*, 1982; Perrild *et al.*, 1983), high dose glucocorticoids, iobenzamic acid and tyropanoic acid (Wenzel, 1981). Propylthiouracil (Geffner *et al.*, 1975) and iodide will tend to reduce the T_4 also because of a direct inhibiting effect on the thyroid gland.

How then is one to sort out whether a patient with

an abnormal T_4 or T_3 has or has not got thyroid disease? Direct measurement of fT_4 or fT_3 by radioimmunoassay after equilibrium dialysis will be normal in most circumstances but note that fT_4 can be elevated by sodium iopodate (Bürge *et al.*, 1976), propranolol (Kristensen & Weeke, 1977; Cooper *et al.*, 1982; Wilkinson *et al.*, 1985 this issue) and acetylsalicylic acid (Langer *et al.*, 1978) and decreased by phenytoin (Larsen *et al.*, 1970), phenylbutazone (Abiodun *et al.*, 1973) and fenclofenac (Humphrey *et al.*, 1980). Likewise the fT_3 can be reduced by sodium iopodate (Beng *et al.*, 1980), amiodarone (Burger *et al.*, 1976), propranolol (Wilkins *et al.*, 1985), in pregnancy (Ramsay, 1984), fever, renal failure, following surgery, cirrhosis and disseminated malignancy (Cavalieri & Rapoport, 1977).

In most cases where hypothyroidism is suspected because of low thyroid hormone results, but the patient is really euthyroid, the basal thyroid stimulating hormone (TSH) levels will be within the normal range. Borderline high TSH results can be sorted out by means of the thyrotrophin releasing hormone (TRH) test (Hall *et al.*, 1973) when an exaggerated response will suggest hypothyroidism, particularly if thyroid antibodies are also present. The TRH test is also useful in the converse situation, that of suspected hyperthyroidism. A flat response of TSH to TRH (Hall *et al.*, 1973) is compatible with the diagnosis. The only situation in which one might get a drug-induced flat response is if a patient is on high dose (e.g. 8 mg) dexamethasone (Cavalieri & Rapoport, 1978). Even here the response in a euthyroid patient is not completely flat (Wenzel, 1981) and a normal response can be achieved by increasing the dose of TRH (Otsuki *et al.*, 1973).

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