Clinical Algorithms

Hyperlipidaemia

LILIAN E MURCHISON

Hyperlipidaemia is defined as excess concentrations of cholesterol or triglyceride, or both, in plasma. In the general population plasma lipid concentrations show a continuous distribution, and it is difficult to say which lipid concentrations constitute the upper limits of normal or which justify treatment. Most practitioners would accept as raised cholesterol concentrations above 6·5 mmol/l (251 mg/100 ml) and fasting triglyceride concentrations above 1·5 mmol/l (133 mg/100 ml) for females and 2·1 mmol/l (186 mg/100 ml) for males (the 90th percentile figures in a carefully screened London population[1]). In practice, the decision of how far to investigate and treat hyperlipidaemia with the aim of preventing ischaemic heart disease is based not only on serum lipid concentrations but also on considerations such as the age of the patient, a family history of early onset atherosclerotic disease, and the presence of other risk factors such as hypertension. Patients with severe familial hyperlipidaemia may require prophylactic treatment or treatment not only of atherosclerosis but also of xanthomata and, when appreciable hypertriglyceridaemia is present, of abdominal pain or pancreatitis. Although most cases of hyperlipidaemia may be diagnosed and managed by the family practitioner or general physician, the rarer severe disorders may require the diagnostic facilities and skills of specialised centres.

Classification

Hyperlipidaemia may develop as a result of various disorders, in which case it is known as secondary hyperlipidaemia. Primary hyperlipidaemias include all those not shown to be secondary and are often genetically determined.

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PRIMARY HYPERLIPIDAEMIAS

Because cholesterol and triglyceride are unevenly distributed in the four major lipoprotein categories hyperlipidaemias may be more usefully considered in terms of hyperlipoproteinaemia. The most widely accepted classification is the World Health Organisation's modification[2] of the original Fredrickson description of types I to V based on serum lipoprotein patterns, which has been followed, with increasing knowledge, by a genetic classification (table). Types I, IIa, IIb, IV, and V are due to excessive concentrations of lipoproteins that are normally present in the serum, whereas in type III the abnormal lipoprotein concentration results from accumulation of the cholesterol rich remnant formed during degradation of very low density lipoprotein.

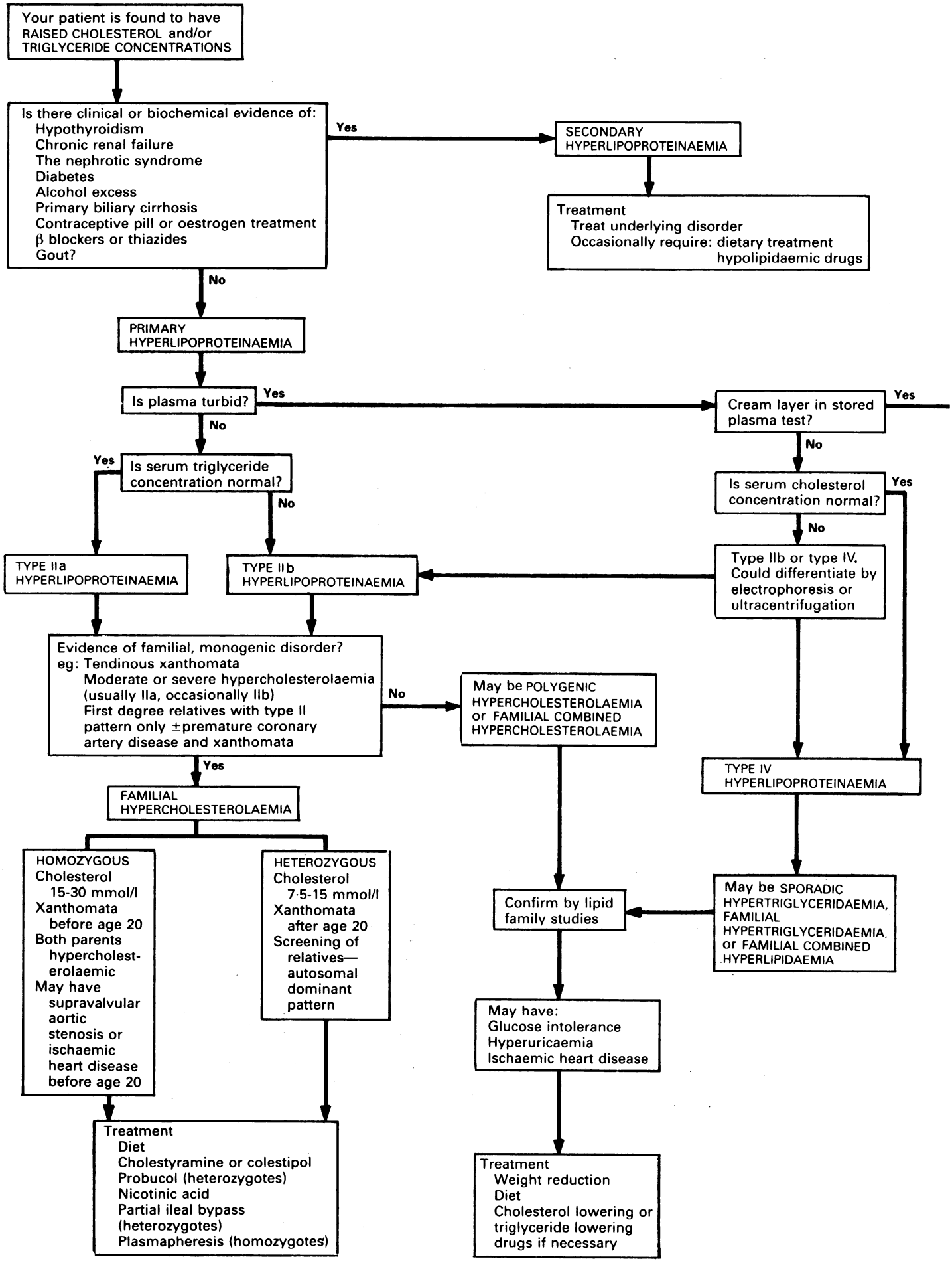
Classification and characteristics of hyperlipidaemias

Type*	Prevalence	Lipoprotein abnormality	Usual changes in plasma lipid concentrations		Stored plasma test		Genetic classification†
			Cholesterol	Triglyceride	Top layer	Infranatent	
I	Rare	Chylomicrons	+	+++	Cream	Clear	Familial deficiency of lipoprotein lipase or activator
IIa	Common	Low density (β) lipoprotein	++	Normal	Nil	Clear	Familial hypercholesterolaemia (uncommon) or familial combined hyperlipidaemia
IIb	Common	Low density (β) and very low density (pre-β) lipoproteins	++	++	Nil	Clear or slightly turbid	Familial combined hyperlipidaemia or (rarely) familial hypercholesterolaemia
III	Uncommon	"Broad-β" (floating-β") lipoprotein	++	++	Slight cream	Turbid	Familial hyperlipoproteinaemia type III
IV	Common	Very low density (pre-β) lipoprotein	Normal or +	++	Nil	Turbid	Familial hypertriglyceridaemia or familial combined hyperlipidaemia
V	Uncommon	Very low density (pre-β) lipoprotein and chylomicrons	+	++	Cream	Turbid	Familial hyperlipoproteinaemia type V or severe familial hypertriglyceridaemia

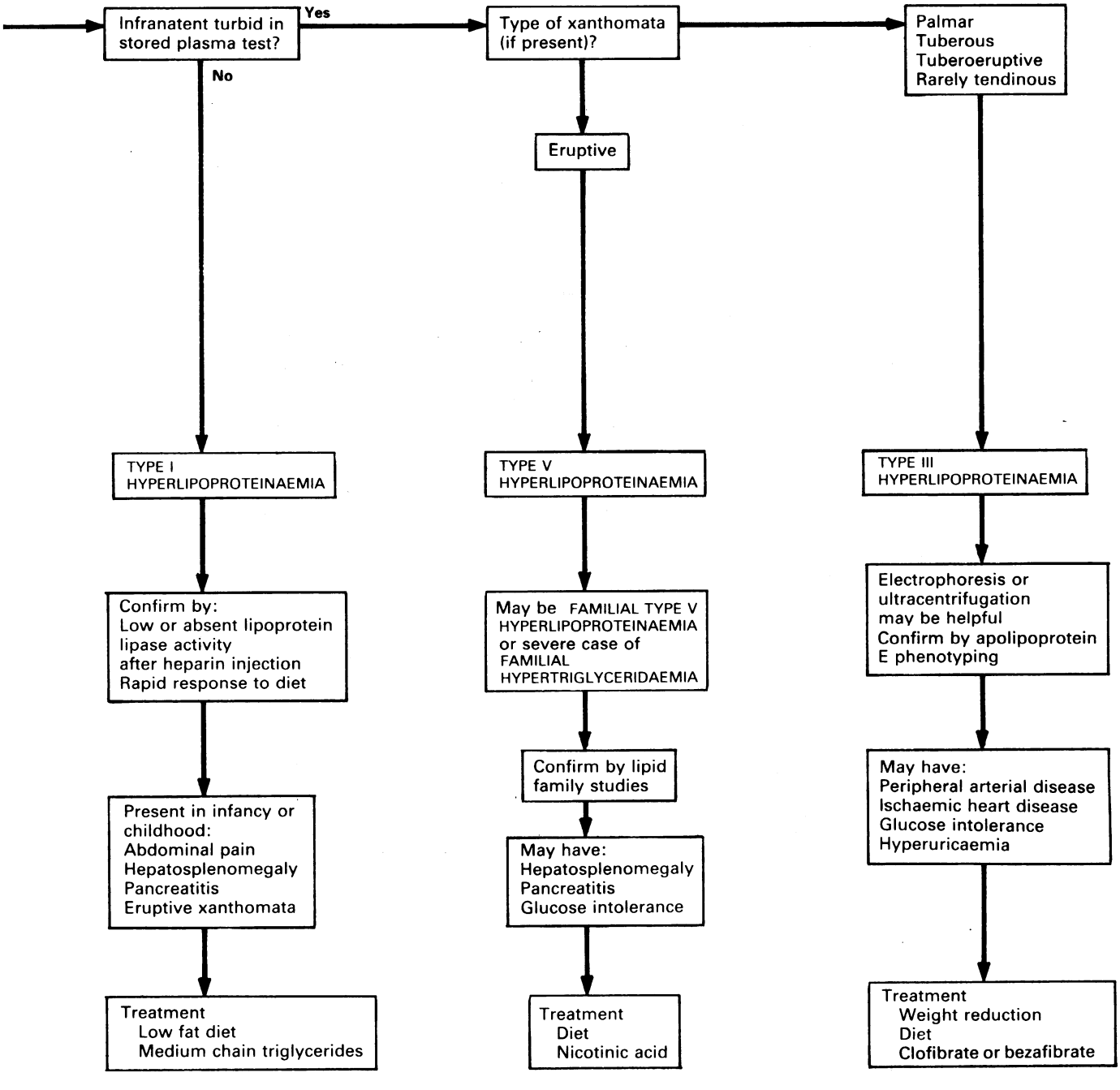
*WHO classification.[2] †Fredrickson *et al.*[3]

Most patients can be classified for clinical purposes by serum cholesterol and triglyceride concentrations and a stored plasma test. An increase in serum total cholesterol usually indicates increased concentrations of low density lipoprotein (β lipoprotein). Occasionally, however, mild hypercholesterolaemia may be due to increased concentrations of high density lipoprotein cholesterol (a condition not associated with untoward consequences and possibly even protective against ischaemic heart disease). Conversely, some patients with raised low density lipoprotein concentrations may not have increased serum total cholesterol. In addition, some of the hyperlipidaemias in which there is an increase of both cholesterol and triglyceride concentrations may be difficult to characterise further without measurement of lipoprotein.

Most hyperlipidaemic subjects owe their abnormality to a complex interaction of polygenic and environmental factors, and fewer than one in five have one of the six familial hyperlipoproteinaemias, which it is thought may be single gene disorders (table).[3] Patients with three of these disorders (familial deficiency of lipoprotein lipase or its activator producing type I pattern, familial hypercholesterolaemia with type IIa or rarely type IIb pattern, and familial type III hyperlipoproteinaemia) can be distinguished on the basis of characteristic clinical and biochemical abnormalities. Patients with the three other probably monogenic disorders (familial hypertriglyceridaemia with type IV or, if



Hyperlipidaemia



severe, type V pattern, familial combined hyperlipidaemia with type IIb, IIa, or IV patterns, and familial type V hyperlipoproteinaemia) can be distinguished from patients with multifactorial hyperlipidaemia only by lipid studies in relatives.

SECONDARY HYPERLIPIDAEMIAS

Various conditions such as hypothyroidism, diabetes, the nephrotic syndrome, chronic renal failure, dysproteinaemias, pregnancy and oral contraceptives, alcohol excess, idiopathic hypercalcaemia, primary biliary cirrhosis, gout, and drugs such as β adrenergic antagonists and thiazides may cause hyperlipidaemia. Some are typically associated with hypercholesterolaemia or mixed hyperlipidaemia—for example, hypothyroidism commonly results in type IIa or IIb patterns—and some with hypertriglyceridaemia —alcohol may result in type IV or V patterns—but there are many exceptions.

Diagnosis

HISTORY

Inquiry should be made for symptoms suggestive of disorders causing secondary hyperlipidaemias, possible manifestations of hyperlipidaemia such as xanthomata or abdominal pain with or without pancreatitis, and vascular complications of hyperlipidaemia such as ischaemic heart disease or peripheral arterial disease. A careful family history should be elicited with respect to early onset atherosclerotic disease or xanthomata indicating familial hyperlipidaemias, or hypothyroidism or diabetes suggesting possible causes of secondary hyperlipidaemias.

EXAMINATION

This should be directed at detecting: possible causes of secondary hyperlipidaemia such as hepatic, renal, or endocrine disease; clinical manifestations of hyperlipidaemia such as corneal arcus, xanthomata (xanthelasma, tendinous, tuberous, planar, palmar, or eruptive), and lipaemia retinalis; and possible complications such as ischaemic heart disease or peripheral arterial disease.

INVESTIGATIONS

Determining whether hyperlipidaemia is secondary—Routine urine analysis may show glucose, protein, or bile pigments. Hypothyroidism should be excluded by estimating thyroid stimulating hormone and thyroxine concentrations, and blood urea and uric acid concentrations, liver function tests, serum calcium (in paediatric practice), and serum protein electrophoresis may point to other disorders causing hyperlipidaemia. The finding of a macrocytic blood picture with or without an increase in serum γ-glutamyltransferase activity may be helpful in recognising alcohol induced hypertriglyceridaemia.

Confirming and classifying hyperlipidaemia—If hyperlipidaemia is thought to be present at least two estimations of cholesterol and triglyceride concentrations with minimal venostasis after an overnight (12-14 hour) fast should be obtained in view of day to day variations in lipid concentrations. These estimations are best made about a week apart, while the patient continues his usual food intake, and should be taken at least three months after a major illness such as myocardial infarction. If the serum triglyceride concentration is raised or serum is lipaemic, or both are true, a stored plasma test should be carried out by allowing a tube of separated serum or plasma to stand vertically overnight in a refrigerator (not a freezer) and inspecting for a cream layer (chylomicrons) or turbidity of the infranatent, or both. Estimation of high density lipoprotein cholesterol concentration is within the competence of most laboratories. Less reliance is placed on lipoprotein electrophoresis than formerly, but it may indicate the presence of the broad β band of type III hyperlipoproteinaemia and helps in the recognition of raised high density lipoprotein concentrations as a cause of mild hypercholesterolaemia. Measurement of lipoprotein by ultracentrifugation is time consuming and expensive but may be valuable in the management of some severe hyperlipidaemias. In certain primary hyperlipidaemias the diagnosis may be confirmed by specific tests available in special centres. In homozygous familial hypercholesterolaemia the absence of high affinity, low density lipoprotein receptors can be shown in cultured skin fibroblasts or blood mononuclear cells. In familial deficiency of lipoprotein lipase or activator, lipoprotein lipase may be assayed in adipose tissue, or in plasma after heparin injection, or activator deficiency confirmed by immunoassay. The abnormal apo-E isoprotein pattern in type III hyperlipoproteinaemia can be confirmed by isoelectric focusing.

Assessing vascular complications—Electrocardiography may help in the diagnosis of ischaemic heart disease.

Screening of relatives—Confirmation of appreciable primary hyperlipidaemia is an indication for investigation of lipid concentrations in first degree relatives.

Treatment

If treatment of hyperlipidaemia is deemed desirable most patients can be managed by such measures as weight control, dietary modification, or reduction in alcohol intake and only a minority require hypolipidaemic drugs. Attention should also be given to coexisting risk factors such as cigarette smoking and hypertension.

DIET

Correction or even partial correction of obesity is a valuable first step in the management of hyperlipidaemia. With the exception of hypertriglyceridaemia due to defects in the lipoprotein lipase system (in which a low fat diet is necessary), a single set of dietary modifications achieves satisfactory lipid reduction in many hypercholesterolaemic and hypertriglyceridaemic patients. This consists of reducing the intake of saturated fatty acids from the 20% of the average British diet to 8-10% of energy requirements, with polyunsaturated fatty acids providing 7-10% of energy, cholesterol intake being reduced to less than 300 mg/day, and intake of complex carbohydrates and fibre being increased.

References

1 Lewis B, Chait A, Wootton IDP, *et al*. Frequency of risk factors for ischaemic heart disease in a healthy British population. *Lancet* 1974;i:141-6.
2 Beaumont JL, Carlson LA, Cooper GR, Fejfar Z, Fredrickson DS, Strasser T. Classification of hyperlipidaemias and hyperlipoproteinaemias. *Bull WHO* 1970;43:891-915.
3 Fredrickson DS, Goldstein JL, Brown MS. The familial hyperlipoproteinaemias. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease*. 4th ed. New York: McGraw-Hill, 1978:604-55.

Some laboratories are now offering "cytotoxic" testing to identify food allergy or intolerance. What tests are done and are they of any value?

The identification of foods or food components causing symptoms of food intolerance in individuals is extremely difficult. In practice a time consuming series of elimination diets is probably one of the more satisfactory procedures available.[1] The difficulties of this approach have led many workers to search for a less demanding and more specific approach. It was claimed that the white blood cells of patients exhibiting symptoms degenerate and die in the presence of the specific foods producing symptoms.[2] This "cytotoxic" approach is difficult to reproduce and is believed to be of little diagnostic value.[1]—D A T SOUTHGATE, head nutrition and food quality division, Food Research Institute, Norwich.

1 Royal College of Physicians and British Nutrition Foundation. Food intolerance and food aversion. *J R Coll Physicians Lond* 1984;18:3-41.
2 Black AP. New diagnostic method in allergic disease. *Paediatrics* 1956;17:716-23.