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Hyperlipoproteinaemia in gout

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It has previously been noted that the plasma urate concentration is often raised in essential hyperlipoproteinaemia (Harris-Jones, 1957). Indeed, secondary gout complicating the primary lipid disorder is recognized (Strejček and Kučerová, 1968). However, the mechanism of this hyperuricaemia is obscure, and there is little data on the effect of various plasma lipid-lowering agents on plasma urate levels (Oliver, 1962; Trevaks and Lovell, 1965; Strejček and Kučerová, 1968).

Conversely, moderate elevations of plasma triglyceride levels have been reported in patients with primary gout (Berkowitz, 1964; Feldman and Wallace, 1964; Barlow, 1968), although the influence of gout therapy on the lipid levels is unknown.

In the present study the effect of probenecid and allopurinol on the serum triglycerides, cholesterol, and lipoprotein pattern in patients with primary gout is reported. In addition, observations were made on the clearance from plasma of an intravenous triglyceride emulsion before and after therapy, to elucidate the role of abnormal triglyceride removal mechanisms in the hyperlipidaemia of gout.

Material and methods

Serum urate levels were estimated by an automated procedure (Technicon no. N-13b). The upper limit of normal for men is 7·0 mg./dl.

Serum triglyceride levels were estimated by the automated procedure of Cramp and Robertson (1968). The upper limit of triglyceride concentration apparently increases during adult life. In a recently studied series of fifty metabolically normal male subjects over the age of 40 years, the mean fasting serum triglyceride concentration was 102 mg./dl., standard deviation 30 (Greenhalgh and Rowe, 1970), giving a probable upper limit of normal of 162 mg./dl. Serum cholesterol was measured by an automated procedure (Technicon no. N-24).

Lipoprotein electrophoresis was performed on hyperlipidaemic sera using the method of Chin and Blankenhorn (1968).

Fat tolerance tests were conducted by a method modified from that of Boberg, Carlson, and Hallberg (1969), in which the disappearance from plasma of an intravenous dose of the fat emulsion 'Intralipid' (Vitrum, Stockholm) is measured. The fat load was 0·1 g./kg. body weight. The fractional turnover rate of the triglyceride tracer dose is normally 4·9 per cent. per min. to 11·1 in subjects below 28 years of age, and 2·6 to 5·8 in subjects above 38 years.

33 patients, all males, were studied. 32 were thought to have primary gout and one essential hyperuricaemia without gout. Their ages ranged from 32 to 75 years (mean 53) and the duration of disease from 1 to 22 years (mean 8·6). None had overt diabetes mellitus and all but two had fasting blood sugar levels of less than 90 mg./dl. All had normal blood urea levels.

The patients took no therapy, other than colchicine 1 mg. daily, for at least 3 weeks before the initial estimations. Fasting serum triglyceride, cholesterol, and urate levels were then measured and a fat tolerance test performed. Treatment with therapeutic doses of probenecid or allopurinol was commenced or resumed in 24 patients and the biochemical tests repeated after 3 to 10 weeks of continuous therapy. During the whole study the patients ate their usual diets.

Results (Table, opposite)

Serum urate levels in patients receiving no therapy ranged from 7·4 to 12·4 mg./dl. (mean 9·5). In the 24 patients subsequently investigated during probenecid or allopurinol therapy, urate levels ranged from 3·4 to 9·5 mg./dl. (mean 5·7) indicating a significant drug effect ($P < 0·001$).

Thirteen patients had fasting serum triglyceride levels exceeding 162 mg./dl; seven of these had concentrations of more than 200 mg./dl including three (Patients 6, 8, and 26) with gross elevations of pre- and post-therapy levels. All patients with hypertriglyceridaemia showed an increase in pre-β lipoprotein bands on electrophoresis of fasting serum (Figure, overleaf), except Patient 6 in whom both pre-β lipoproteins and chylomicra were present in large amounts.

The mean serum triglyceride levels for the group as a whole was 210 mg./dl. and showed no significant change (to a mean of 236 mg./dl.) after probenecid or allopurinol therapy. However, in nine of the 24

Table *Serum urate, cholesterol, and triglyceride concentrations (mg./dl.) and fractional turnover rate of fat emulsion (per cent./min.) before and after gout therapy*

Patient No.	*Therapy*	*Serum urate*		*Serum triglyceride*		*Fractional turnover rate*		*Serum cholesterol*	
		Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	Probenecid	11·1	5·8	87	67	3·9	5·2	ND	150
2		9·3	7·4	104	48	4·3	5·8	ND	200
3		9·3	3·6	72	62	4·1	3·2	320	345
4		9·2	4·1	205	182	3·1	2·6	160	220
5		12·4	7·7	170	86	2·8	3·6	ND	180
6		10·5	6·4	1300	2380	1·1	1·3	220	385
7		9·2	5·0	106	65	3·9	4·1	210	190
8		10·7	6·9	1300	480	0·87	1·9	270	190
9		9·1	9·5	65	52	9·3	9·3	185	160
10		7·5	3·7	87	107	2·0	4·1	175	170
11		8·6	4·4	62	145	2·1	2·4	260	245
12		10·6	5·0	175	174	ND	ND	170	170
13		ND	5·5	ND	80	ND	ND	ND	220
14		ND	6·7	ND	163	ND	ND	ND	260
15	Allopurinol	7·7	3·4	175	117	4·5	4·3	215	ND
16		8·0	4·5	138	100	3·2	4·8	235	225
17		7·6	5·8	98	104	3·6	3·2	205	190
18		8·6	5·6	192	255	4·1	4·5	220	210
19		7·4	5·1	130	309	2·4	2·8	260	260
20		10·1	6·8	158	148	2·2	1·8	180	175
21		10·9	8·1	137	96	6·4	9·3	175	165
22		10·4	5·1	112	137	4·3	3·5	200	205
23		9·6	5·8	61	54	4·3	8·2	225	200
24		11·3	6·6	100	212	5·5	5·5	255	255
25		8·2	6·0	188	132	2·7	ND	195	185
26		10·0	4·9	340	490	1·5	ND	205	185
27		ND	5·6	ND	106	ND	ND	ND	195
28		ND	4·3	ND	139	ND	ND	ND	170
29		ND	5·5	ND	170	ND	ND	ND	185
30		ND	6·2	ND	122	ND	ND	ND	230
31	None	7·4	ND	136	ND	ND	ND	185	ND
32		7·7	ND	135	ND	ND	ND	200	ND
33		7·9	ND	138	ND	ND	ND	180	ND
Mean		9·5	5·7	210	236	3·7	4·3	212	211

ND = not done

patients triglyceride levels fell by 15 per cent. or more (from a mean of 266 to 132 mg./dl.).

The fractional turnover rate of triglyceride during the fat tolerance test showed no significant change after drug administration. In eight of 21 patients, however, the rate of plasma clearance of injected triglyceride increased significantly after therapy—from a mean of 3·3 per cent./min. to 6·1 per cent./min. ($P = 0·03$). In six of these eight patients this increase was associated with a reduction in serum triglyceride concentration.

The mean serum cholesterol level was 212 mg./dl. before and 211 mg./dl. after therapy. Patient 3 had moderate hypercholesterolaemia (345 mg./dl.), due to hyperbetalipoproteinaemia. In this patient the pre-β lipoprotein band was normal. The hypercholesterolaemia in Patient 6 was associated with, and likely to be due to, a massive increase in pre-β lipoprotein and chylomicra.

Discussion

A surprisingly high incidence of hypertriglyceridaemia was found in this series of patients with hyperuricaemia or gout. Levels exceeding 162 mg./dl. occurred at some stage of the study in thirteen out of the 33 subjects, and levels greater than 200 mg./dl. were recorded in seven. In twelve of the hypertriglyceridaemic subjects lipoprotein electrophoresis showed an excess of pre-β lipoprotein which is usually ascribed to hypertriglyceridaemia of endogenous origin (Frederickson, Levy, and Lees, 1967). Patient 6 with gross elevation of plasma triglyceride showed chylomicronaemia as well as an excess of pre-β lipoprotein (the Type V pattern of Fredrickson's classification). In addition, Patient 3 had a moderate excess of β lipoprotein. However, it is noteworthy that raised triglyceride levels were far more prominent in our patients than was hyper-

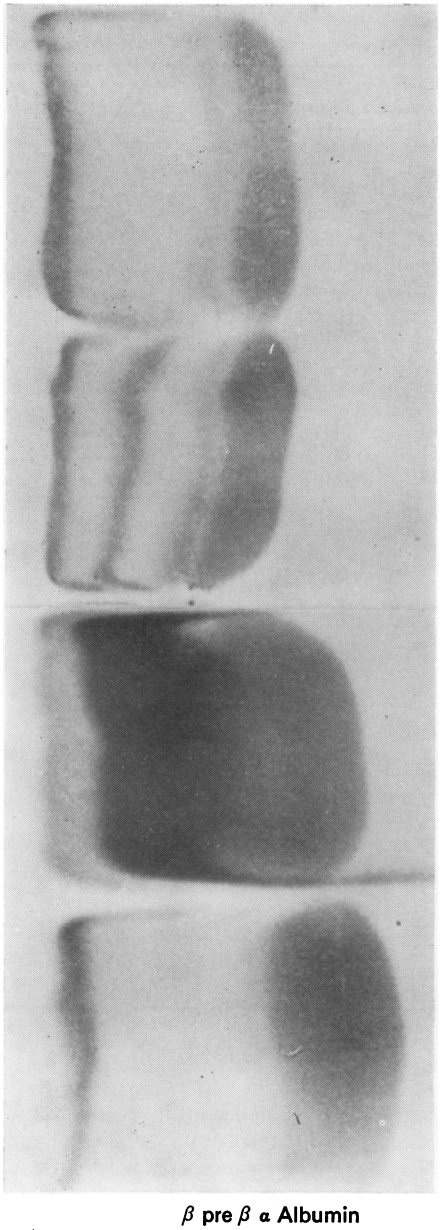

FIGURE *Lipoprotein electrophoresis on cellulose acetate (Oil-Red-O stain) of fasting serum from two normal subjects and Patients* 4 *and* 8. *Note moderately increased pre-β and in Patient* 4 *and the gross increase in Patient* 8.

cholesterolaemia and confirms the earlier observations of Berkowitz (1964).

It has only recently been appreciated that patients with various hyperlipoproteinaemias may present with gout (Strejček and Kučerová, 1968). Patients 6 and 8 had been treated in the gout clinic for many years after a diagnosis of classical tophaceous primary gout; Patient 26 was being treated for asymptomatic idiopathic hyperuricaemia. The distinction between primary gout and essential hyperlipidaemia would appear to be very difficult in some patients. Plasma lipid values and lipoprotein patterns do not provide a means of distinguishing between primary and acquired disorders of lipid metabolism, and the family history may be non-contributory. Chronic alcoholism may be associated with hypertriglyceridaemia and can also precipitate hyperuricaemia and gout; but abstention quickly corrects the abnormalities (Gebbie and Prior, 1967). However, in none of our three patients with gross hypertriglyceridaemia was alcoholism apparent.

The present study has failed to reveal any consistent direct influence of serum urate concentration on triglyceride metabolism in patients presenting with gout. Despite effective reduction in urate levels by probenecid or allopurinol, the series as a whole showed no secondary effect on serum triglyceride concentration or on peripheral uptake of an injected triglyceride emulsion. Despite this overall lack of drug effect upon serum triglyceride, nine of the 24 treated patients did show a moderate to marked reduction of triglyceride concentrations as urate levels fell. Of these, six showed a concomitant increase in triglyceride fractional turnover rate indicative of accelerated triglyceride removal. Only two patients had accelerated removal without significant falls in triglyceride levels, and in both of these the initial lipid levels were already normal. Since there is a hyperbolic relationship between triglyceride levels and fractional turnover rate, substantial differences in turnover rate may exist between subjects with normal plasma triglyceride concentrations (Boberg and others, 1969). Although it is not proven that an increased rate of plasma triglyceride removal caused the fall in lipid levels noted, this would appear to be at least partially responsible in six patients.

While the mechanism or mechanisms linking urate and triglyceride metabolism await further elucidation, the present study emphasizes the practical need to measure serum lipid levels in all patients with gout. Some forms of hyperlipidaemia are associated with the premature development of atherosclerosis (Dawber, Moore, and Mann, 1957; Allbrink and Man, 1959; Fredrickson and others, 1967). The application of recent advances in the recognition and treatment of such disorders of lipid metabolism may prove of value to a substantial minority of patients with gout.

Summary

The effects of probenecid and allopurinol on the serum triglyceride and cholesterol have been studied in patients with gout. Triglyceride levels greater than 200 mg./dl. were detected in 21 per cent. of patients, three of whom may have had unsuspected primary hyperlipoproteinaemia. Hypercholesterolaemia was far less common.

Although there was no overall significant fall in lipid levels after therapy, in some patients triglyceride concentrations fell in conjunction with a reduction in serum urate levels: in most of these an enhanced peripheral triglyceride removal appeared the likely mechanism. In view of the prognostic implications of hyperlipoproteinaemia and the availability of treatment, serum lipids should be measured in all patients with gout.

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