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CASE REPORT

LIVER DAMAGE AND ISONIAZID ALLERGY

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SUMMARY

A patient with pulmonary tuberculosis developed jaundice and manifestations of generalized allergic reaction while receiving combined treatment with streptomycin, *p*-aminosalicylate and isonicotinic acid hydrazide. Amongst various tests for allergy, the lymphocyte transformation test provided evidence of allergy to isonicotinic acid hydrazide. Follow-up suggested successful 'desensitization', and plasma glutamic oxaloacetic transaminase showed only a temporary tendency to rise whilst desensitization was being carried out.

INTRODUCTION

Both *p*-aminosalicylate (PAS) and isonicotinic acid hydrazide (Isoniazid, INAH) can produce liver damage by more than one mechanism. *p*-Aminosalicylate may produce a cholestasis of the chlorpromazine type (Simpson & Walker, 1960). Both PAS and INAH also may rarely produce a hepatitis-like condition (Paine, 1958; Cohen, Kalser & Thomson, 1961), which may be followed by extensive and fatal liver necrosis. These drugs may also affect the liver as part of generalized allergic reaction (Simpson & Walker, 1960; Bickers *et al.*, 1961), but overt liver disease under these conditions is rare (Sherlock, 1965, 1968).

The availability of relatively new immunological techniques allowed us to investigate in detail one patient who developed liver disease and manifestations of allergy whilst receiving the three major anti-tuberculosis drugs, streptomycin, PAS and INAH.

Case Report

The patient was a male, age 42, who was admitted to University College Hospital for treatment of pulmonary tuberculosis. One month after he had been receiving streptomycin, PAS and INAH, he complained of headache and malaise, which were followed by the appearance of a maculopapular rash, urticaria, high temperature (38·8°C), cervical and axillary lymph node enlargement and eosinophilia (8% of a total leucocyte count of 14,000/mm^3).

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These manifestations were very suggestive of allergy, presumably to drugs, and, therefore, anti-tuberculosis therapy was discontinued. Subsequently, the patient developed jaundice; his liver was tender but not enlarged and the spleen was not palpable. Bilirubin and marked excess of urobilinogen were found in urine, and stools were pale. It was thought that this condition might have been part of a generalized allergic reaction or virus hepatitis. Liver function tests were carried out as in Table 1, which also shows the quick rate of recovery from hepatocellular damage. It should be mentioned that this patient had had jaundice 28 years previously.

TABLE 1. Liver function tests

Date (1968)	Serum bilirubin		Flocculation tests			Plasma enzymes	
	Total (mg/100 ml)	Direct	Colloidal red	Cephalin cholesterol	Thymol turbidity (units)	GOT*	Alkaline phosphatase†
12 June	5·2	+++	+++	+++	18	1880	50·0
19 June	1·4	+				155	24·0
26 June			+	+++	9	37	14·0
3 July	0·6	−	±	++	14	23	11·0
10 July			±	++	9	16	
17 July			±	++	8	20	7·0
7 August			±	+	7	18	

* GOT = Glutamic oxaloacetic transaminase (Karmen units/min/ml).
† Alkaline phosphatase (King-Armstrong units/100 ml).

Skin tests with INAH and PAS were negative, but a wide erythematous area appeared 18 hr after the intradermal injection of 100 μg of streptomycin. Two types of *in vitro* tests for immediate-type hypersensitivity were carried out: the antigen-induced histamine release from the patient's leucocytes (Lichtenstein & Osler, 1964) and the detection of serum reagins by passive

TABLE 2. Incorporation of tritiated thymidine by lymphocyte cultures (counts/min)

Patient	Control (saline)	Isonicotinic acid hydrazide	Sodium aminosalicylate	Streptomycin
Father	624	42,053	846	961
(17 June 1968)	385	28,474	780	1020
	611	28,087	—	1858
	676	—	—	—
Father	605	2441	391	588
(1 July 1968)	373	—	471	573
Son	300	422	601	957
(1 July 1968)	671	422	726	—

— = Tubes where cultures have failed.

sensitization and histamine release from human lung (Assem & Schild, 1968). The results of these test were negative. On the other hand, the lymphocyte stimulation (transformation) test (Chalmers *et al.*, 1967) produced some useful information. Isoniazid produced a considerable proliferative activity of the cultures of the patient's lymphocytes, as shown by a marked increase in the incorporation of [^{3}H]thymidine (Table 2). Streptomycin caused a less marked response, but the effect of PAS was probably insignificant. Table 2 also shows a negative lymphocyte stimulation test (LST) in the patient's son, who had been treated at the same time for

tuberculous hilar lymphadenitis, and who had clinically-established diagnosis of allergy to INAH (manifested by skin rash and fever).

A course of progressive desensitization was started by streptomycin, followed by PAS, and then INAH (Fig. 1). Cycloserine was also given for a period of 8 weeks, while desensitization was being carried out. Chlorpheniramine (Piriton) was given during the whole course of desensitization and liver function tests, particularly plasma glutamic oxaloacetic transaminase (PGOT, Fig. 1), were repeated regularly. This course was essentially uneventful, apart from the interruption of anti-tuberculosis therapy for 2 days, when PGOT showed a tendency to rise.

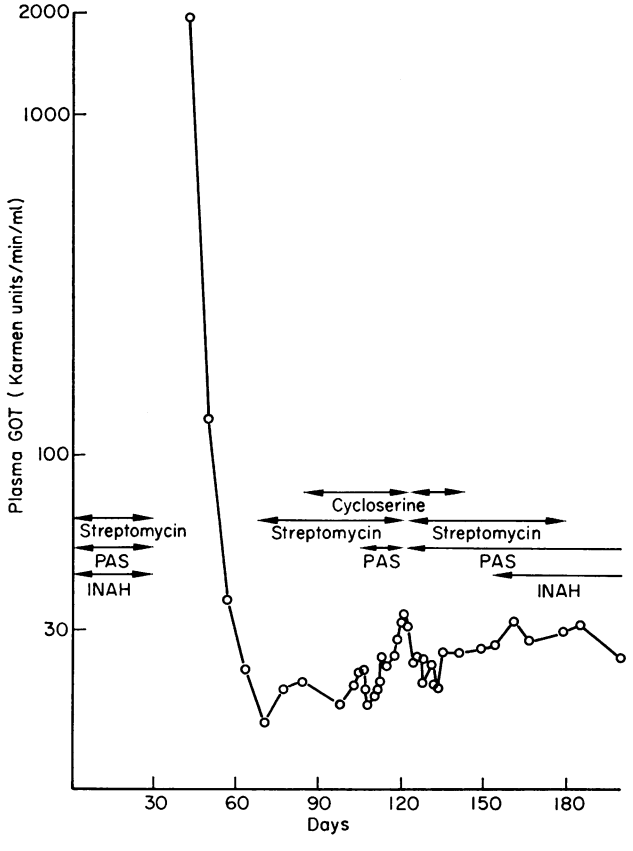

FIG. 1. Course of treatment and plasma glutamic oxaloacetic transaminase levels.

DISCUSSION

The strongly positive LST provided evidence of allergy to INAH in the father. Since negative results were obtained in tests which are specific for immediate-type hypersensitivity, allergy to INAH in this patient is most probably a delayed-type hypersensitivity. The concomitant liver damage may also be due to the same allergy, although this cannot be proved conclusively. The lack of reaction during the readministration of the suspected allergen does not exclude this possibility, as it may be explained by 'desensitization'. In patients who had developed chlorpromazine sensitivity-type cholestasis, re-exposure to this drug does not

produce a recurrence of this condition in nearly 60%, and a similar explanation seems to be generally accepted (Sherlock, 1968).

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