In contrast to the results of Dr. Alliott and others my patients showed a significant fall in Pa_{O_2} after salbutamol and a significant rise in Pa_{O_2} after isoprenaline/phenylephrine. FEV_1 response was identical with both aerosols, the dosage employed being salbutamol 200 μg, isoprenaline 320 μg, and 480 μg phenylephrine. Within the limitations of the indirect Fick C_{O_2} method, cardiac output appeared to be equally affected by both preparations (a probably insignificant rise). The rise in Pa_{O_2} after isoprenaline/phenylephrine was accompanied by a fall in Pa_{CO_2} and a reduction in V_D/V_E ratio. There was no evidence to suggest that the likelihood or degree of Pa_{O_2} fall with salbutamol was related to the baseline value.

It is difficult to know how much the inclusion of "pure" asthmatics in the series of Dr. Alliott and colleagues may have influenced the mean FEV_1 response. I would suggest, however, that chronic bronchitics with a significant degree of reversibility of airways obstruction may be more suitable subjects for this type of trial since they tend to remain stable with reproducible bronchodilator response between exacerbations. On the other hand "pure" asthmatics between attacks may not respond at all, although they are more likely to demonstrate the maximal effect of a given bronchodilator when on the upswing after an acute attack.

	Isoprenaline/ phenylephrine	Salbutamol
FEVI (litres)	+ 0·33 (± 0·05) P < 0·01	+ 0·32 (± 0·03) P < 0·01
Pa_{O_2} (mm Hg)	+ 4·72 (± 1·83) P < 0·05	− 4·0 (± 1·35) P < 0·02
Pa_{CO_2} (mm Hg)	− 3·8 (± 1·08) P < 0·01	− 1·1 (± 0·61) N.S.
V_D/V_E (%)	− 4·3 (± 1·27) P < 0·01	+ 0·3 (± 2·15) N.S.
Q_T (litres/min)	+ 0·93 (± 0·38)	+ 1·06 (± 0·53)

Mean changes (± S.E.) and P values

Both the results of Dr. Alliott and colleagues and my own suggest that both aerosols in the usual doses have relatively little effect on beta-1 adrenergic receptors. My results suggest that isoprenaline/phenylephrine improves the physiological state, and their results suggest that salbutamol may have a greater bronchodilator action. It should not be forgotten, however, that Professor Dollery's group has recently suggested[2] that the longer acting preparations such as salbutamol may be more likely to produce a state of resistance to beta-2 adrenergic stimulation.—I am, etc.,

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Serum Transaminases and Salicylate Therapy

SIR,—In support of the interesting observations of Dr. A. S. Russell and others (22 May 1971, p. 428) I would like to present some further data about increased transaminase levels in children with rheumatic fever while on aspirin therapy.

After the accidental finding of high levels of glutamic-oxalacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) in two of our rheumatic fever patients on aspirin therapy, the salicylate level and liver function tests were closely followed in all similar patients and some previous records were also reviewed.

Rheumatic fever No. of patients	No. with raised transaminases	No. with salicylate level >30mg/100ml	Initial level SGOT units	Initial level SGPT units	Increased level SGOT units	Increased level SGPT units
14	10	9	10–40	5–27	51–300	47–275
Rheumatoid arthritis No. of patients						
3	2	2	15–23	5–26	170–200	165–225

Forty-one children fulfilled the modified Jones criteria for rheumatic fever and had SGOT and SGPT determinations at least at time of admittance to hospital. In no single case were these enzymes found to be raised at this time, and this was unrelated to the interval between the first clinical sign of disease and the determination of the transaminases. In eight children there were signs of active carditis but the transaminases were nevertheless normal. This is in contradiction to the observations of Nydick *et al.*[1] Twenty-nine of the 41 patients were treated with aspirin (90-120 mg/kg) but in only 14 children were the transaminases checked repeatedly together with salicylate levels. To this group three patients with juvenile rheumatoid arthritis have been added. The total of 17 patients thus represent all the aspirin treated children since 1969 when a possible relationship between this drug and raised transaminases was suspected.

It can be seen from the Table that the incidence of increased transaminases is rather high, but this, with one exception, is confined to those patients in whom the salicylate level was found to be higher than 30 mg/100 ml on at least one occasion. The earliest increase in serum enzymes was noted 10 days after institution of treatment, usually appearing two to three weeks after the aspirin was started. Increased transaminases were found so long as a high level of salicylate was present, the drop being very sharp (three to five days) after stopping treatment or reducing the aspirin dosage. These observations are in accord with previous reports on this subject.[1] Data on large series of aspirin-treated patients with transaminase determinations are still unavailable, possibly because the rise in transaminases is seldom accompanied by clinical or biochemical abnormalities. Only two of our patients had mild hepatomegaly; two had increased alkaline phosphatases, whereas serum bilirubin, prothrombin time, thymol turbidity, and Weltman reactions were normal in all patients. The bromsulphthalein excretion test was normal in the two patients on whom it was performed.

Acute hepatic dysfunction was recently reported in juvenile rheumatoid arthritis by Kornreich, Malouf, and Hanson[2] as an entity different to that described by Schaller, Beckwith, and Wedgwood.[3] In the light of the additional data here presented, it seems that salicylates, followed by gold compounds or indomethacin, may have played a much more important part in the induction of hepatic dysfunction in most of the cases reported by this group.

As an increased level of transaminases probably indicates cellular death, it would appear desirable that every child on aspirin therapy for rheumatic fever or rheumatoid arthritis should have these enzymes checked routinely together with the salicylate level. It is probable that a salicylate level of less than 30 mg/100 ml at any moment will keep the transaminases within the normal range.—I am, etc.,

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Folate Deficiency and Anticonvulsant Drugs

SIR,—We were interested in the article by Dr. J. D. Maxwell and others (29 January, p. 297) suggesting that the folate deficiency occurring after administration of anticonvulsant drugs may be due to hepatic enzyme induction. In 1967-8 we estimated glutamate formiminotransferase and methylene tetrahydrofolate dehydrogenase, as well as serum and liver folates, in rats fed on or injected with phenobarbitone, diphenylhydantoin, or a mixture thereof. We showed[1] that the activity of both enzymes was usually increased.

Immature male or female Wistar albino rats were fed on a diet based on casein, with sucrose, lactose, fat, mineral salts, and vitamins added. In terms of the main types of nutrients, the diet provided 60% carbohydrate, 20% protein, 10% fat, 1% vitamins, and 9% mineral salts. Diets both deficient in and supplemented with folic acid (1 mg/kg diet) were used. In some experiments phenobarbitone (1, g/kg diet), diphenylhydantoin (1 g/kg), or a combination of both drugs (0·5 g each/kg) were added to the diet; in experiment No. 2 phenobarbitone (4 mg once or twice daily) was injected intraperitoneally into each animal. In all experiments control animals not receiving the drugs were maintained. The rats were killed between 5 and 29 days after starting the drugs and enzyme activities and folate were determined in the livers and folate was determined in the serum.

Glutamate formiminotransferase was determined as described elsewhere[2] and methylene tetrahydrofolate dehydrogenase was determined by the method of Kisliuk.[3] The determination of serum folate was by a modification of the method of Spray[4] and extracts of liver for the determination of hepatic folate were prepared by the method of Bennett, Berry, Chanarin, and Ardeman.[5]

The salient results are shown in the Table. Enzyme activities are expressed as units/100 g body weight because the drugs caused enlargement of the liver. In most experiments the drug-treated animals had significantly increased activities of both enzymes in the liver. Nevertheless, except for the serum folates in experiment No. 1 and the livers of the group treated with diphenylhydantoin in experiment No. 6, there were no significant differences in folate levels. It is possible that the experiments were terminated too early for such differences to be detected.

Enzyme Activities and Folate Levels in Rats Treated with Anticonvulsant Drugs

Exp. No.	Sex and Number of rats	Folic Acid 1 mg/kg diet	Phenobarbitone 1 g/kg	Phenobarbitone 4 or 8 mg by injection daily	DPH† 1 g/kg	Phenobarbitone +DPH 0·5 g/kg each	Glutamate formimino-transferase (Units/100 g body weight) Mean	S.D.‡	Methylene tetrahydrofolate dehydrogenase (Units/100 g body weight) Mean	S.D.	Serum folate (ng/ml) Mean	S.D.	Liver folate (µg/g wet liver) Mean	S.D.
1	M 10	0	0	0	0	0	18·3	3·3	8·8	0·8	53·8	24	7·1	1·8
	10	0	+	0	0	0	31·3*	5·4	11·5*	2·3	33·0*	13	8·9	3·9
	10	+	0	0	0	0	17·6	3·0	7·9	1·3	86·0	16	11·7	3·2
	10	+	+	0	0	0	33·4*	5·1	13·8*	2·1	30·0*	11	8·9	1·8
2	F 7	+	0	0	0	0	23·7	3·6	10·3	1·2	—		—	
	7	+	0	+	0	0	49·0*	8·7	17·0	1·9	—		—	
	M 6	+	0	0	0	0	20·8	2·4	7·4	0·5	—		—	
	6	+	0	+	0	0	32·6*	2·4	11·1*	2·5	—		—	
6	M 7	0	0	0	0	0	12·7	1·5	7·4	1·3	17·5	9·7	7·1	1·5
	7	0	0	0	0	+	32·0*	4·5	11·1*	1·3	14·6	8·6	8·2	2·5
	7	0	0	0	+	0	15·6*	1·1	8·0	1·1	13·5	7·8	5·0*	0·9
7	M 5	+	0	0	0	0	12·0	2·1	8·1	1·8	30·4	26	10·1	2·5
	5	+	0	0	0	+	24·7*	2·7	10·4*	1·0	24·5	9	12·0	4·7
	5	+	0	0	+	0	13·5	4·8	6·8	1·5	37·7	20	10·1	2·5

* Mean significantly different from the mean for the conrol animals at the 5% level or more
† Diphenylhydantoin ‡ S.D. Standard deviation

These results support the hypothesis of Dr. Maxwell and his colleagues. They have not yet been prepared for detailed publication, but a full account of the experiments is available.[1]—We are, etc.,

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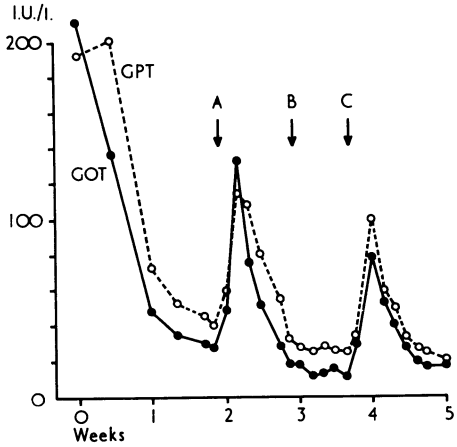
Hepatotoxicity of Sulphamethoxypyridazine

SIR,—Hepatotoxic properties are considered to be uncommon in the newer sulphonamides. The development of jaundice concurrently with sulphonamide therapy may be from drug hepatitis, but there is also a risk of labelling a viral hepatitis as a sulphonamide hepatitis. The causal relationship of sulphomamides can promply be confirmed or excluded by a hypersensitivity reaction provoked by administration of a test dose. The causal relationship of the newer sulphonamides to hepatitis has been so established in five cases only.[1-4] In the two cases observed in our clinic[4] the causal agent was a combination of sulphamethoxypyridazine and sulphamethizole. Since then the same sulphonamide has been shown to be the cause of two further cases of hepatitis. All these four cases were observed in our clinic within 11 months. In one case the causal agent was confirmed to be sulphamethoxypyridazine.

A 34-year-old woman was admitted to the hospital because of jaundice while taking tablets containing 250 mg of sulphamethoxypyridazine and 250 mg of sulphamethizole for a urinary tract infection. The dose had been four tablets daily for three weeks. Previously she had been prescribed the same tablets twice without untoward effects. In addition she had been taking oral contraceptives for about one year. On admission all medication was withdrawn. Serum total bilirubin was 12·8 mg/100 ml (conjugated 12·0); serum alkaline phosphatase was 60 IU/l. (upper limit of normal 46); and ornithine carbamoyltransferase 1·64 IU/l. (upper limit of normal 0·40). Tests for urine bilirubin and urobilinogen were positive and for serum Au-antigen and alpha-fetoprotein negative. There were no signs of haemolysis judged haematologically or by serum haptoglobin concentration or serum lactic dehydrogenase isoenzyme determinations. There were no other relevant findings. After return to normal of the laboratory values test doses of sulphonamide components were given as shown (see Figure).



Serum aspartate aminotransferase (GOT) and alamine aminotransferase (GPT) responses when two tablets of sulphonamide containing 250 mg of sulphamethoxypyridazine and 250 mg of sulphamethizole were given (A). At B 500 mg of sulphamethizole and at C 500 mg of sulphamethoxypyridazine was administered orally.

It is evident that sulphamethoxypyridazine caused a similar rise of serum enzymes as the combination of the two sulphonamides, whereas on administration of sulphamethizole no reaction could be seen. The hypersensitivity reactions were milder in this patient than in the other patients tested by us. There was no rise in body temperature or serum bilirubin. Liver biopsy, performed after the last exhibition to sulphonamide, revealed nonspecific changes pointing to reactive hepatitis without intrahepatic cholestasis.

Since the patient had also taken oral contraceptives which might have contributed to the hepatitis, she was put back on the pill after discharge from the hospital. This was considered to be safe immediately after hepatitis on the basis of our earlier study.[5] Serum enzyme activities remained normal during two menstrual cycles.

The occurrence of four cases of sulphonamide hepatitis within 11 months in one clinic which does not specialize in hepatic disease seems to indicate that this illness is more common than generally thought. In all our cases sulphamethoxypyridazine was one component and was confirmed to be the causal agent in the case tested. This sulphonamide seems to be specially hepatotoxic since, according to the present sales records, drugs containing this sulpha comprise only 29% of the total amount of sulphonamides sold in Finland.—I am, etc.,

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Australia Antigen in Chronic Liver Disease

SIR,—The varying presence of Australia Antigen (Au-Ag) in chronic liver diseases in different countries is now clearly established.[1] In some the incidence is high and in others it is low or nil. It seems unlikely that these differences are due entirely to differences in laboratory techniques used, and they might be important in establishing the aetiology of chronic liver diseases in relation to different geographical conditions.

We have studied 126 cases of chronic liver disease, confirmed by biopsy, from a population with a high incidence of cryptogenic and posthepatitis cirrhosis compared with alcoholic cirrhosis. There was a very high incidence of Au-Ag in chronic aggressive hepatitis both with complement fixation and immunodiffusion in agarose compared with a relatively low frequency in chronic persistent hepatitis (see Table). The incidence was also high in cases of post-hepatitis and cryptogenic cirrhosis.