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		DPH† 1 g/kg	Pheno- barbitone +DPH 0.5 g/kg each	Glutamate formimino- transferase		Methylene tetrahydrofolate dehydrogenase		Serum folate (ng/ml)		Liver folate (µg/g wet liver)	
			1 g/kg	4 or 8 mg by injection daily			(Units/100 g body weight)		(Units/100 g body weight)		Mean	S.D.	Mean	S.D.
							Mean	S.D.‡	Mean	S.D.				
1	M	10	0	0	0	0	18.3	3.3	8.8	0.8	53.8	24	7.1	1.8
		10	+	0	0	0	31.3*	5.4	11.5*	2.3	33.0*	13	8.9	3.9
		10	+	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	23.7	3.6	10.3	1.2	—	—	—	—
		7	+	0	+	0	49.0*	8.7	17.0	1.9	—	—	—	—
	M	6	+	0	0	0	20.8	2.4	7.4	0.5	—	—	—	—
		6	+	0	+	0	32.6*	2.4	11.1*	2.5	—	—	—	—
6	M	7	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	+	15.6*	1.1	8.0	1.1	13.5	7.8	5.0*	0.9
		7	0	0	0	+	12.0	2.1	8.1	1.8	30.4	26	10.1	2.5
7	M	5	+	0	0	0	24.7*	2.7	10.4*	1.0	24.5	9	12.0	4.7
		5	+	0	0	+	13.5	4.8	6.8	1.5	37.7	20	10.1	2.5
		5	+	0	0	+								
		5	+	0	0	+								

* Mean significantly different from the mean for the control 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 sulphonamides can promptly 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 clinic⁴ 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 alanine 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.

Presence of Australia Antigen in Chronic Liver Diseases

Disease	Number of cases	Number and Percentage of Cases Au-Ag Positive	
		Complement Fixation	Immunodiffusion
Chronic Hepatitis*			
Aggressive	22	16 (72.2)	11 (50.0)
Persistent	18	3 (16.6)	2 (11.1)
Cirrhosis			
Posthepatitis	17	6 (35.2)	4 (23.5)
Cryptogenic	43	13 (30.2)	8 (18.6)
Alcoholic	11	1 (9.9)	1 (9.9)
Other Chronic Liver Diseases ..	15	1 (6.6)	1 (6.6)

*Classified according to De Groote *et al.*²

The reasons for these findings are not clear. It is uncertain whether in Au-Ag negative cases the antigen is undetectable by means of the techniques presently available or whether other aetiological factors such as infective hepatitis virus or paramyxoviruses may be implicated. Our data, however, seem to emphasize the importance of serum hepatitis virus in the pathogenesis of chronic aggressive hepatitis and cirrhosis in southern Italy.—We are, etc.,

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- ¹ Prince, A. M., *Gastroenterology*, 1971, **60**, 913.
² De Groote, J., *et al.*, *Lancet*, 1968, **2**, 626.

Aluminium Containers

SIR,—Aluminium and aluminium salts have generally been considered as inert. There are scanty references to the possible dangers from aluminium. Spira¹ has written numerous papers on fluorosis and pointed out that toxic amounts of fluoride can be produced from aluminium cooking utensils. Dr. V. Parsons and others (30 October 1971, p. 273) noted the association of raised concentrations of aluminium in bone in patients with long-standing uraemia treated by dialysis and discussed its significance. Drs. H. Thurston and J. D. Swales (20 November 1971, p. 490) considered that the toxic effects of aluminium upon growth depended on phosphate depletion: their current work is on the effect of administering food containing aluminium hydroxide to animals. Jenkins and Blagdon² described the use of improved containers for long-term low temperature storage of blood and considered that aluminium containers are safe and satisfactory. It is obvious that they assume that aluminium is inert. However, they point out that a number of canisters were submitted to the Department of Health and Social Security for chemical tests, and that in the contained water after sterilization aluminium was present equivalent to 250 µg/500 ml. Recently Professor G. M. Berlyne and his colleagues³ in experiments on rats have shown that aluminium salts can be harmful particularly when administered to those with kidney damage.

I would stress that it is no longer safe to regard aluminium and aluminium salts as at present used as inert. There are possible dangers from the widespread practice of using aluminium containers for cooking and canning foods, as well as in various medicaments. Further toxicological analysis should be carried out, and in particular on

blood stored at low temperature, to prevent possible harmful intravenous administration of aluminium compounds.—I am, etc.,

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- ¹ Spira, L., *Journal of Laryngology and Otolaryngology*, 1943, **58**, 151.
² Jenkins, W. J., and Blagdon, J., *Journal of Clinical Pathology*, 1971, **24**, 685.
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Subviral Particles in Paget's Breast Carcinoma

SIR,—In the course of our ultrastructural studies of human breast cancers some essential features emerged from the study of Paget's carcinoma. These were (1) the extensive contact between normal and malignant cells through connecting desmosomes and common milk canaliculi; (2) the presence of abnormal desmosomes between malignant cells; (3) the presence of enormous tumour cells (up to 10 times the diameter of neighboring normal cells) which surround and engulf normal epithelial cells. The normal cells so incorporated appear well preserved and present many vesicles indicative of pinocytosis, suggesting that they derive nourishment by appropriating the cytoplasmic juices of the tumour cells; (4) the presence in the nuclei of some tumour cells of tubular and granular structures 220 to 250 Å in diameter, similar to those observed in human sarcomas and in collagen diseases¹ and interpreted as aberrant paramyxovirus nuclear capsids or subviral particles from an unknown virus.²

Paget's breast carcinoma; subviral particles in the nucleus.

or as ribonucleoprotein strands of a human oncogenic virus of type C or some related class.³

The apparently peaceful coexistence of normal and tumour cells suggests that tumour cells are already compatible with the tissue from which they derive at the time of their first appearance. We submit that tumour cells arise and gain acceptance because they are in some important respects similar to normal cells—with which they even share some desmosomes and milk canaliculi.—We are, etc.,

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Asystole after Verapamil

SIR,—In their study of the immediate effects of intravenous verapamil in cardiac arrhythmias (11 March, p. 660) Dr. L. Schamroth and others noted no adverse clinical effects to the administration of a dose of 10 mg. I should like to report an instance where asystole occurred within one minute of the injection of 7 mg of the drug.

A 57-year-old man with a history of six previous episodes of supraventricular tachycardia was referred two hours after the sudden onset of palpitations, and supraventricular tachycardia was confirmed on the electrocardiogram. His general condition was satisfactory, his pulse rate was 160 a minute, his blood pressure 90/70 mm Hg, and there were no signs of heart failure. Prior to this attack he had been taking a prophylactic daily dose of 600 mg of practolol. He was given 20 mg of practolol intravenously which had no effect on his heart rate or blood pressure. In view of the reported efficacy of verapamil in converting this arrhythmia, 10 mg were drawn up in a syringe half an hour later and intravenous injection at the rate of 1 mg/minute was started with blood pressure and E.C.G. control. After 7 mg had been administered, the patient reported he was feeling very faint; he was clammy and his systolic blood pressure had fallen to 70 mm Hg. Administration of the drug was stopped and one minute later, asystole suddenly occurred. After three vigorous thumps on the chest electrical activity was restored with reappearance of the supraventricular tachycardia. The ventricular rate was still 160 a minute; however, the pulse was palpable at the wrist, the blood pressure was unrecordable, and the patient, who had briefly regained consciousness following the period of asystole, became unconscious once more, and his pupils started to dilate. Immediate D.C. shock reverted the arrhythmia to sinus rhythm with first degree heart block at a rate of 60 a minute, and consciousness was restored. The conduction defect lasted 10 minutes, and the level of the blood pressure gradually rose to 120/80 mm Hg half an hour later.

The dangerous situation encountered here might have been due to an abnormal individual response or to the fact that verapamil was given in addition to practolol. A large number of the patients studied by Dr. Schamroth and colleagues were also digitized, but we are not informed as to