

TABLE I—VITAMIN A, CARDIOVASCULAR RISK FACTORS, AND MORTALITY FROM CANCER AND CARDIOVASCULAR DISEASE

	Deaths						Survivors*
	Heart disease	Stroke	Cancer of				
			Lung	Stomach	Colon	Other sites	
Number	87	16	39	16	13	52	397
Age at death (yr)	65±9	67±8	65±7	64±8	68±6	66±8	
Age at BS III (yr)	61±2	63±2	62±5	59±7	64±3	61	60-64
Systolic blood pressure (mm Hg)	154±21‡	159±24‡	149±18	146±17	150±18	146±21	146±19
Serum cholesterol (mg/dl)	235±44†	205±47‡	224±45	212±44	203±29‡	219±40	227±41
Cigarette smokers (%)	45%	63%	74%	56%	31%	44%	42%
Amount smoked (Cigarettes/day)	13	17	19	17	16	12	13
Serum vitamin A (IU/dl)	286±60	288±124	280±78	248±44*	275±56	277±75	275±67
Subjects with vitamin A measurement	78	12	36	16	12	44	357

\*The corresponding age cohort at BS III.

† $p < 0.05$ ; ‡ $p < 0.01$ .

compared in the men who died and in the survivors, the corresponding age cohort (397 men aged 60-64) at BS III. Heart disease and stroke victims have significantly higher systolic blood pressure. Cholesterol is increased in heart disease and significantly lower in stroke. Cancer patients have average cholesterol levels with the notable exception of those with subsequent cancer of the colon, who, as others have found,<sup>4</sup> have significantly lower lipid levels. Smoking was most prevalent in lung cancer victims.

In evaluating the serum vitamin A levels serum lipids have to be taken into account since vitamin A correlates strongly with total cholesterol. This explains the above average vitamin A levels in heart disease. However, stroke victims had higher than average vitamin A levels despite the low serum cholesterol. The noteworthy exception to previous reports is the normal vitamin A level in those with subsequent lung cancer. The only significantly low serum vitamin A level was observed in those with subsequent stomach cancer. In analysing the distribution of the serum vitamin A levels (table II) we observed a roughly normal distribution for

### REDUCTION OF VANADATE, A POSSIBLE EXPLANATION OF THE EFFECT OF PHENOTHIAZINES IN MANIC-DEPRESSIVE PSYCHOSIS

SIR,—It has been suggested that vanadate may be involved in the aetiology of manic-depressive illness.<sup>1</sup> Lithium diminishes the inhibition of  $\text{Na}^+ - \text{K}^+$  ATPase by vanadate,<sup>2</sup> and drugs which reduce vanadate to vanadyl (e.g., ascorbic acid and methylene-blue) may be of therapeutic value.<sup>3,5</sup> Phenothiazines, which are accepted treatments for mania, may also act in depression<sup>4,5</sup> and as prophylactics.<sup>6</sup> Though thioxanthines such as flupenthixol may be of therapeutic value in mania and may also be antidepressant,<sup>7</sup> they, like tricyclic antidepressants, have been reported to increase the occurrence of mania.<sup>8,9</sup> The following results show that phenothiazines but not thioxanthines nor tricyclic antidepressants catalyse the reduction of vanadate by NADH, hence offering a possible explanation for their therapeutic action in manic-depressive psychosis.

0.3 ml of 2.5 mmol/l NADH was mixed with 0.3 ml FAD (10 mg/l), 0.15 ml of 20 mmol/l sodium metavanadate, and 0.15 ml of 1 mmol/l drug, and the volume was made up to 3.9 ml with 10 mmol/l "tris" buffer pH 7.2. Controls without drug, without vanadate, and without drug and vanadate were also set up. The reaction was followed by measuring the oxidation of NADH spectrophotometrically at 365 nm.

Chlorpromazine, thioridazine, chlorprothixene, amitriptyline, carbamazepine, diazepam, glutathione, and methylene-blue were used. Methylene-blue reacted so rapidly that it was used at a concentration of 0.1 mmol/l. Methylene-blue was most effective, but glutathione, chlorpromazine, and thioridazine also catalysed the reaction: chlorprothixene, amitriptyline, carbamazepine, and diazepam were ineffective (fig. 1).

The effect could account for some of the therapeutic effect of phenothiazines in manic-depressive psychosis. The basic ring structure of phenothiazines and methylene-blue are similar (fig. 2). Since vanadate is slow to dissociate from  $\text{Na}^+ - \text{K}^+$  ATPase, this would account for the slow onset of action of these drugs in manic-depressive psychosis despite rapid appearance of other effects such

TABLE II—DISTRIBUTION OF CASES ACCORDING TO VITAMIN A PERCENTILES AT BS III

Vitamin A percentile	Cardiovascular		Cancer			
	Heart disease	Stroke	Lung	Stomach	Colon	Other
0-30	14	4	13	8	2	14
31-70	36	4	12	6	7	15
71-100	28	4	11	2	3	15

cardiovascular and cancer victims except for the gastric carcinoma subjects, 8 of whom were at or below the 30th percentile and only 2 of whom were above percentile 70.

Thus our results indicate that subjects with low vitamin A levels are at risk for stomach cancer. In contrast the serum retinol concentration in subjects with cancers at other sites is similar to that observed in the surviving cohort. The Basle population seems to have higher average serum retinol levels than the British group studied by Wald et al.<sup>1</sup> Despite a good vitamin A supply, the proportion of deaths that were due to cancer (38%) was high, indicating that other factors beside a low serum vitamin A concentration may be important in the aetiology of cancer.

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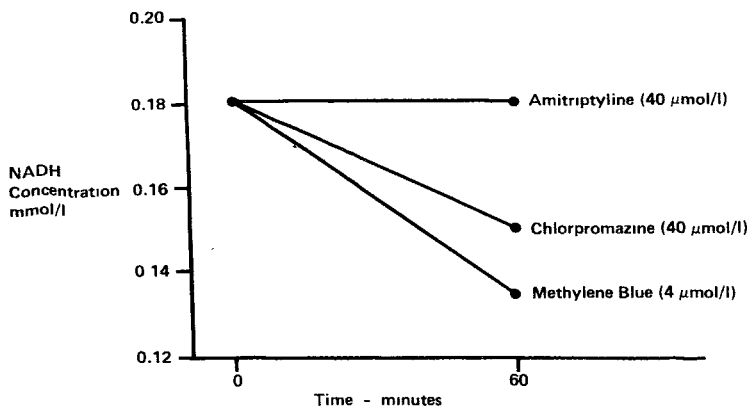


Fig. 1—The oxidation of NADH by vanadate in presence of drugs and FAD.

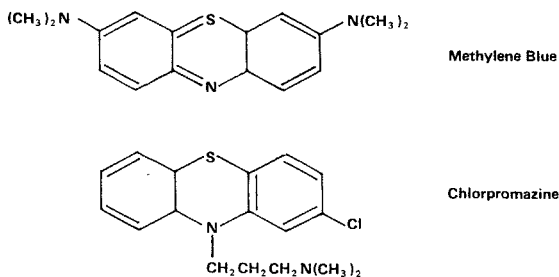


Fig. 2—Formulae of chlorpromazine and methylene-blue.

as sedation. Presumably reduction of vanadate to vanadyl would diminish the binding and would therefore increase the excretion of vanadium—again a slow effect but one which would not be immediately reversed on discontinuation of the drug. However, the drugs must also have other separate pharmacological effects—e.g., sedation and dopamine receptor blockade—which may also be of therapeutic benefit in this disorder.

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### INTRAVENOUS IMMUNOGLOBULIN IN ANTIBODY DEFICIENCY SYNDROMES

SIR,—Patients with hypogammaglobulinaemia syndromes have to have regular doses of immunoglobulin by injection. Side-effects are common and the discomfort of large intramuscular injections has often endangered effective prophylaxis. Among 26 hypogammaglobulinaemic Swedish patients reviewed<sup>1</sup> 12 had not been given adequate prophylaxis, resulting in impaired lung function and decreased weight and height if the disease had started before the age of 15.<sup>1</sup>

Patients can be protected, with few side-effects, by intravenous injections of specially prepared immunoglobulin preparations.<sup>1-4</sup> Many preparations have been modified by enzymic degradation, reduction and alkylation, exposure to low pH, or S-sulphonation.<sup>2</sup> Native unmodified antibodies retaining all biological activities would be advantageous.<sup>5</sup> We are using such a preparation composed of  $\geq 90\%$  7S IgG and with only traces of the IgG-fragments and dimers often seen in larger amounts in immunoglobulin

preparations in addition to IgG polymers.<sup>1</sup> The preparation is a Cohn fraction II from pooled plasma purified by 'DEAE-Sephadex' and stabilised with 5% albumin and 2·5% glucose. It has been given in doses of 5–10 g in 142 intravenous infusions 1 ml/min (more slowly at first) every second or third week to eight patients with common variable immunodeficiency and one with IgA, IgG2, and IgG3 deficiency. The preparation ('Gammonativ'; KabiVitrum, Stockholm) has very little IgA. A similar preparation has been given uneventfully to other IgA deficient patients who lack IgG2 and profit from immunoglobulin prophylaxis.<sup>6</sup>

Seven of the nine patients had previously reacted, usually strongly, to i.m. and/or i.v. injections of other preparations. During the 142 infusions with gammonativ there were two occasions when the temperature rose by 1·1°C (one patient had a cold). One patient had temporary anuria, but this was in a patient on assisted ventilation after cardiac arrest, with respiratory failure, and several simultaneous infusions. After recovery this patient has received 15 gammonativ injections without side-effects. The nine patients have had few infections during the 6–8 months of this prophylaxis.

Gammonativ is an unmodified IgG preparation for intravenous use that seems to be safe. Therapy must be sufficient if chronic and ultimately lethal lung changes are to be prevented. The prevalence of common variable hypogammaglobulinaemia in Sweden is 2–3 per 100 000; if we add the cases, now being found more often, of IgG2-deficiency,<sup>1,6</sup> the number of patients requiring immunoglobulin prophylaxis is not inconsiderable.

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### HALLUCINOGENIC FUNGI

SIR,—Dr Young and colleagues (Jan. 23, p. 213) describe an "epidemic" of abuse of hallucinogenic fungi in Glasgow. A similar epidemic occurred in Dundee between Sept. 13 and Oct. 17, 1981. 44 patients (mean age 18 years), chiefly schoolchildren and unemployed youths, were seen in the admissions and emergency department of Ninewells Hospital after ingestion of liberty caps (*Psilocybe semilanceata*). Large numbers of young people were eating these mushrooms and those presenting did so because of a dysphoric reaction to the experience, and 4 patients thought they were about to die.

The 44 patients seen were assessed according to a proforma prepared in the light of our previous experience with this condition.<sup>7</sup> All but 4 patients had dilated pupils. Other evidence of sympathetic stimulation was less frequent, a heart rate above 100/min being noted in 10 patients, diastolic blood pressure of 100 mm Hg or more in 17 patients, and hyperreflexia in 16 patients. Flushing of the upper trunk, neck, and face was noted in 8 patients; 23 patients were nauseated or had vomited, while 9 complained of upper abdominal pain, and in 2 cases this was severe enough to be the cause of presentation. Distortions of perception were very common and were usually visual although only 4 patients were frankly hallucinating. Paraesthesiae affecting the limbs and face occurred in 16 patients and 2 were ataxic.

Patients presented to the department an average of 3·8 h (range 1–8 h) after ingesting the mushrooms, and after a short period of observation 26 were sufficiently well to be discharged from the accident department in the care of a responsible adult. 18 patients were admitted to hospital and all had fully recovered within 12 h. In most patients therefore the effects of the hallucinogen are shortlived.

We have found that gastric intubation can be difficult in these young patients who are often already distressed and not infrequently aggressive. Furthermore the mushrooms may block

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