Protective Effect of Trace Elements other than Selenium against Dietary Necrotic Liver Degeneration

RATS fed on diets containing certain yeasts as their sole source of protein develop a dietary necrotic liver degeneration, leading to early and rapid death. Necrogenic diets are deficient in three factors, vitamin E [1], cystine [2] and a 'Factor 3' [3], each of which will alone prevent the manifestations of disease. Potent Factor 3 concentrates have been prepared from casein hydrolysates[4] and, recently, Schwarz and Foltz[5] have shown that similar concentrates prepared from kidney powder hydrolysates contain selenium in bound form. Addition of sodium selenite to rat diets (to supply 4 μgm. of selenium per 100 gm. of diet) gave complete protection against death from liver necrosis during the experimental period of thirty days, indicating that selenium might be part of Factor 3. Schwarz and Foltz have inferred that "selenium is an essential trace element".

We were prompted to investigate the addition of certain other trace elements to necrogenic diets, particularly those which, it was considered, might take part in oxidation-reduction mechanisms. Table 1 shows the results obtained by the addition of a number of trace elements at levels below their toxic levels (where these are known)[6]. Lead (alone) and a group of four metals, cerium, mercury, titanium and vanadium (together), were inactive. Molybdenum, osmium and cobalt (together) delayed the deaths by necrosis beyond 130 days in three rats out of seven. In the same test, the protective effect of selenium, cystine and α-tocopherol has been demonstrated. In a second test (Table 2), molybdenum, osmium and cobalt were given separately as well as in combination. Each of the three metals had some activity at the levels employed, but not all the animals receiving the supplement were protected. Further studies are in progress.

Table 1. EFFECT OF ADDITIONS TO THE NECROGENIC DIET*

Supplement	p.p.m.	No. of rats †		Remarks
		Total	Alive at 88 days	
Nil		6	0	
Sodium selenite	0·05	7	7	7 alive at 200 days
L-Cystine (0·6 per cent)		7	7	6 ,, ,, ,, ,,
DL-α-Tocopherol acetate (100 mgm./kgm.)		8	8	7 ,, ,, ,, ,,
Lead acetate	0·5	10	1	Survivor died at 89 days
Ammonium molybdate	0·5	7	3	Survivors died at 130, 154 and 170 days
Osmium tetroxide	1·0			
Cobalt sulphate	1·0			
Ceric sulphate	1·0			
Mercuric chloride	1·0	8	1	Killed. Liver normal
Titanous chloride	1·0			
Ammonium meta-vanadate	5·0			

* Basal diet (per cent): dried bakers' yeast, 30; vitamin E-free lard, 5; sucrose, 55; salts, 5; B vitamins in glucose, 5; vitamins A, D and K orally. The salt mixture contained the following trace elements: iodine, fluorine, copper, manganese and aluminium.

† Norwegian hooded rats.

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Heparin and Christmas Factor

HEPARIN has been shown to combine with Chargaff's[1] lung thromboplastin, which contains phospholipid. It inhibits the formation of intrinsic plasma thromboplastin[2], and Douglas[3] has shown that it must inhibit blood coagulation at an early stage. Heparin is also known[4] to combine specifically with the β-lipoproteins of plasma or serum and to depress the plasma β-lipoprotein concentration when injected *in vivo*. Christmas factor has been shown to be present in a crude α- and β-globulin fraction of plasma[5] and it may contain phospholipid[5].

A normal thromboplastin generation test was carried out using normal absorbed plasma, serum and platelets but with the prior addition of a suitable concentration (0·85 unit/ml.) of heparin. Little thromboplastin was formed. If the addition of heparin to the normal mixture is delayed until 3 min. after recalcification when the formation of thromboplastin is already maximal, the addition of heparin does not then affect the result; that is, maximal thromboplastin activity persists. Thus it is probable that heparin at this concentration prevents the formation of thromboplastin, but does not prevent its action once it is formed, and does not exhibit

Table 2. EFFECTS OF MOLYBDENUM, OSMIUM AND COBALT

Supplement	Element (p.p.m.)	No. of rats	No. dying	Mean age at death (days)	Range (days)	Survivors at 100 days	Remarks*
Nil		10	9	60	42–92	1	Livers grossly necrotic
Ammonium molybdate	0·5	9	5	50	35–67	4	Post-necrotic scarring in two livers†
Osmium tetroxide	1·0	10	6	58	40–86	4	Livers normal
Cobalt sulphate	1·0	10	6	55	40–78	4	Post-necrotic scarring in one liver
Ammonium molybdate	0·5	9	5	55	37–84	4	Post-necrotic scarring in two livers
Osmium tetroxide	1·0						
Cobalt sulphate	1·0						

* Survivors killed and examined at 100 days.
† In all livers the scarring was confined to the left lobes and was accompanied by enlargement of the right central lobe.