reduces the cellular necrosis provoked by E. Preliminary experiments show that M also exerts a hepatoprotective effect with respect to fatty loading of the liver induced by E, reducing the high lipid content and preventing the onset of histologic fatty degeneration lesions. Bearing in mind that M inhibits the release of adrenal hormones,[7] incriminated in the toxic action of E and in lipid mobilisation,[11] it is not excluded that its effect would occur also at this level.

In conclusion, the experimental data sustain the advantage of using M in the treatment of alcoholism in comparison with D, thus suppressing not only the need for alcohol drinking but also exerting an antitoxic action with regard to the acute and subacute E toxicity.

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The influence of psychotropic drugs and ambient temperature on glycogen and reducing substances in mouse brain and liver*

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CHLORPROMAZINE alters the pattern of glucose metabolism in mouse brain *in vivo*. Following administration of the drug, a single dose of ^{14}C glucose is more slowly converted to lipids and protein and there is a higher proportion of radioactive counts in the acid soluble extract of the brain homogenate which contains amino acids and sugars.[1] Using a glucose oxidase method chlorpromazine has been shown to increase the acid hydrolysable fraction of mouse brain carbohydrate, i.e. glycogen and/or glucose phosphates.[2] A possible cause of these changes is the fall in body temperature produced by chlorpromazine.[3] In this experiment the ambient temperature of mice was maintained between 31° and 33° and the effects of administration of chlorpromazine, imipramine and pentobarbitone on brain reducing substances and glycogen were measured.

Adult albino mice (SAS/ICI) of either sex weighing 36–48 g were used. Ambient temperatures were controlled by placing perspex mouse boxes in a L.T.B. incubator. Each mouse box contained

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TABLE 1. THE INFLUENCE OF PSYCHOTROPIC DRUGS ON THE CONCENTRATION OF REDUCING SUGARS IN MOUSE BRAIN HOMOGENATES BEFORE AND AFTER ACID HYDROLYSIS (mg glucose/g wet wt. tissue)

Drug	Ambient temperature (°C)	BRAIN										LIVER									
		Non-hydrolysed					Hydrolysed					Non-hydrolysed					Hydrolysed				
		No.	Mean	S.E.	t	p	No.	Mean	S.E.	t	p	No.	Mean	S.E.	t	p	No.	Mean	S.E.	t	p
Control	31–33	9	0·04	0·02	0·8	0·4	9	2·50	0·20	0·9	0·3	8	4·56	0·89	1·8	0·05	8	17·38	4·02	3·1	0·01
Chlorpromazine	31–33	9	0·07	0·02		0·5	9	2·65	0·31		0·4	9	6·18	0·33		0·1	9	34·52	3·88		0·001
Control	21	7	0·12	0·04	4·1	0·1	7	2·82	0·23	0·3	0·7	6	4·30	0·18	1·7	0·1	6	13·66	1·98	6·5	<0·001
Chlorpromazine	21	6	0·40	0·05		0·001	6	2·75	0·09		0·8	6	4·81	0·23		0·2	6	37·70	3·09		
Control	31–33	6	0·13	0·03	2·3	0·02	6	1·95	0·24	1·0	0·3	6	3·26	0·31	0·3	0·7	6	16·46	3·30	1·2	0·2
Pentobarbitone	31–33	6	0·28	0·06		0·005	6	2·27	0·21		0·4	6	3·07	0·49		0·8	6	11·22	2·91		0·3
Control	31–33	9	0·06	0·04	1·3	0·2	9	2·53	0·31	0·4	0·7	9	4·28	0·19	1·1	0·2	9	19·62	3·30	0·4	0·6
Imipramine	31–33	8	0·16	0·08		0·3	8	2·66	0·30		0·8	8	4·60	0·21		0·3	8	21·59	4·57		0·7

three test and three control mice. The test mice were injected i.p. with 6·25 mg/kg chlorpromazine, 12·5 mg/kg imipramine or 30 mg/kg pentobarbitone. A further test group of mice had received 1 mg/kg chlorpromazine on 6 days a week from day 2 of life until the time of the experiment (150–160 days). The control mice were injected with 0·25 ml of 0·85% saline. After 3–3½ hr the animals were killed by cervical dislocation, and the brains and livers were rapidly removed and washed in ice-cold water. The tissues were then blotted, weighed on a torsion balance and homogenised at 0° in deionised water (100 mg/ml) using an MSE rotary blade homogeniser. An aliquot of the homogenate was analysed for reducing substances using the method of Folin and Wu.[4] Another aliquot of the homogenate was heated with an equal volume of 2N HCl to 100° in a boiling water bath for 2 hr. The assay for reducing substances was then carried out on the acid hydrolysed solution. The first assay was a measurement of reducing sugars and sugar phosphates. The second assay measured the latter plus the glucose liberated from complete hydrolysis of tissue glycogen.

Administration of chlorpromazine to animals maintained in an environment of 21° resulted in significant increases in brain-reducing sugars and in liver glycogen (Table 1). Similar treatment produced no significant change in brain sugar content in mice maintained at 31°–33° although the rise in liver glycogen persisted. Pentobarbitone (30 mg/kg) was sufficient to produce unconciousness in the mice. This drug raised the concentration of cerebral-reducing sugars to approximately double the control values. No changes in the liver were observed. Imipramine produced no significant changes in cerebral and hepatic sugar and glycogen content. Mice do not readily exhibit signs of imipramine excitement due to rapid metabolism of the drug in this species.[5] For this reason a group of six rats were treated with 12·5 mg/kg imipramine and the carbohydrate content of brain and liver were compared as above with that of six control rats. No significant differences occurred. Chronic administration of chlorpromazine to mice (ambient temperature 21°) resulted in no alterations in brain or liver reducing sugars and glycogen.

Crossland and Rogers[6] have observed a decrease in brain glycogen in rats with catatonia induced by bulbocapnine or audiogenic seisures. This was most marked in the free, non-particulate fraction of the glycogen and was accompanied by an increase in brain glucose. The rise in brain glucose was not dependent on a rise in blood glucose. In our experiment, chlorpromazine (which can also induce catatonia) only raised the levels of cerebral-reducing sugars in animals in an ambient temperature of 21° and had no effect on total glycogen. However, our technique of glycogen extraction and measurement was different from that used by Crossland and Rogers. Our results suggest that at least part of the increase in brain-reducing substances could be related to the inability of animals treated with chlorpromazine to maintain normal body temperature in an ambient temperature of 21°. This effect was greatly diminished by raising the ambient temperature or by chronic administration of the drug. Chronic administration of chlorpromazine, in man at least, may result in an increased tolerance of the peripheral vasomotor system to the drug with little change in the response of the central nervous system.[7] If the increase in brain-reducing sugars is secondary to a fall in body temperature then the normal level of brain-reducing sugars following chronic administration could be a result of such an adaptation.

With pentobarbitone an increase in brain-reducing sugars occurred in brains of mice maintained in an ambient temperature of 31°–33°. No such change occurred in the liver and therefore there was not a reflection of a generalised rise in extracellular glucose. Also, the total brain glycogen did not alter. This is evidence against an increase in glycogenolysis, although this possibility is not excluded. A block in glycolysis could result in a raised concentration of glucose in the brain. This could be either due to direct inhibition of glycolytic enzymes or a result of a modification of metabolic control mechanisms. The latter type of drug action has been recently studied by Horn,[8] who demonstrated that quinidine inhibits glycolysis in cardiac muscle by increasing adenosine triphosphatase activity which results in raised tissue levels of adenosine triphosphate. Adenosine triphosphate is a potent inhibitor of phosphofructokinase. This enzyme is not directly inhibited by quinidine but is a rate-limiting reaction in glycolysis.

The levels of brain-reducing sugars in control animals maintained at 31°–33° were significantly lower than that in control mice in an environment maintained at 21° (mean at 31°–30°, 0·07 mg/g; mean at 21°, 0·114 mg/g). This result complements the possibility that the increase in brain-reducing sugars following chlorpromazine administration is secondary to the fall in body temperature induced by the drug. The increase in brain sugar induced by cold could be a result of the decreased glucose utilisation which occurs in hypothermic animals.[9]

In both sets of chlorpromazine-treated mice there was an increase in liver glycogen, although this was more marked in the set housed at 21°. By contrast the increase in brain sugars in the pentobarbitone-treated group was accompanied by no change in total liver glycogen. This also suggests a generalised disturbance induced by chlorpromazine as opposed to a more selective effect of pentobarbitone on brain glucose utilization.

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Inhibition of biosynthesis of cholesterol by salicylate

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IT IS now known that salicylate inhibits the incorporation of acetate into long-chain fatty acids in rat liver[1] and produces a decrease in serum cholesterol[2] and free fatty acids in man[3] and experimental animals.[4] It has been shown recently that the effect of salicylate on the biosynthesis of long-chain fatty acids is probably connected with inhibition of the activity of acetyl-CoA carboxylase.[5] In view of the fact that mevalonate is derived, at least partly, from malonyl-CoA,[6,7] it is possible to suggest that the reduction in serum cholesterol brought about by salicylate may also be due to the inhibition of acetyl-CoA carboxylase.

In the present work, the effect of salicylate on cholesterol biosynthesis was studied.

METHODS

The incorporation of 1-^{14}C-acetate and 2-^{14}C-mevalonate into cholesterol was studied by using 700 g supernatant fractions of rat liver homogenate. The reaction mixture contained 2 ml of homogenate; NADPH, 3·5 μmoles; NADH, 3·5 μmoles; 1-^{14}C-acetate, 2 μc (3·5 μmoles) or 2-^{14}C-mevalonate, 0·1 μc (2·6 μmoles). In the flasks containing the labelled acetate, $KHCO_3$ (3 mg) was added. Sodium salicylate was used in a concentration of 10^{-3} M. The total volume of mixture was 2·5 ml. It was incubated for 1 hr at 37° in a shaker. Other details of the methods and techniques used for the extraction of labelled sterols and fatty acids have been described earlier.[8]

RESULTS AND DISCUSSION

The data presented in the table show that in all three experiments, salicylate, in a concentration of 10^{-3} M, reduced the incorporation of acetate into the sterol fraction by 26–34 per cent. The decrease