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Relation of Ethanol Metabolism to Several Factors in the Rat

THE most important site for the oxidation of alcohol is the liver. Various experimental approaches, for example, the artificial perfusion of surviving liver with blood containing alcohol, oxidation of alcohol by liver slices and liver brei, diminished alcohol oxidation following either hepatectomy or damage to the liver, and the demonstration that the eviscerated animal metabolizes alcohol very slowly, have all indicated that the liver is of major importance in the metabolism of ethanol[1].

Eggleton[2], in an extensive study in cats, attempted to find one or more of the important factors responsible for the varying rates of alcohol metabolism between individuals of the same species. It was found that the rate of ethanol metabolism correlated more nearly with liver-weight than with body-weight or surface area. In the present study, instead of using mongrel animals, we have attempted to obtain consistent results by using a pure strain of rat, for example, Sprague-Dawley females. Additionally, an attempt was made to determine the alcohol-oxidizing capacity of liver by modifying the methods of Bücher and Redetski[3] and Marshall and Fritz[4] for use in the coenzometer (Macalaster Bicknell Co.). It is evident in Table 1, summarizing the findings in 17 female rats, that the results obtained with this modified method fail to correlate significantly with the rate of alcohol metabolism where the latter is expressed in terms of the amount of alcohol disappearing from the blood[5]. The finding of Eggleton[2] in the cat that the rate of metabolism is more closely related to liver-weight than to body-weight is confirmed in the rat.

Table 1. RELATION BETWEEN RATE OF ETHANOL METABOLISM (*Disappearing Ethanol*) AND SEVERAL VARIABLES

	Mean ± *S.D.**	Cor. Coef.
Ethanol metabolism (Ethanol disappearing) (mgm./kgm./hr.)	249·0 ± 57·9	—
Liver oxid. capacity, wet basis (mgm./gm. liver/hr.)	2·74 ± 0·40	0·291*
Liver oxid. capacity, N_2 basis (mgm./gm. N_2/hr.)	103·6 ± 14·0	0·382*
Liver-weight (gm.)	7·5 ± 0·6	0·485*
Body-weight (gm.)	327·0 ± 29·4	0·082*
Liver-weight : body-weight (per cent)	2·31 ± 0·27	—

* Mean ± Standard Deviation of Mean ; *$P > 0\cdot05$.

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Effect of Tranquilizing Drugs on Survival from Experimental Diphtheric Intoxication

THE exotoxin of virulent diphtheria bacilli represents an extreme example of a potent biochemical stressor in susceptible mammalian species. Giroud *et al.*[1] have shown that in animals intoxicated with a lethal dose of diphtheria toxin, the hormone content of the adrenal cortex is diminished by as much as two thirds. Attempts to influence the course of diphtheria toxæmia through the use of cortical hormones or adrenocorticotrophic hormone have met with no success[2,3,4], although a decrease in adrenal hæmorrhages has been noted[5].

In view of the potent pharmacological activity of the tranquilizing drugs in stress states, it seemed of interest to determine the effects of such agents upon experimental diphtheric stress. Since mice and rats are refractory to the toxin, large male guinea pigs were employed.

Using groups of eight or more animals paired by weight, age and source, four major tranquilizers were evaluated. These drugs, representing each of the four chemical classes of tranquilizing drugs were meprobamate, chlorpromazine, reserpine and hydroxyzine. Diphtheria toxin, partially purified from broth, with an LD$_{50}$ of approximately 3×10^5/ml., was used as the challenge. A dose of 0·1 ml. undiluted, sterile toxin was injected intraperitoneally, and

Table 1. SURVIVAL TIME OF GUINEA PIGS TREATED PRIOR TO CHALLENGE WITH DIPHTHERIA TOXIN

(A) TRANQUILIZER TREATMENT

Survival time as % of Control ± Standard Error	Significance of difference from Control	Experimental treatment (single injection, i.p.) (mgm./kgm.)	Survival time* of Controls ± Standard Error	Degrees of Freedom
140 ± 7	$P < 0\cdot001$	Meprobamate 400	100 ± 5	14
115 ± 4	$P < 0\cdot02$	Meprobamate 300	100 ± 3	15
111 ± 14†	$P > 0\cdot4$	Meprobamate 500	100 ± 4	18
110 ± 4	$P > 0\cdot1$	Reserpine 1·0	100 ± 5	14
103 ± 2	$P > 0\cdot4$	Meprobamate 200	100 ± 3	15
100 ± 4	$P > 0\cdot9$	Chlorpromazine 25	100 ± 3	14
96 ± 2	$P > 0\cdot3$	Hydroxyzine 2·5	100 ± 3	14
94 ± 6	$P > 0\cdot3$	Hydroxyzine 25	100 ± 3	14
92 ± 10	$P > 0\cdot4$	Reserpine 0·1	100 ± 5	14
89 ± 3	$P > 0\cdot05$	Reserpine 1·4	100 ± 3	14
87 ± 3	$P < 0\cdot01$	Reserpine 2·5	100 ± 3	18
60 ± 8	$P < 0\cdot001$	Chlorpromazine 200	100 ± 3	14
(B) MISCELLANEOUS TREATMENT				
106 ± 3	$P > 0\cdot1$	Chloral Hydrate 400	100 ± 3	14
101 ± 4	$P > 0\cdot8$	Tubocurarine 0·25	100 ± 3	13
97 ± 3	$P > 0\cdot4$	Pentobarbital 20	100 ± 3	14
76 ± 17**	$P > 0\cdot1$	Hexobarbital 100	100 ± 3	13

* The overall mean survival time for all controls was 13 hr. and the average standard error for all control groups was 25 min. (3 per cent).

† The large standard error associated with the dose of 500 mgm./kgm. meprobamate can be attributed to 2 early deaths from the drug (which is close to the LD$_{50}$ at this dose). If these two deaths are removed from the calculations, survival time for this group was 131 ± 6 per cent of its control, which with 16 degrees of freedom is a significant increase, $P < 0\cdot001$.

** The large standard error is attributed to the fact that 3 animals died within three hours when given 100 mgm./kgm. hexobarbital. If the calculations are made without these 3 animals, the survival time of the group is 110 ± 6 per cent of its control. Witn 10 degrees of freedom, this increase is not significant, $P > 0\cdot1$.