Abstract—The effect of ethyl alcohol on the blood glucose level was observed on normal as well as fasting rabbits. Although normal animals did not exhibit a significant hypoglycemic response, severe hypoglycemia followed ethanol administration in fasting rabbits. Estimation of liver glycogen content revealed that the animals developing hypoglycemia also had a diminished liver glycogen, whereas a hypoglycemic response was absent in those animals where the liver glycogen was within normal limits.

Ethanol induced hypoglycemic states have been recognised since 1941 (1, 2) and that ethanol itself is the cause was suggested by Cummins in 1961 (3). Westerfeld and Schulman (4) have postulated that the effect of alcohol is the result of two opposing factors 1) stimulation of carbohydrate metabolism which tends to decrease blood sugar level and 2) glycogenolysis which tends to increase blood sugar level at the expense of liver glycogen.

Neame and Joubert in 1961 (5) ascribed hypoglycemic response after ethanol to increased utilisation and decreased synthesis of liver glycogen. The most important factor in the depletion of liver glycogen is however starvation, often associated with alcoholism.

Review of literature reveals that many attempts including the studies on liver glycogen estimation in experimental animals, clinical studies by doing liver biopsy and glucagon tests have been made to elucidate the possible causative factor for the hypoglycemic response to ethanol (6-8) yet the exact mechanism of causation remains obscure. One author has attributed it to the failure of normal glycogenolysis or neoglucogenesis (9).

In view of the above observations, our present study is an attempt to determine whether or not a relationship exists between ethanol induced hypoglycemic response and liver glycogen contents in experimental animals both normal and starved.

MATERIALS AND METHODS

For this study a total of thirty healthy rabbits of both sexes weighing 1.5 to 2 kg were selected at random, and kept on a standard diet. The study was conducted as follows:

1. In a group of ten normal rabbits, a fasting blood sample was obtained from the marginal ear vein and blood glucose estimation was done. Each animal was given 6 ml per kg. of 15 v/v % alcohol by intragastric intubation and blood glucose estimations of three blood samples taken at an hourly interval were done by Micromethod of Astoor and King (10).

2. A second group of ten rabbits was fasted for 48 hr and similar studies on blood glu-
cose estimations were done before and after the administration of ethanol as in para 1.

3. Liver glycogen estimation

Animals were sacrificed by a blow on head. The liver was quickly removed and the study done on:

(a) Five normal rabbits given water only (serving as controls).
(b) Five normal rabbits, on which studies on blood glucose levels before and after ethanol had already been done.
(c) Five rabbits fasted except for water for 48 hr.
(d) Five rabbits who were fasted for 48 hr and on which blood sugar estimations before and after the administration of ethanol had already been done.

The liver glycogen estimation was done by the method of HAWK and SUMMERSON (11).

RESULTS

Effect of ethanol on normal animals

Ethanol administration did not alter blood glucose level to any significant extent in normal rabbits, as seen in Table 1.

Effect of ethanol on fasting (48 hr) animals

As is clear from Table 2, profound hypoglycemia was present after ethanol to rabbits, fasted for 48 hr.

Effect of ethanol on liver glycogen content in normal animals

The liver glycogen content was found to be within normal limits in normal animals not exhibiting hypoglycemic response to ethanol as seen in Table 3.

| Rabbit No. | Fasting | Blood glucose in mg per 100 ml. |
|------------|---------|---------------------------------|
|            |         | 1 hr | 2 hr | 3 hr |
| 1          | 74      | 83   | 80   | 81   |
| 2          | 67      | 49   | 45.4 | 36   |
| 3          | 105     | 90.3 | 98.6 | 100.5|
| 4          | 100     | 111  | 83   | 59   |
| 5          | 117     | 100  | 111  | 106  |
| 6          | 111     | 100  | 100  | 100  |
| 7          | 97      | 92.5 | 87.3 | 90.5 |
| 8          | 90.7    | 85   | 89   | 80   |
| 9          | 86      | 90   | 85   | 80   |
| 10         | 80      | 85   | 87   | 85   |

Mean value: 92.77
't' test: P>0.05
S.E.M.: ±5.1
TABLE 2. Effect of alcohol on blood glucose level in fasted (48 hr) animals.

| Rabbit No. | Fasting | Blood glucose in mg per 100 ml | After ethanol |
|------------|---------|-------------------------------|--------------|
|            |         | 1 hr                          | 2 hr         | 3 hr         |
| 1          | 80.9    | 66.9                          | 58           | 54           |
| 2          | 97.5    | 82.2                          | 65.5         | 45           |
| 3          | 90.9    | 87.5                          | 70.7         | 57           |
| 4          | 103.3   | 98.7                          | 80.5         | 60           |
| 5          | 111.1   | 95.2                          | 87.3         | 55           |
| 6          | 97.6    | 67.3                          | 80           | 50           |
| 7          | 85      | 80                            | 57.5         | 52           |
| 8          | 88      | 74                            | 58           | 50           |
| 9          | 90.9    | 64.5                          | 74.1         | 45           |
| 10         | 87.3    | 60                            | 69           | 60           |

Mean value 93.2
't' test 3.1
P<0.01
S.E.M. ±2.86

TABLE 3. Glycogen content in grams per 100 grams of liver.

| Normal animals | Normal animals after ethanol |
|----------------|-----------------------------|
| Rabbit No.     | Wt. of liver | Glycogen content | Rabbit No. | Wt. of liver | Glycogen content |
| 1              | 27.22        | 9.2              | 1          | 20.35        | 9.9              |
| 2              | 30.00        | 7.8              | 2          | 18.30        | 11.03            |
| 3              | 35.77        | 9.7              | 3          | 22.7         | 9.2              |
| 4              | 24.88        | 8.9              | 4          | 30.58        | 9.4              |
| 5              | 18.14        | 10.88            | 5          | 16.43        | 9.7              |

Mean value 9.3
S.E.M. ±0.5
't' test 0.3
P>0.05
S.E.M. ±0.31

TABLE 4. Glycogen content in grams per 100 grams of liver.

| Fasted animals | Fasted animals after ethanol |
|----------------|-----------------------------|
| Rabbit No.     | Wt. of liver | Glycogen content | Rabbit No. | Wt. of liver | Glycogen content |
| 1              | 21.7         | 5.4              | 1          | 23           | 3.04             |
| 2              | 25.0         | 6.70             | 2          | 24.63        | 0.91             |
| 3              | 26.5         | 7.4              | 3          | 29.90        | 3.1              |
| 4              | 28.97        | 5.7              | 4          | 28.06        | 3.43             |
| 5              | 20.73        | 5.07             | 5          | 25.13        | 2.8              |

Mean value 6.04
S.E.M. ±0.44

Mean value 2.66
S.E.M. ±0.51
't' test 3.76
P<0.01
Liver glycogen content was found to be severely depleted in fasting animals who had developed hypoglycemia after ethanol, as is clear from Table 4.

Further scrutinization of the results shows that the blood glucose level bears a linear relationship to liver glycogen, as demonstrated in Fig. 1.

**DISCUSSION**

When reviewing the results of the present study, it is apparent that the animals fasted for 48 hr exhibited a profound degree of hypoglycemia after administration of ethanol as compared to an insignificant fall in blood sugar in normal animals. These findings are in accordance with the results obtained by Lochner and Madison in 1963 (12, 13), Lochner et al. in 1967 (14) and others.

In such cases, the hypoglycemia could be the consequence of either an increase in peripheral glucose utilisation or a decrease in hepatic output of glucose. The hepatic glucose output is mainly derived from gluconeogenesis from aminoacids, lactate, and glycerol. The administration of ethanol has an immediate effect on carbohydrate metabolism resulting not only in decreased hepatic glucose output but also in an inhibition of peripheral glucose utilisation which varies from animal to animal.

The studies were conducted to determine the possible cause of hypoglycemia by doing liver glycogen estimations as explained above. It was observed that the animals develop-
ing significant hypoglycemia also had a severely depleted liver glycogen content (P<0.01) as compared to their counterparts who were not given ethanol (P>0.05), demonstrating thereby, that the possible cause for fall in blood sugar could be the interference with gluconeogenesis as well as glyconeogenesis. No change was observed, however, in liver glycogen content of normal animals after the administration of ethanol.

The importance of glycogen depletion has also been suggested by clinical as well as experimental studies by Tennet (15), Neame and Joubert (5) and Field et al. (6).

In our opinion, the fall in liver glycogen is not the result of a rapid breakdown of hepatic glycogen as there was no corresponding increase in the blood glucose level but rather a decrease was observed in ethanol treated rabbits.

Although there is no significant hypoglycemia or decrease in liver glycogen content in normal animals, the possibility that ethanol also decreases the hepatic gluconeogenesis in these animals cannot be ignored. In such animals with ample stores of liver glycogen, the decrease in gluconeogenesis could be obscured by a simultaneous increase in glycogenolysis which would maintain the output of glucose from the liver for several hours.

The mechanism by which ethanol causes such response could possibly be a consequence of changes in D.P.N. and D.P.N.H. levels in the liver, resulting from metabolism or oxidation of ethanol which inhibits enzymes responsible for gluconeogenesis.

Our present study thus leads to the conclusion that ethanol does cause hypoglycemia after 48 hr of fasting and this response has a linear relationship to the diminished liver glycogen content.

REFERENCES
1) BROWN, T.M. AND HARVEY, A.M.: J. Am. med. Ass. 117, 12 (1941)
2) TUCKER, H.S.G., JR & PORTER, W.B.: Am. J. med. Sci. 204, 556 (1942)
3) CUMMINS, L.H.: J. Paediat. 58, 213 (1961)
4) WETERFELD, W.W. AND SCHULMAN, M.P.: J. Am. med. Ass. 170, 197 (1959)
5) NEAME, P.B. AND JOUBERT, S.M.: Lancet 11, 893 (1961)
6) FIELD, J.B., WILLIAMS, H.E. AND MORTIMORE, G.E.: J. clin. Invest. 42, 497 (1963)
7) ARKY, R.A. AND FRIENKEL, N.: Metab. Clin. Exptl. 13, 547 (1964)
8) ARKY, R.A. AND FRIENKEL, N.: Arch. Intern. Med. 114, 501 (1964)
9) HEGGARTY, H.J.: Br. Med. J. 1, 280 (1970)
10) ASTOOR, A.M. AND KING, E.J.: Biochem. J. 56, 4 (1954)
11) HAWK, P.B., OSCAR, B.L. AND SUMMERSON, W.H.: Practical Physiological Chemistry, p. 883 (1965)
12) LOCHNER, A. AND MADISON, L.L.: Clin. Rev. 11, 40 (1963)
13) LOCHNER, A. AND MADISON, L.L.: Diabetes 12, 361 (1963)
14) LOCHNER, A., WULF, J. AND MADISON, L.L.: Metab. Clin. Exptl. 16, 1 (1967)
15) TENNET, D.M.: Quart. J. Stud. Alcohol. 2, 263 (1941)