13. Shaffer, M. F., Milner, K. C., Clemmer, D. I., Potash, L., Shaffer, L. S., *ibid.*, 1954, v4, 992.

14. Hwang, K., Primack, N., *Antibiotic. Ann.*, 1956-57, New York, Med. Encyclopedia, Inc., p755.

15. Sylvester, J. C., Kirchmeyer, F. J., Farago, P. J., *ibid.*, p.781.

16. Benavides, L., Rangel-Rivera, L., Kumate, J., Carillo, J., Vasquez, V., Franco-Gomez, A., *Bol. Méd. Hosp. Infant.* (Mex.), 1962, v3, (English edition), 113.

17. Jennings, J. C., Olson, B. H., *Antibiot. and Chemother.*, 1958, v8, 245.

18. Hopps, H. E., Smadel, J. E., Bernheim, B. C., Danauskas, J. X., Jackson, E. B., *J. Immunol.*, 1961, v87, 162.

19. Benavides, L., Franco-Gomez, A., Gomez-Pagola, J., *ibid.*, 1960, v17, 765.

20. Parker, R. H., Chiv, V. S. W., Hoeprich, P. D., *Arch. Int. Med.*, 1963, v111, 799.

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Studies on 2-Deoxy-D-Glucose-Induced Hyperglycemia.* (29432)

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It has been demonstrated that 2-deoxy-D-glucose (2-DG) is a powerful inhibitor of glucose utilization *in vivo*(1-5). This inhibition brings about hyperglycemia, which is increased further by the release of epinephrine from the adrenal medulla(6). Other studies have shown that the cellular glucopenia induced by 2-DG produces certain histologic changes in the pancreatic islets, which suggest increased activity of both the A- and the B-cells(7). The purpose of this study was to find out whether a stimulation of pancreatic A-cells and an increase in glucagon secretion contribute to 2-DG-induced hyperglycemia.

Materials and methods. Mongrel dogs of both sexes, weighing between 10 and 15 kg were fasted overnight and anesthetized with pentobarbital sodium (35 mg/kg I.V.). The pancreato-duodenal (P-D) artery was cannulated as described previously(8). 2-DG (500 mg, standard dose per animal, dissolved in saline 1 ml/kg) was injected into the artery, a technique which allows perfusion of the pancreas with a relatively high concentration of 2-DG, while leaving the rest of the organism unaffected by the sugar. Control injections were made into an exposed femoral vein. Some animals were pretreated with dihydroergotamine (DHE; 0.4 mg/kg), injected intravenously 35 minutes before injection of 2-DG.

Blood samples were obtained from a femoral vein for duplicate glucose determinations according to Nelson(9). The statistical significance of the results was calculated according to Fisher(10).

Results. All results are given in the form of curves representing changes in blood sugar concentration from the average of 3 pre-injection values. These were taken 30 minutes, 15 minutes and immediately before the injection of 2-DG.

The results show that injections of 2-DG into the P-D artery caused a statistically significant hyperglycemia ($p<0.01$) lasting approximately 30 minutes. A still greater hyperglycemic effect, lasting approximately 45 minutes, was obtained by injecting 2-DG into the femoral vein ($P<0.001$). No changes from pre-injection levels were observed in animals pretreated with DHE. Previous experiments had demonstrated that injections of saline into the P-D artery do not modify blood glucose concentration significantly(8).

Discussion. These studies confirm the hyperglycemic effect of 2-DG, even in doses 10 times smaller than those used by other investigators. They also confirm the fact that DHE blocks this hyperglycemic response. The role of the pancreas in these phenomena is not clear. The fact that the hyperglycemic

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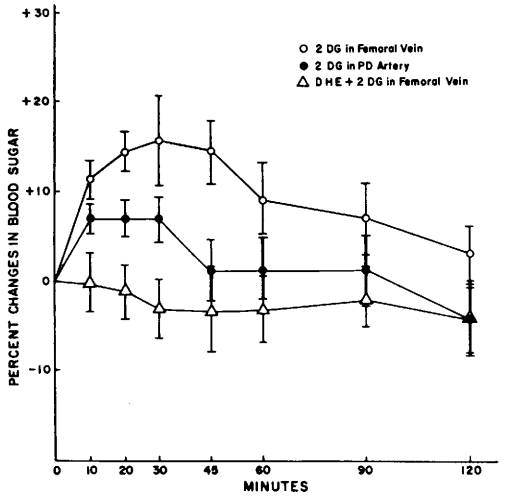

FIG. 1. Changes in blood glucose concentration following injection of 2-DG into femoral vein (○—○; 24 dogs); pancreato-duodenal artery (●—●; 15 dogs); or femoral vein of dogs pretreated with DHE (△—△; 11 dogs).

effect is smaller after intrapancreatic than after intrafemoral injections, suggests that the release of glucagon-like materials is not a factor. It suggests further that part of the 2-DG injected into the P-D artery may be removed by the liver or the pancreas itself, thus decreasing the amount available for epinephrine release. The fact that DHE blocks 2-DG-induced hyperglycemia is in agreement with this hypothesis, since DHE blocks the hyperglycemic effect of epinephrine, but not that of glucagon(11). No evidence of B-cell stimulation and insulin release was found in these experiments, in agreement with the observation that 2-DG does not cause insulin secretion by perfused rat pancreas *in vitro* (12). These results suggest that the histologic findings of increased B-cell activity reported by Hokfelt *et al*(7) were probably due to the hyperglycemia present in their animals and not to a direct stimulation of the islets by 2-DG.

It is concluded that the response of whole intact animals to 2-DG is probably due to two mechanisms: 1) an immediate release of epinephrine by the adrenal medulla and, possibly, by organs in the pancreato-duodenal area(11) and, 2) when large doses of 2-DG are used, a sustained generalized inhibition of glucose utilization which, in turn, may stimulate further epinephrine release.

Summary. Small doses of 2-deoxy-D-glucose were injected into the pancreato-duodenal artery or into the femoral vein of normal dogs. The route of administration did not markedly affect the intensity and duration of the hyperglycemic response. The response was prevented by pre-treatment with dihydroergotamine. It is concluded that 2-DG does not stimulate the release of glucagon-like materials from the pancreas and that, probably, the observed hyperglycemia was due to secretion of epinephrine and inhibition of glucose utilization. No evidence of insulin release was obtained in these experiments.

1. Wick, A. N., Drury, D. R., Moriter, T. N., PROC. SOC. EXP. BIOL. AND MED., 1955, v89, 579.

2. Landau, B. R., Lubs, H. H., *ibid.*, 1958, v99, 124.

3. Brown, J., *Metabolism,* 1962, v11, 1098.

4. Altszuler, N., Dunn, A., Steele, R., Bishop, J. S., DeBodo, R. C., *Am. J. Physiol.*, 1963, v204, 1008.

5. Kipnis, D. M., Cori, C. F., *J. Biol. Chem.*, 1959, v234, 171.

6. Hokfelt, B., Bydgeman, S., PROC. SOC. EXP. BIOL. AND MED., 1961, v106, 537.

7. Hokfelt, B., Hultquist, G., *ibid.*, 1961, v107, 66.

8. Pozza, G., Galansino, G., Hoffeld, H., Foà, P. P., *Am. J. Physiol.*, 1958, v192, 497.

9. Nelson, N., *J. Biol. Chem.*, 1947, v153, 375.

10. Fisher, L. A., *Statistical Methods for Research Workers*, Edinburgh, Oliver, 1950.

11. Galansino, G., D'Amico, G., Kanameishi, D., Berlinger, F. G., Foà, P. P., *Am. J. Physiol.*, 1960, v198, 1059.

12. Grodsky, G. M., Batts, A. A., Bennett, L. L., Vcella, C., McWilliams, N. B., Smith, D. F., *ibid.*, 1963, v205, 638.

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