

THE SUPRARENAL SYSTEM AND CARBOHYDRATE METABOLISM *

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Prior to the experiments of Blum¹ in 1901, when he demonstrated that injections of a watery extract of the adrenal glands constantly give rise to glycosuria in dogs, very little attention had been given to the action of the suprarenal secretion on metabolism. Claude Bernard's² conception of an internal secretion enunciated in 1855, and the publication, in the same year, of Thomas Addison's book containing his observations on the association of a definite clinical syndrome with pathologic changes in the adrenal glands, prepared the way for Brown-Séquard's³ well known experiments. His conclusions, though in part erroneous, were epoch-making. Because of the stimulus it supplied to investigations in the new field of internal secretion, the value of this work was tremendous. But so far as the adrenals were concerned, these early researches had been confined chiefly to studies of their effect on blood pressure, local changes in the tissues and blood vessels at the site of injection, and to general symptoms following extirpation experiments.

Abundant experimental data, and much speculation as to the rôle of the adrenal secretion in carbohydrate metabolism has accumulated in the fifteen years since Blum's observation. This work has, for the most part, represented efforts to discover the mechanism by which the suprarenal system, and more particularly the adrenal glands themselves, intervene in sugar metabolism, with the idea constantly present that they may be implicated in the perversions of metabolism in diabetes mellitus.

In addition, however, to the glycosuric effects of epinephrin injections, there are other observations which indicate that the adrenals affect the metabolism of carbohydrates. Porges⁴ and later Bernstein⁵ reported a lowering of blood sugar in Addison's disease, while Fuchs

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1. Blum: *Deutsch. Arch. f. klin. Med.*, 1901, **71**, 146; and *Arch. f. d. ges. Physiol. (Pflüger's)*, 1902, **90**, 628.

2. Bernard, Claude: *Leçons de physiologie expérimentelle au Collège de France*, Paris, 1855.

3. Brown-Séquard: *Compt. rend. Soc. de biol.*, 1889, pp. 415, 420, 430, 451.

4. Porges: *Ztschr. f. klin. Med.*, 1909, **69**, 341.

5. Bernstein: *Berl. klin. Wchnschr.*, 1911, **48**, 1874.

and Roth⁶ found, after injections of epinephrin, a distinct rise in the respiratory quotient in patients with this disease. Porges⁷ also showed that the blood sugar in adrenalectomized dogs regularly falls during the time that the animal survives. The experiments of Bierry and Mallozel⁸ confirmed this observation. They found that the concentration of sugar in the blood, after extirpation of the adrenals, fell to one fifth or one half of the original amount and remained there. They also showed that these animals were more resistant to epinephrin injections than normal animals so far as the production of hyperglycemia is concerned. More will be said about these observations later on in discussing the phase of carbohydrate metabolism affected by the adrenal secretion. It is obvious, however, from what has been said, that the adrenal glands by means of their internal secretion, and in particular by the active principle of the medullary portion, play some part in carbohydrate metabolism. The possibility that this power to alter and in part control the metabolism of sugar bears some relation to the pathogenesis of diabetes mellitus is, of course, of the greatest importance, and one which has formed the chief stimulus to the investigations. With this possibility in mind we shall review the experimental work and hypotheses which have been offered to explain the mechanism by which the secretion of the adrenals affects the storage and combustion of carbohydrates.

But before entering on a consideration of this question it will be well to recall briefly the important facts in normal carbohydrate metabolism. Carbohydrate food enters the body by the alimentary tract in the form of sugars and starches. By the action of diastatic enzymes of the saliva and pancreatic secretion the latter are split into sugars. In the intestine, chiefly in the upper portion of the small intestine, the sugars are acted on by the enzymes of the intestinal mucosa, namely, invertase, maltase and lactase, and thereby converted into one or other of the monosaccharids. By far the largest portion of the ingested carbohydrate is absorbed in the form of dextrose, but levulose and galactose have also been demonstrated in the portal blood. In the liver, glycogen is formed from these sugars and stored within the hepatic cells, probably by the action of an enzyme (glycogenase?) which is present in the liver cells. This formation of glycogen, which depends chiefly on glucose, but also to a slight extent on levulose and galactose, is called glycogenesis. Whenever the cells of the body, especially the striated muscles, require glucose for heat or energy needs, the glycogen stored in the liver is broken down by the glycogenase, and glucose is discharged into the hepatic veins, and thus to the general circulation.

6. Fuchs and Roth: *Ztschr. f. exper. Path. u. Therap.*, 1912, **10**, 187.

7. Porges: See Note 4.

8. Bierry and Mallozel: *Compt. rend. Soc. de biol.*, 1908, **60**, 232.

This process by which glucose is formed from glycogen is termed glycogenolysis. The tissues of the body either burn the glucose thus brought to them by the blood stream, forming carbon dioxid and water as the end-products, or they store it as glycogen. So accurately adjusted is this mechanism by which the liver supplies the circulating blood, and, indirectly, the tissues, with glucose, according to the tissue requirements, that the concentration of the glucose of the blood remains practically constant, despite great variations in the quantities the tissues use. Normal well-fed dogs made to run on the treadmill almost to the point of exhaustion show little, if any, alteration in the glucose concentration of the blood, despite the enormous consumption by the muscular tissues entailed during such exercise. Under physiologic conditions the blood sugar is kept between 70 and 100 mg. per 100 c.c. of blood. But in order that these processes shall proceed in this way it is essential that the islands of Langerhans be functioning. Removal of the pancreas promptly upsets this mechanism; the blood sugar rises, glycosuria appears, the glycogen stores become impoverished, and the animal presents an essentially complete picture of diabetes mellitus.

Any disturbance in this mechanism for sugar control is promptly shown by changes in sugar concentration of the circulating blood. Overproduction by the liver, that is, hyperglycogenolysis, is at once followed by a rise in the sugar of the blood. Diminished or arrested consumption, that is, a disturbance in glycolysis, produces a similar result.

Following an injection of epinephrin there occurs some disturbance in the physiologic sequence of events just outlined, a disturbance manifested by the appearance of considerable quantities of sugar in the urine. One or more of the several phases of carbohydrate metabolism must, therefore, be affected either in rate or character. We must consider each of the possibilities: does epinephrin alter the process of sugar absorption from the intestine; or is it in the processes of formation or breaking down of glycogen that it intervenes; or does it affect the oxidation of the sugar; or does it act on the internal secretion of the pancreas, rendering it incapable of exerting its normal control of sugar metabolism; or, finally, does it simulate the action of phlorizin and lower the threshold for sugar excretion by the kidneys?

There is, perhaps, one further possibility which, alone, could hardly account for the epinephrin effects, but as an ancillary factor, might play a part. This is glyconeogenesis, or the formation of glucose from protein. If epinephrin caused the breaking down of the protein molecule and the liberation of the carbohydrate fraction, this could increase the effects of such a carbohydrate disturbance as epinephrin produces; but with glyconogenic, glycogenolytic and glycolytic processes proceeding

normally, glyconeogenesis could not explain the metabolic changes following an increase of the circulating epinephrin. Such an increased production of carbohydrate would be quite comparable to carbohydrate feeding in a normal animal—the excess would either be stored as glycogen or oxidized.

It is not necessary to discuss the possibility that epinephrin affects the process of sugar absorption by the intestines; suffice it to say that there is neither theoretical reason nor experimental evidence pointing to any such action.

We shall, therefore, proceed to examine the experimental data and the conclusions which may be drawn from them in so far as they throw light on the remaining theoretically possible explanations of the mechanism of the epinephrin action.

Blum's results were promptly confirmed (Zuelzer,⁹ Metzger,¹⁰ Herter and Richards,¹¹ Paton,¹² Lazarus¹³), and it soon became well established that the injection of 1.0 mg. of epinephrin per kilo of body weight is followed by a glycosuria which appears in one half to two hours, and may last a few hours to a day or longer. Moreover, it does not matter whether a saline extract of the fresh gland be employed or one of the pure products, such as the adrenalin chlorid (Aldrich,¹⁴ Takamini¹⁵), the epinephrin of Abel,¹⁶ adrenin, or the synthetic product.¹⁷ •

First Zuelzer⁹ and then Metzger¹⁰ and Paton¹² showed that the glycosuria is accompanied by an hyperglycemia, thus ruling out the possibility that the mechanism is similar to that of phlorizin diabetes, in which, despite glycosuria, there is hypoglycemia, and probably a lowering of the threshold for sugar excretion by the kidney. Vosburg and Richards¹⁸ obtained, after epinephrin injections, a more marked hyperglycemia in well fed animals than in those which had been starved, suggesting thus that the glycogen stores had been called on to give up glucose to the blood. Pollak¹⁹ showed that both hyperglycemia and glycosuria are more readily produced by subcutaneous than by intravenous or intraperitoneal administration. He explains this by the assumption that the carbohydrate mechanism is more sensitive to epinephrin than the vasoconstrictors, and that the slow absorption after subcutaneous injections allows the epinephrin concentration of the blood to rise only to a level at which the carbohydrate mechanism is

9. Zuelzer: Berl. klin. Wchnschr., 1901, **38**, 1209.

10. Metzger: München. med. Wchnschr., 1902, **12**, 478.

11. Herter and Richards: Med. News, New York, 1902, **80**, 201.

12. Paton: Jour. Physiol., 1903, **29**, 286.

13. Lazarus: Cited by Shafer, Brit. Med. Jour., 1908, **1**, 1277.

14. Aldrich: Am. Jour. Physiol., 1901, **5**, 457.

15. Takamini: Am. Jour. Pharm., 1901, **11**, 523.

16. Abel: (Hoppe-Seyler's) Ztschr. f. Physiol. Chem., 1899, **28**, 318.

17. Amberg: Arch. Intern. de Pharmakol., 1902, **11**, 57.

18. Vosburg and Richards: Am. Jour. Physiol., 1903, **9**, 35.

19. Pollak: Arch. f. exper. Path. u. Pharmakol., 1909, **61**, 149.

affected, while the more rapid entrance of the epinephrin into the circulation after intravenous or intraperitoneal injection raises the concentration in the blood sufficiently high to cause vasoconstriction. Consequently a diminished amount of blood passes through the liver, and thus less glucose is mobilized. Straub²⁰ and Ritzmann,²¹ on the basis of infusion experiments, have shown that the glycosuria runs almost parallel with the epinephrin concentration of the blood, and Ritzmann

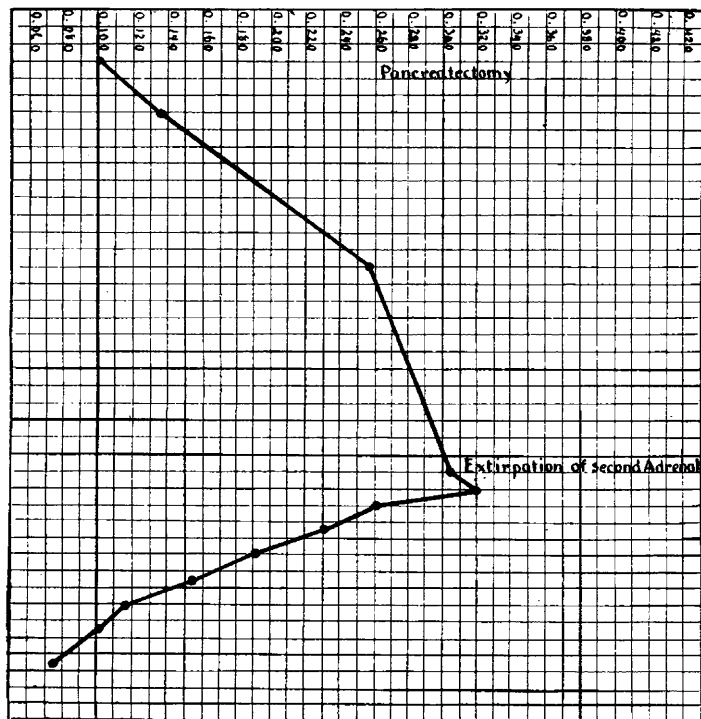


CHART 1.—Blood sugar curve in depancreatized dog, with extirpation of adrenals. Ordinates = per cent. reducing substance in blood. Abscissa = time: Each square = two hours.

puts forward the idea that epinephrin acts to maintain, by sympathetic stimulation, a *Zuckertonus* as well as a *Gefässtonus*. Underhill's²² experiments with epinephrin infusions corroborate Ritzmann's results. Satisfactory investigations as to the parallelism between sugar and epinephrin concentrations in the blood are lacking.

Of considerable importance in determining how and where epinephrin acts is, first, the question of the effect of epinephrin injections on the glycogen content of the liver, and, second, whether or not it is

20. Straub: München. med. Wchnschr., 1909, **56**, 493.

21. Ritzmann: Arch. f. exper. Path. u. Pharmacol., 1909, **61**, 231.

22. Underhill: Jour. Biol. Chem., 1911, **9**, 13.

still capable of causing hyperglycemia and glycosuria after the glycogen depots of the body have been exhausted.

The first of these questions has been definitely settled. Doyon and Kareff,²³ Gatin-Gruzewska,²⁴ Agadschanianz²⁵ and Pollak²⁶ have shown that epinephrin diminishes the quantity of glycogen in the liver. Schirokauer and Wilenko²⁷ went a step further and showed that the increased glycogenolysis in animals treated with epinephrin is not dependent on an increased production of liver diastase. Furthermore, Gatin-Gruzewska²⁴ and Agadschanianz²⁵ demonstrated that the muscles also lose glycogen. So far as I am aware there are no trustworthy experiments contradicting this conclusion.

If the second of these questions could be answered affirmatively, it would constitute a strong support for the view that epinephrin acts not merely on the liver, causing it to discharge glycogen, but also that it is capable of raising the concentration of the blood sugar, either by interfering with the glycolytic processes in the tissues or by inducing glycogenesis, or by inhibiting the pancreas. It becomes necessary, therefore, to examine more closely the evidence on which conclusions have been based as to the effect of epinephrin on animals whose livers have been rendered glycogen-free.

Blum,¹ in his early communications, asserted that epinephrin glycosuria occurred even when the glycogen stores had been exhausted before the injection, but his conclusion was based on the assumption that starvation alone will remove all the glycogen from the liver. This is open to question, because Pflüger²⁸ has shown that a dog after starving twenty-eight days still contains enough glycogen to form 100 gm. of sugar. Ringer²⁹ found no increase in glycosuria following epinephrin injections after the liver had been rendered glycogen-free by phlorizin. This, however, is not convincing proof, because little is known of the action of phlorizin, beyond the fact that it lowers the threshold for sugar excretion by the kidney. It may also interfere with the mechanism involved in epinephrin glycosuria. Paton¹² and Herter and Richards¹¹ offered evidence in support of Blum. They found that dogs which had been either fasted or fed on a diet of material from which no glycogen could be formed and then phlorizined, still responded with glycosuria to epinephrin injections. It seems doubtful, however, that the animals were glycogen-free before the injection. Frank and Isaac³⁰ found that after dogs were poisoned with phos-

23. Doyon and Kareff: *Compt. rend. Soc. de biol.*, 1904, **56**, 66.

24. Gatin-Gruzewska: *Compt. rend. Acad. de sc.*, **142**, 1165.

25. Agadschanianz: *Biochem. Ztschr.*, 1907, **2**, 148.

26. Pollak: *Arch. f. exper. Path. u. Pharmacol.*, 1909, **61**, 153.

27. Schirokauer and Wilenko: *Ztschr. f. klin. med.*, 1910, **70**, 257.

28. Pflüger: *Arch. f. d. ges. Physiol.*, 1902, **91**, 119.

29. Ringer: *Jour. exper. Med.*, 1910, **12**, 105.

30. Frank and Isaac: *Ztschr. f. exper. Path. u. Therap.*, 1910, **7**, 326.

phorus no hyperglycemia followed epinephrin injections. Phosphorus is known to cause a disappearance of the liver glycogen, but the absence of epinephrin glycosuria during such a profound metabolic disorder as phosphorus causes does not settle the question. Velich³¹ found no epinephrin glycosuria after extirpation of the liver in frogs. Falta and

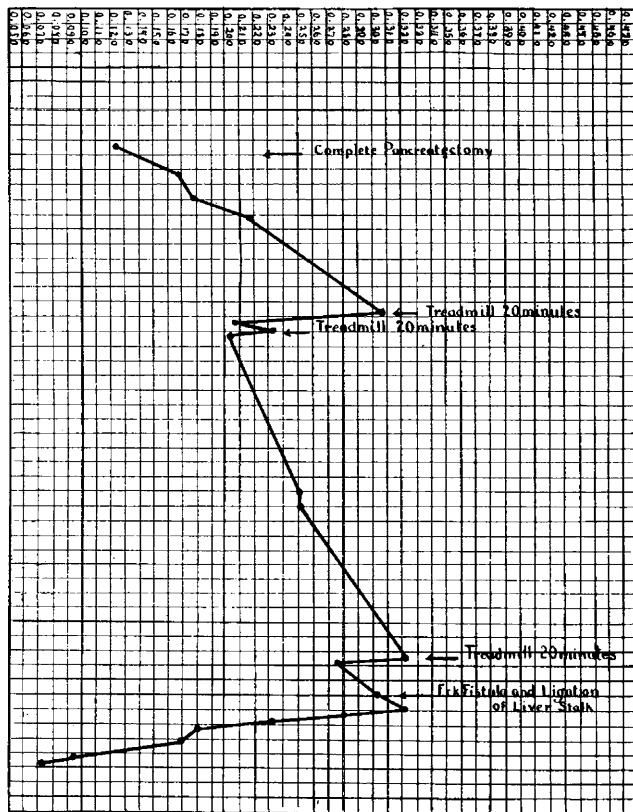


CHART 2.—Blood sugar curve in depancreatized dog with Eck fistula and ligation of liver stalk. (The first portion of this curve was made for another experiment in which the effect of exercise on the blood sugar was being studied.) The rapid and uninterrupted drop in the amount of reducing substance in the blood after the liver was excluded from the circulation is very striking. Ordinates represent per cent. of reducing substance in the blood. Abscissa = time: Each square = two hours.

Priestly,³² using rabbits, tied off the liver vessels and found that, despite epinephrin injections, the blood sugar fell to 0.04 per cent. The conclusion from this seems to be that the liver glycogen is essential for the maintenance of the blood sugar level, and that the glycogen stores

31. Velich: Virchows Arch. f. path. Anat., 1906, **184**, 345.

32. Falta and Priestley: Berl. klin. Wchnschr., 1911, **48**, 2102.

in the muscles are inadequate for this. Michaud's³³ experiments on dogs with Eck's fistulas are important. In only one out of six dogs did epinephrin cause a rise in blood sugar. His animals remained in good condition after the operative interference, a condition which has usually been lacking in experiments aimed to settle this point, and one which has doubtless contributed to the contradiction of results. Pollak³⁴ induced convulsions with strychnin in starved rabbits, presumably glycogen-free. Although it did not produce hyperglycemia, epinephrin did cause a disturbance in carbohydrate metabolism, shown by the deposition of glycogen in the liver.

It is not easy to give a definite interpretation of the experimental data mentioned; experiments of many types have been performed to determine whether the glycosuric and hyperglycemic action of adrenal persists without available glycogen in the liver, but, as the above mentioned investigations show, there has been by no means a uniformity in the results. Perhaps the experiments of Pollak³⁴ and Michaud³³ are the most significant; from them we may conclude, with some reserve, however, that an available supply of glycogen in the liver is essential for the production of hyperglycemia by epinephrin injections, and, furthermore, that an excess of epinephrin in the blood stimulates the formation of glycogen in a glycogen-free liver. But there are other reasons, besides those advanced by Pollak, which lead us to believe that epinephrin has some influence on glycogen formation, as well as on glycogenolysis. Schwarz,³⁵ using rats, because they survive adrenalectomy for a long time, determined the glycogen content (Pflüger's method) after both adrenals had been extirpated, and found only mere traces or complete absence of glycogen. He concludes that after adrenalectomy the power to store glycogen is lost. This work has been confirmed by Kahn and Starkenstein,³⁶ who not only demonstrated a loss of liver glycogen following adrenalectomy, but demonstrated also that such animals acquire an unusual tolerance for epinephrin.

I have administered large quantities of glucose intravenously and by the alimentary tract to adrenalectomized dogs, and have found that when, by thus saturating the organism with sugar, the concentration of sugar in the blood has been raised to 560 mg. per 100 c.c., little or no glycogen is demonstrable in the liver cells when stained by Best's method. Control animals which have been starved, but not adrenalectomized, receiving the same amounts of sugar per kilo body weight, show abundant glycogen granules in the liver cells. Since we know that an excess of epinephrin in the blood causes a discharge of gly-

33. Michaud: *Verhandl. d. deutsch. Kongr. f. inn. Med.*, Wiesbaden, 1911, p. 561.

34. Pollak: *Arch. exper. Path. u. Pharmacol.*, 1909, **61**, 166.

35. Schwarz: *Arch. d. ges. Physiol. (Pflüger's)*, 1910, **134**, 259.

36. Kahn and Starkenstein: *Arch. f. d. ges. Physiol. (Pflüger's)*, 1911, **139**, 181.

cogen from the liver, the observation that a diminished amount of epinephrin in the blood is associated with an absence of glycogen, carries with it the conclusion that epinephrin performs a double function, so far as glycogen metabolism in the liver is concerned. It is necessary for glycogenesis, and when present in excess it stimulates glycogenolysis. Or, stated in another way, when it is absent, glycogen storage is inhibited; when it is present in excess, the transformation of glycogen to glucose is accelerated.

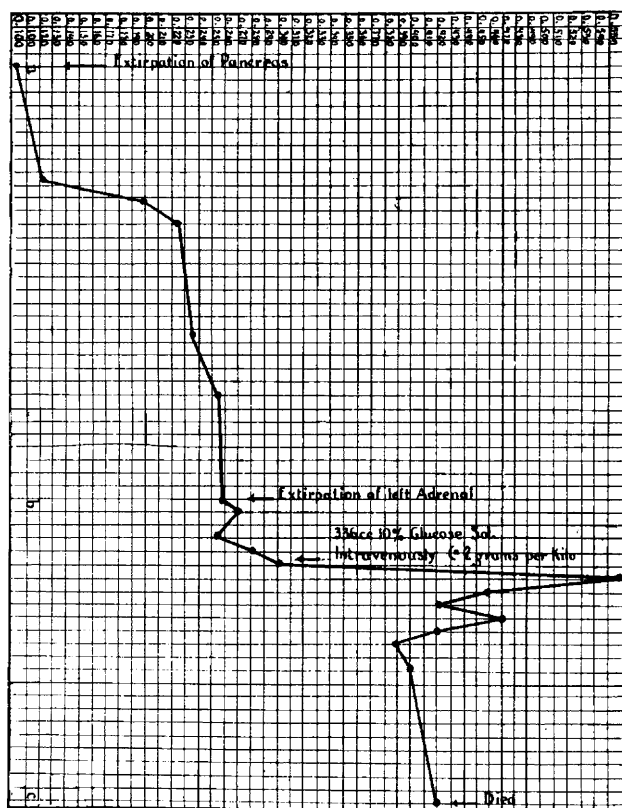


CHART 3.—Blood sugar curve in depancreatized dog after extirpation of the adrenals, followed by intravenous injection of glucose solution—2 gm. per kilo. Ordinates = per cent. of reducing substance in blood. Abscissa = time: a-b each square = two hours; b-c each square = one-half hour.

Having now satisfactory evidence that the internal secretion of the adrenals intervenes in carbohydrate metabolism in these two ways, we must proceed to examine the data which throw light on the chemical or physical processes by which these functions are performed. We can imagine that such a mechanism is dependent on direct hormone action within the liver cells, the epinephrin acting, on the one hand, on the glucose brought by the portal blood, converting it to glycogen, and, on

the other hand, on the glycogen of the liver, converting it to glucose. Or we can think of it as producing its effects by controlling the blood supply of the liver, the changes in the condition of the carbohydrate in the liver being then dependent on the constriction or dilatation of the blood vessels. We may also, as some investigators hold, believe that its action depends on a specific power to affect the internal secretion of the pancreas. Finally, if it could be shown that glycogenesis and glycogenolysis are controlled by nervous impulses carried by the sympathetic, the well known stimulating effects of epinephrin on sympathetic nerve endings might conceivably explain the mechanism.

That there is an intimate relation between the nervous system and the sugar content of the blood has long been well known. Sixty-one years ago Claude Bernard² published the results of his observations on the appearance of glycosuria following puncture of the floor of the fourth ventricle. Many investigators have been interested since then in studying experimentally the mechanism by which piqûre glycosuria is brought about.

Naunyn³⁷ found a hyperglycemia of 0.81 per cent. four hours after piqûre. Because of the inexactness of the methods of blood sugar determination, these early observations are open to question. Bang, Ljungdahl and Bohm,³⁸ however, found a blood sugar of 0.38 per cent. after piqûre in rabbits, and this has been confirmed by others. Eckhardt³⁹ and later Pflüger⁴⁰ agreed with the opinion of Bernard that the stimuli produced by piqûre are carried directly to the liver by way of the splanchnics. Blum's¹ discovery of epinephrin glycosuria, however, suggested at once that epinephrin might be a factor in piqûre glycosuria. That the secretion of epinephrin is under the control of the sympathetic has been well established (Asher,⁴¹ Popielski,⁴² Tscheboksareff⁴³). Pollak⁴⁴ showed that piqûre and other centrally acting causes of hyperglycemia are ineffective if the splanchnics are severed, and Macleod and Pearce,⁴⁵ by electric stimulation of the splanchnics, produced hyperglycemia. The results of Waterman and Smit,⁴⁶ who, using the Meltzer-Ehrmann reaction as a test for increase of epinephrin in the blood, claimed to have demonstrated an increase following piqûre, have met with some opposition. Later researches by Kahn,⁴⁷

37. Naunyn: Arch. f. exper. Path. u. Pharmakol., 1874, **3**, 85.

38. Bang, Ljungdahl and Bohm: Beitr. z. chem. Physiol. u. Path. (Hofmeister), 1907, **10**, 1.

39. Eckhardt: Beitr. z. Anat. u. Physiol., 1869, **4**, 4, 138.

40. Pflüger: Das Glykogen, Ed. 2, 1905.

41. Asher: Centralbl. f. Physiol., 1910, **137**, 927.

42. Popielski: Arch. f. d. ges. Physiol., 1911, **139**, 571.

43. Tscheboksareff: Centralbl. f. Physiol., 1910, **137**, 137.

44. Pollak: Arch. f. exper. Path. u. Pharmakol., 1909, **61**, 376.

45. Macleod and Pearce: Am. Jour. Physiol., 1912, **29**, 419.

46. Waterman and Smit: Arch. f. d. ges. Physiol. (Pflüger's), 1908, **124**, 198.

47. Kahn: Arch. f. d. ges. Physiol. (Pflüger's), 1912, **144**, 251 and 396.

Lopez,⁴⁸ and v. Brucke⁴⁹ failed to confirm the findings of Waterman and Smit. It should be remembered that the tests for epinephrin in the blood are not as precise as could be desired⁵⁰ and the results reported should not be too readily accepted. There are four more or less reliable physiologic tests for the presence of minute quantities of epinephrin in the blood: (1) its mydriatic (dilatatory) action on the pupil of the excised frog's eye; (2) its effect in raising the arterial blood pressure; (3) its power of lessening the rhythmic contractions of the longitudinal coat of the intestine immersed in Ringer's solution; (4) its stimulating action on the rhythmical contractions which occur in the excised uterus of the virgin rabbit in oxygenated Ringer's solution. The reason for caution in interpreting such results is that serum may contain substances which stimulate and substances which inhibit⁵¹ the action of epinephrin. Borberg,⁵² using an improved technic for the Meltzer-Ehrmann reaction, found a marked rise in the adrenalin content of the adrenal vein after diabetic puncture. Kahn,⁵³ moreover, on the basis of indirect evidence, believed that piqûre caused a discharge of epinephrin. He found a decrease of chromaffin substance in the adrenals after piqûre, and assumed from this that there was an increased secretion. Jarisch⁵⁴ was unable to confirm this. Trendelenburg and Fleischhauer⁵⁵ offered further indirect evidence against the view that piqûre is followed by an increased concentration of epinephrin in the blood. They determined the amount of epinephrin which, by continuous intravenous infusion, would produce a glycosuria equivalent to that following piqûre, and observed that when such amounts of epinephrin were in the blood there was at the same time a marked rise in the blood pressure. Since this is absent after piqûre, they believe that an hyper-adrenalinemia is not the essential factor in piqûre glycosuria.

Further evidence as to the rôle of the adrenals in the production of piqûre hyperglycemia and glycosuria is found in the numerous experiments on the effect of piqûre or splanchnic stimulation after extirpation of the adrenals. Mayer⁵⁶ did piqûre on twenty-five adrenalectomized rabbits and failed to produce glycosuria. Landau⁵⁷ confirmed this. Kahn⁵⁸ found that after extirpation of the adrenals rabbits showed no glycosuria. In later experiments,⁵³ however, he found

48. Lopez: Arch. f. d. ges. Physiol. (Pflüger's), 1912, **145**, 311.

49. Von Brucke: München. med. Wchnschr., 1911, p. 1389.

50. Macleod: Diabetes, London, 1913.

51. Stewart: Jour. Exper. Med., 1911, **14**, 377.

52. Borberg: Dissertation, Kopenhagen, 1912.

53. Kahn: Arch. f. d. ges. Physiol. (Pflüger's), 1911, **140**, 209.

54. Jarisch: Ztschr. f. exper. Path. u. Therap., 1913, **13**, 520.

55. Trendelenburg and Fleischhauer: Ztschr. f. d. ges. exper. Med., 1913, **1**, 369.

56. Mayer: Compt. rend. Soc. de biol., 1906, **60**, 1123.

57. Landau: Experimentelle Nebennieren-Studien, Dorpat, 1908.

58. Kahn: Arch. f. d. ges. Physiol. (Pflüger's), 1909, **128**, 519.

that piqûre causes a loss of chromaffin substance from the adrenals, and from this concluded that piqûre stimulates the secretion of epinephrin. Freund and Marchand⁵⁹ found that piqûre in adrenalectomized animals is followed by marked hyperglycemia, but they found no sugar in the urine. They concluded that its hyperglycemic action does not depend on the adrenals, but results from direct stimulation of the liver. Wertheimer and Battez⁶⁰ found that dogs and cats exhibit a difference in their reaction to piqûre. Adrenalectomized cats showed a marked glycosuria (3.63 to 17.5 gm.) after piqûre, but dogs on which they performed similar experiments, showed none. Gautrelet and Thomas⁶¹ stimulated the splanchnics after extirpation of the adrenals and found no glycosuria.

That the blood sugar curves⁶² after epinephrin injections and after piqûre are different affords some evidence against the view that the mechanism is similar, but the great variability of the curves after piqûre makes deductions from this hazardous.

Perhaps the most illuminating experiments dealing with this problem are those of Macleod⁶³ and his collaborators. Realizing that the disturbances of respiration and circulation following piqûre vitiate, in part at least, the hyperglycemic effects of this procedure, he demonstrated that the cava blood contains an increased quantity of reducing substance after stimulation of the great splanchnic nerve with the adrenals intact. After excision of the gland on the left side, stimulation of the nerve on the same side causes no rise in the blood sugar. Gautrelet and Thomas⁶¹ had obtained results similar to these, but since this did not prove that the hyperglycemia was due to an increased secretion of epinephrin, Macleod went further and elaborated a type of experiment first done by Kaufmann.⁶⁴ He sectioned the nerve path between the adrenals and the liver, that is, the hepatic plexus. When this was done he found that stimulation of the left splanchnic was only rarely followed by an increase in the sugar of the blood, and that when this occurred it was less intense than usual. The conclusion from this is that it cannot be merely an increased epinephrin secretion which causes the hyperglycemia. He then applied electrical stimulation directly to the hepatic plexus and found that when the adrenals were intact such stimulation caused a striking hyperglycemia, whether the fibers central to the point of stimulation were cut or uncut. In the absence of the adrenal glands, however, stimulation of the hepatic plexus had no effect. The conclusion arrived at from these experi-

59. Freund and Marchand: *Arch. f. exper. Path. u. Pharmacol.*, 1914, **76**, 324.

60. Wertheimer and Battez: *Compt. rend. Soc. de biol.*, 1914, **86**, 617.

61. Gautrelet and Thomas: *Compt. rend. Soc. de biol.*, 1909, **67**, 233.

62. Bang: *Der Blutzucker*, Wiesbaden, 1913, p. 113.

63. Macleod: *Diabetes*, London, 1913, and Macleod and Pearce: *Am. Jour. Physiol.*, 1912, **29**, 419.

64. Kaufmann: *Arch. de Physiol.*, 1895, **27**, 266.

ments is that only when the adrenal glands are intact is it possible, by stimulation of the nerves supplying the liver, to excite hyperglycogenolysis and hyperglycemia. Some influence exercised by the adrenal glands is evidently essential for the functional integrity of the nerves which control the process of glycogenolysis. That this rôle of activating the receptive substance which, according to the experiments of Elliott⁶⁵ and others, is believed to lie between the nerve terminations and the cell substance, is not out of harmony with the fact that an excess of epinephrin in the blood causes an increase of glycogenolysis, is shown by other experiments of Macleod. Hyperglycemia was produced by injecting epinephrin into the portal vein after the sympathetic stimuli had been stopped by cutting the hepatic plexus. This explanation of the mechanism by which epinephrin produces its glycosuric effect has recently been substantiated by the work of Freund.⁶⁶ Taking advantage of the fact that rabbits have a collateral liver circulation through diaphragmatic vessels which is sufficient to prevent necrosis when the hepatic artery is tied, he cut the hepatic artery and hepatic plexus before doing piqûre. His results were not entirely constant, but on the whole indicated that piqûre does not cause hyperglycemia unless the nerve path between adrenals and liver is intact. Hence piqûre hyperglycemia is not dependent on an increase of epinephrin in the blood.

The possibility that the internal secretion of the adrenals interferes with the pancreatic control of carbohydrate metabolism by a specific inhibitory action, is an attractive theory, but one for which sound experimental proof is still lacking. In the first place it is not yet clear just what rôle in carbohydrate metabolism is played by the pancreas. The secretion which performs this function has never been isolated. The effects of removal of the gland are well known, but just how it acts when present, it is impossible to say. From the work of Hédon⁶⁷ and later that of Lombroso,⁶⁸ MacCallum⁶⁹ and Forschbach⁷⁰ it may be accepted as an established fact that the pancreas, independent of its external secretion, and of the nerve connections, performs an important function in the mobilization or utilization of glucose, and that probably this is accomplished by an internal secretion. Investigators are divided on the question of whether or not the hyperglycemia and glycosuria of pancreatic insufficiency are due to a primary underconsumption or a primary overproduction, and it is not necessary for our present purpose to discuss this question, except insofar as it

65. Elliott: Compare Swale Vincent: *Ergebn. der Physiol.*, 1910, **9**, 451.

66. Freund: *Arch. f. exper. Path. u. Pharmacol.*, 1914, **76**, 311.

67. Hédon: *Compt. rend. Soc. de biol.*, 1890.

68. Lombroso: *Ergebn. der Physiol.*, 1910, **9**, 1.

69. MacCallum: *Bull. Johns Hopkins Hosp.*, 1909, **20**, 265.

70. Forschbach: *Deutsch. med. Wchnschr.*, 1908, **34**, 910; *Arch. f. exper. Path. u. Pharmacol.*, 1908, **60**, 131.

involves the theory advanced by Eppinger, Falta and Rudinger⁷¹ regarding the specific interaction of the adrenals and pancreas. They found that in depancreatized dogs injections of epinephrin caused an increase in the sugar excretion, and a rise of the D:N ratio, but the objection has been made that they offer no proof that the diabetes was complete before the epinephrin was injected. Ringer²⁹ failed to produce an increase in the glycosuria of fully phlorizinized dogs by epinephrin injections. Zuelzer's⁷² observations that injections of pancreas extract rendered epinephrin nonglycosuric seemed to support the view that after pancreatectomy the diabetic manifestations appear because the internal secretion of the adrenal is then permitted, free from pancreas opposition, to act as a stimulus on the sugar output of the liver; but it was later shown that⁷³ many irritating substances when injected intraperitoneally have the same inhibitory effect on epinephrin glycosuria. Frugoni,⁷⁴ however, found that the inhibitory effect is obtained when the extract and epinephrin are injected subcutaneously. Loewi found that after removal of the pancreas the serum has an increased mydriatic power, and believes that this is due to the action of the epinephrin in the serum from which the inhibiting pancreatic secretion has been removed. He found human diabetic patients more susceptible to epinephrin mydriasis than normal controls.

Biedl and Offer⁷⁵ found that the lymph from the thoracic duct contains something which antagonizes the action of epinephrin on the excised frog's eye, and also inhibits epinephrin glycosuria. Believing this substance to be the internal secretion of the pancreas, they support the view of a mutually inhibitory action by the pancreas and adrenals.

A few experiments on the effect of adrenal extirpation on pancreatic diabetes in animals have been attempted. The difficulty here has been that the animals die so soon after removal of the adrenals that conclusions drawn from blood sugar determinations while the animals were in a moribund state are untrustworthy. Frouin⁷⁶ extirpated about three quarters of the adrenal substance from animals which had previously been rendered diabetic by removal of the pancreas. He found that the intensity of the diabetes was decreased as compared with controls. Mayer⁷⁷ destroyed by cauterization the adrenals of depancreatized dogs, but the animals survived the operation only an hour. In experiments on cats he removed the adrenals in two stages, and found that they then lived two to five hours after the operation. In each of three cases there was a fall in the blood sugar.

71. Eppinger, Falta and Rudinger: *Ztschr. f. klin. Med.*, 1909, **66**, 1.

72. Zuelzer: *Berl. klin. Wchnschr.*, 1909, **46**, 1209.

73. Von Fürth and Schwarz: *Biochem. Ztschr.*, 1911, **31**, 113.

74. Frugoni: *Berl. klin. Wchnschr.*, 1908, **45**, 1606.

75. Biedl and Offer: *Wien. klin. Wchnschr.*, 1907, **20**, 1530.

76. Frouin: *Compt. rend. Soc. de biol.*, 1908, **60**, 216.

77. Mayer: *Compt. rend. Soc. de biol.*, 1908, **60**, 219.

I have studied the effect of adrenal extirpation in the following way: The right adrenal, being the more difficult of the two to remove, is extirpated at the first operation. The animal is then allowed a week or more in which to make a complete recovery from the operation. Such dogs show no signs of adrenal insufficiency. At the second operation the pancreas is removed. When the blood sugar has risen to a diabetic level the left adrenal is extirpated. This is an easy operation, and can be done through a lumbar incision in twenty minutes. During the time that the animal survives, frequent blood sugar determinations are made, and the results plotted in a curve. Such an experiment on a dog is represented in Chart 1. It will be seen that following removal of the pancreas the blood sugar rose rapidly from the normal level (0.100 per cent.) to 0.305 per cent. Then the second adrenal (left) was removed. After a short rise, doubtless due to nerve stimulation during the operation, the blood sugar rapidly and uninterruptedly fell to normal. The dog survived the operation twenty-three hours, and during the first five or six hours after recovery from the anesthetic remained in good condition. This experiment has been repeated several times with the same result. The complete results of these experiments will shortly be published.

We see, therefore, that a considerable mass of evidence has accumulated to support the theory of a specific interaction between the adrenals and pancreas. None of it, however, is completely convincing. We shall revert to this question later on, after having considered the possibility that the adrenal secretion affects the power of the tissues, particularly of the muscles, to utilize sugar.

But first the explanation offered by Edmunds⁷⁸ and recently supported by the work of Mann and Drips⁷⁹ must be mentioned. Benedicente⁸⁰ and Pemberton and Sweet⁸¹ believed that because there is a diminished flow of the external secretion of the pancreas following epinephrin injections, there was also an inhibition of the secretion of the islands of Langerhans. Edmunds, however, offered evidence in support of the view that the diminished pancreatic secretion is merely consequent on the vasoconstriction produced by epinephrin. The increased flow after adrenalectomy is due according to Mann and Drips merely to the changes in blood pressure, decreased temperature, etc., incident to the moribund condition. It is, therefore, clear that before the specific relationship between islands of Langerhans and adrenal medulla be accepted, the effect of alterations in the blood supply of the pancreas after adrenalectomy or epinephrin injections must be excluded.

78. Edmunds: *Jour. Pharm. and Exper. Therap.*, 1911, **2**, 559.

79. Mann and Drips: *THE ARCHIVES INT. MED.*, 1915, **16**, 681.

80. Benedicente: *Arch. d. biol.*, 1905, **95**, 1.

81. Pemberton and Sweet: *THE ARCHIVES INT. MED.*, 1908, **1**, 628.

If it could be shown that the suprarenal secretion possesses the power to inhibit the oxidation of sugar by the tissues, it would strongly support the view, which has here and there cropped out in the literature of the subject, that in diabetes the basic fault is an excess of secretion by the adrenals or a diminished inhibition of this secretion by the pancreas. Experiments on the respiratory quotient and heat production supply the most significant facts in determining whether or not epinephrin affects glycolysis.

The respiratory quotient represents the ratio of the amount of carbon dioxid formed to the amount of oxygen required in the combustion of foodstuffs. Glucose, having sufficient oxygen to combine with all the hydrogen present to form water, will require for every molecule of carbon dioxid formed one molecule of oxygen. Plainly, then, the glucose respiratory quotient (R. Q.) is 1. In the case of protein the R. Q. is 0.81. Fat contains relatively less oxygen and consequently has a lower R. Q. This has been found to be 0.70. When, therefore, an animal is burning carbohydrate the R. Q. will be high; if he is burning only protein or protein and fat it will fall somewhere between 0.70 and 0.81.

Wilenko⁸² studied the influence of sugar ingestion and epinephrin administration in rabbits under urethane anesthesia. He found (1) that epinephrin has little or no effect on the R. Q. of fasting rabbits, the carbohydrate stores having presumably been exhausted; (2) that epinephrin depresses the physiologic elevation of the R. Q. after administration of carbohydrate; (3) that intravenously administered glucose in epinephrin animals appears quantitatively in the urine. His conclusion is that epinephrin diminishes the ability of the organism to burn sugar. La Franka⁸³ had previously reported experiments in which he found a lowering of the R. Q. in phlorizin and pancreas glycosuria, but no change after epinephrin administration. Hári⁸⁴ starved dogs twenty-four to thirty-six hours, and then after curarizing them, injected epinephrin intraperitoneally and intravenously. He found that the epinephrin increased the R. Q., indicating that more sugar was burned after the injections than before. Fuchs and Roth,⁸⁵ in two cases of Addison's disease, found a distinct rise in the R. Q. after subcutaneous epinephrin injections. Similar results have been reported by Falta.⁸⁵ Lusk⁸⁶ has attempted to settle this question by experiments with the respiration calorimeter. He found that epinephrin administered twenty-one hours after food ingestion does not prevent the oxidation of glucose in a well-nourished dog. He also injected epi-

82. Wilenko: *Biochem. Ztschr.*, 1912, **42**, 44.

83. La Franka: *Ztschr. f. exper. Path. u. Therap.*, 1909, **6**, 1.

84. Hári: *Biochem. Ztschr.*, 1911, **38**, 23.

85. Falta: *Die Erkrankungen der Blutdrusen*, 1913, p. 428.

86. Lusk: *THE ARCHIVES INT. MED.*, 1914, **13**, 673.

nephrin during a period of glucose absorption, and found no depression of the R. Q. following the injections. During two experimental periods of six hours and five hours, respectively, he found the R. Q. to be 0.98 and 0.99.

The preponderance of evidence, therefore, so far as alteration in the respiratory quotient is concerned, favors the view that epinephrin does not inhibit the combustion of sugar. Efforts⁸⁷ to show that epinephrin can act as an antiferment, inhibiting the action of the glycolytic ferment of the blood, have been unsuccessful.

The observations cited above that the hyperglycemia in experimental pancreas diabetes rapidly disappears after extirpation of the adrenals, or is prevented by simultaneous adrenalectomy, have led to the assumption that in the absence of both pancreas and adrenals the animal is able to oxidize glucose. This is almost equivalent to saying that when the blood sugar of such an animal has fallen to a normal level his diabetes has been cured, and that death comes from adrenal insufficiency, even though the power of carbohydrate combustion has been restored. Such an assumption is gratuitous, because the mechanism regulating the mobilization of sugar is susceptible to so many influences — nervous, circulatory and chemical — that results after extirpation experiments are not convincing. In depancreatized dogs I have observed a return of the blood sugar to normal levels when an Eck fistula was created, and the stalk of the liver ligated. Chart 2 represents the blood sugar curve in such an experiment. The drop in the blood sugar on exclusion of the liver from the circulation is exactly similar to that produced by adrenal extirpation. Further evidence against the antiglycolytic action of epinephrin and the view that adrenalectomy restores to the animal with pancreas diabetes the power to burn sugar, is supplied by the experiment represented in Chart 3. In this experiment the right adrenal was extirpated on December 29. This produced no change in the blood sugar. One month later, after the animal had made a complete recovery, and seemed to be quite well, the pancreas was removed. Three days later the blood sugar was 260 mg. per 100 c.c. The left adrenal was then removed, and 2 gm. of glucose per kilo were injected intravenously. The blood sugar immediately shot up to 560 mg. per 100 c.c. If this animal had had his power of sugar consumption restored he should have shown a steady fall in the blood sugar curve, but this did not occur. The blood sugar took a sharp drop to a level somewhat above the level before the sugar injection and remained there until he died. The sugar excreted in the urine during the last twenty-four hours was 101.8 gm., while during the preceding twenty-four hours it had been 64.9 gm. Since 33.6 gm.

87. Mackenzie: *Jour. Exper. Med.*, 1915, **22**, 757.

were injected it is evident that the intravenously administered glucose was recovered quantitatively in the urine, and there is no evidence that any sugar was burned. Moreover, sections of liver and striated muscle taken immediately after death, fixed in absolute alcohol and stained by Best's picrocarmin method, showed no evidence of glycogen. One may conclude from this that not only was there no restoration of glycolytic power, but also no return of the power to store glycogen after extirpation of the adrenals.

It is evident from this review of the experimental work designed to clear up the problems of the relation of the adrenal secretion to glycolysis, that the weight of evidence favors the view that they are unrelated. Wilenko's experiments on the respiratory quotient changes after epinephrin injections have not been confirmed by other investigators, and Zuelzer's conclusion, founded on a disappearance of reducing substance from the blood after adrenal extirpation, is based on insufficient evidence. We must conclude, therefore, that epinephrin does not interfere with the process of sugar oxidation by the tissues.

CONCLUSIONS

To conclude, it seems that we are justified, from the work that has been done, in accepting the following view of the relation of the suprarenal system to carbohydrate metabolism:

1. Nervous stimuli, especially of the sympathetic, represented by piqure or splanchnic stimulation, are followed by an increased secretion of epinephrin, and this hyperadrenalinemia like that following epinephrin injections, causes hyperglycemia and glycosuria in part by inhibiting glycogenesis, and in part by furthering glycogenolysis.

2. The hyperglycogenolysis thus produced is dependent partly on a direct stimulation of the liver cells and partly on its action in rendering the receptive material between the sympathetic nerve endings and the liver cells more sensitive to nervous stimulation.

3. Epinephrin does not produce its effects by inhibiting glycolysis, and the disturbances in sugar metabolism following its administration have little or nothing to do with the loss of glycolytic power, which is probably a part of the altered metabolism in diabetes mellitus.

4. A specific physiologic relation between the islands of Langerhans and the adrenal medulla is unproved.

5. Adrenalectomized dogs show a diminution of the power to form glycogen from glucose.

6. Following extirpation of the adrenals in depancreatized dogs there is a rapid disappearance of hyperglycemia.

7. Sugar administered to such animals is neither oxidized nor stored as glycogen, but appears quantitatively in the urine.