Effect of Cortisone on Carbohydrate Metabolism Measured by the "Glucose Assimilation Coefficient"

P. A. Bastenie, M.D., V. Conard, M.D., J. R. M. Franckson, M.D.,

Brussels, Belgium

It is generally held that, except for changes in insulin activity, the usual clinical doses of cortisone have but slight effect on the carbohydrate metabolism of normal subjects.[1-4] Among the hundreds of patients treated with cortisone, only a very small number have shown diabetes, usually of transient nature.[5]

By mathematical analysis of intravenous glucose tolerance tests, it is possible to calculate a "glucose assimilation coefficient"[6] and to detect thereby changes in carbohydrate metabolism, which are brought about by cortisone and which escaped other methods of investigation. (In studying cases of mild diabetes in which intravenous glucose tolerance tests were made together with fractionated glycosuria estimations, it has been shown that when the fasting blood sugar level lies between 100 and 150 mg. per 100 cc., by the Shaffer-Hartman method, the greatest part of the glycosuria occurs during the first 15 minutes of the test. Since our first sample was taken at 15 minutes, the curve measures only glucose assimilation. In diabetes, with the fasting blood sugar reaching the renal threshold, the curve is influenced by tissue assimilation and also by renal leakage.)

METHOD

When glucose is injected rapidly into the veins, the blood sugar rises abruptly and reaches a peak within the first 5 minutes. Afterwards it falls, at first sharply, then at a more gradual rate. In normal subjects the glycemia usually reaches its previous value between 45 and 120 minutes. Sometimes, there is a hypoglycemic phase, followed by some slight oscillations.

The first part of the intravenous glucose tolerance test (Figure 1) corresponds to the diffusion of the injected glucose into the blood and the extracellular fluids. The terminal part reflects the action of secondary adaptation mechanisms.

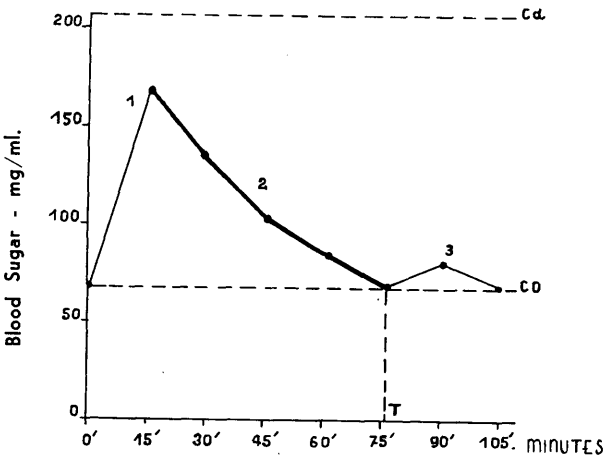

FIGURE 1. Intravenous tolerance test. Mean values.

As to the middle part of the curve, it has been shown by previous work from this laboratory using measurements of the extracellular fluids, that it corresponds to the removal of blood glucose by the tissues and that this process follows an exponential law.

When the logarithms of the blood glucose values, obtained between 15 and 60 minutes, are plotted on semilogarithmic paper they fall exactly on a straight line (Figure 2).

If this line is extended to the time 0, it yields the same value of theoretical blood glucose, as can be calculated by adding to the fasting blood glucose the quantity of injected sugar, divided by the volume of extracellular fluids. This means that the diffusion of

From the Medical Department of Brugmann Hospital, University of Brussels, Belgium.

Presented at the joint meeting of the American Diabetes Association and The Endocrine Society in New York on May 30, 1953.

Address communications to Professor Bastenie, 4 Place A. Van Gehuchten, Brussels, Belgium.

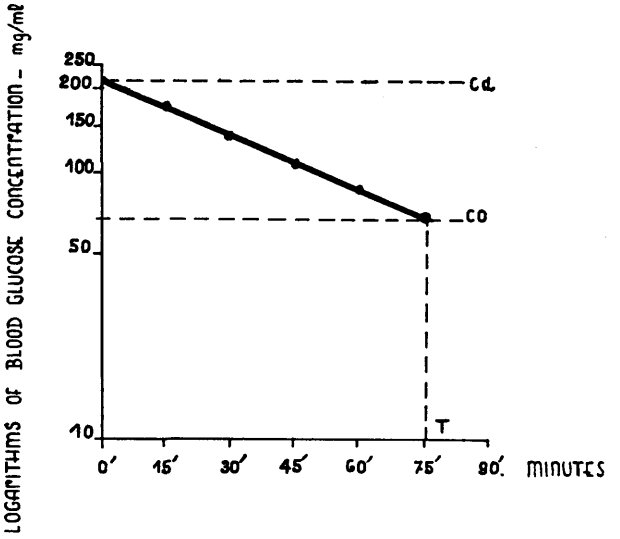

FIGURE 2. Intravenous tolerance test. Semilogarithmic graph of mean values.

the injected glucose is almost instantaneous and thus that after 15 minutes, the disappearance rate of the glucose from the blood is only dependent on its uptake by the tissues.

From the mathematical formula of this exponential curve, it is easy to calculate a factor K, which indicates the slope of the semilogarithmic line, and which thus measures the speed of the glucose disappearance from the blood.

$$K = \frac{\log_{10}C - \log_{10}C'}{t' - t} \cdot 2.3$$

In a first series of 20 hospitalized patients suffering from miscellaneous diseases but without detectable carbohydrate metabolism disorders, the mean value for K, calculated per cent, has been : 1.55 ± 0.31.

Calculation of the factor K on data published by Lozner and coworkers[7] and concerning young and healthy subjects has yielded the value: 1.96. In a group of mild diabetics the value obtained was 0.5.

RESULTS

The changes of the glucose assimilation have been studied in 18 patients submitted to cortisone treatment for rheumatoid arthritis, asthma or periarteritis. These patients were in satisfactory nutritional condition. During the investigation they were maintained on a fairly constant diet.

The values of intravenous glucose tolerance tests are given in Table 1. Statistical analysis (Table 2) using the Student-Fisher test and the pairing system indicates that except for the difference between previous values and values observed after 3 gm., the observed changes (Figure 3) are significant.

COMMENTS

Besides some reduction in insulin activity, the usual tests fail to detect any significant change in carbohydrate metabolism of normal subjects submitted to therapeutic doses of cortisone.

The calculation of the "glucose assimilation coefficient" provides a means for detecting and measuring slight changes in the glucose tolerance. The physiological and mathematical basis of this test has been analyzed in previous work.[6] Application of this method to the study of patients submitted to cortisone treatment indicates appreciable alterations in their glucose tolerance, which are dependent on the duration of the treatment.

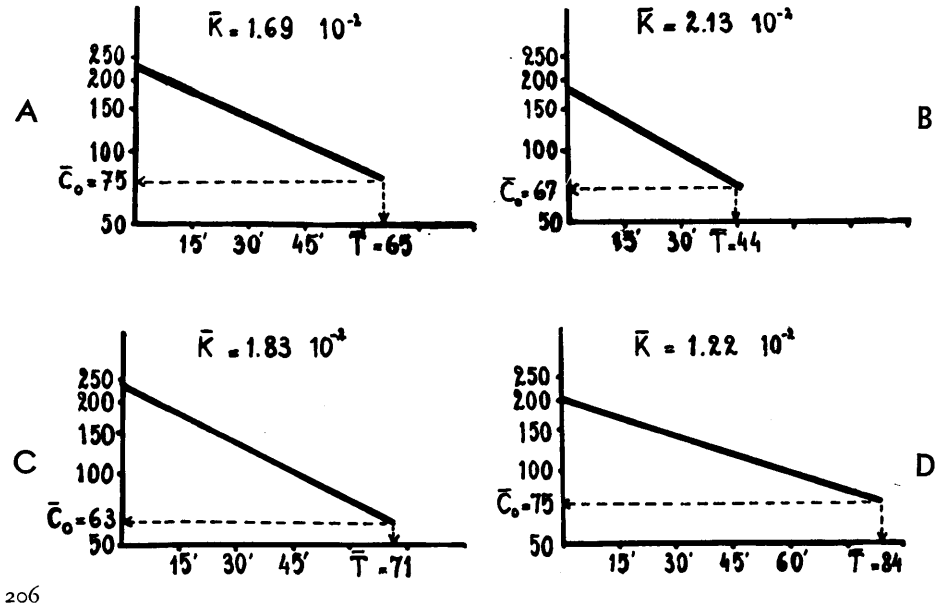

FIGURE 3. Effects of cortisone treatment on glucose tolerance (semilogarithmic lines). A. Before cortisone treatment. B. After 7 days of treatment. C. After 21 days of treatment. D. After protracted treatment.

TABLE 1

Values of blood glucose during intravenous glucose tolerance test (mg. per 100 ml.) (1) before, (2) after 1 gm., (3) after 3 gm. and (4) after 10 or more gm. of cortisone administration

Cases	1. Before Cortisone						2. After 1 gm. Cortisone						3. After 3 gm. Cortisone						4. After 10 gm. Cortisone					
	0′	15′	30′	45′	60′	75′	0′	15′	30′	45′	60′	75′	0′	15′	30′	45′	60′	75′	0′	15′	30′	45′	60′	75′
	mg. per 100 ml.						mg. per 100 ml.						mg. per 100 ml.						mg. per 100 ml.					
1	60	120	97	81	65	55	56	133	114	98	—	68	68	124	103	82	63	(60)	56	140	97	68	(63)	(60)
2	62	133	115	96	92	75							70	112	87	85	64	(71)	61	146	101	83	(80)	(69)
3	51	165	132	106	89	—	81	169	148	121	108	83	79	185	136	112	92	75						
4	50	148	—	84	—	54	66	—	149	135	118	96	73	174	132	114	93	86						
5	55	154	119	96	72	60													64	100	72	(62)	(66)	(62)
6	46	121	92	77	—	51													60	111	90	66	(81)	(66)
7	87	204	170	152	135	113	75	187	162	135	110	(124)	89	—	164	144	113	104						
8	93	211	154	131	109	—	85	214	171	152	126	108	92	190	163	133	118	111						
9	68	160	127	102	(95)	(77)	60	128	100	86	66	(68)	62	146	116	—	75	63	68	219	179	143	113	—
10	60	149	113	82	(80)	(72)	75	132	111	90	—	81	61	—	106	—	—	—	113	190	124	96	(94)	(81)
11	46	130	86	58	(51)	—	75	160	—	102	83	68	70	186	150	115	95	81	63	190	132	94	64	(70)
12	60	158	86	64	—	—							81	209	142	100	(88)	(70)						
13	78	224	160	130	(120)	—	90	161	145	128	110	101												
14	67	174	118	102	72	60													66	169	130	80	(77)	(60)
15	59	157	124	102	89	—	93	152	135	130	113	—												
16	50	140	84	65	—	—	69	171	—	90	—	58												
17	97	203	160	—	95	—	58						72	—	121	99	72	—						
18	50	110	67	41	(39)	(43)	73	167	118	101	72	(83)	68	148	94	(85)	(69)	(65)	62	169	116	—	53	(59)

K factors calculated from above data. Mean±SE_m (Standard error of the mean)

1.84±0.16	1.22±0.11	1.69±0.17	2.13±0.11

TABLE 2

Study of the significance between mean differences by the use of the Student-Fisher "t" test and pairing

$$t = \frac{|\bar{x}|}{\frac{\text{S.D.}}{\sqrt{N}}}$$

$\bar{x}$ = mean value of individual differences between glucose assimilation coefficients
S.D. = standard deviation of the difference
N = number of individuals treated in each group
P = value of probability

Treatment	N	$\bar{x}$	S.D.	t	P
Before cortisone—after 1 gm.	12	1.84 — 1.22 = 0.62	0.44	4.88	0.01>P
Before cortisone—after 3 gm.	11	1.83 — 1.69 = 0.15	0.58	0.83	P>0.1
Before cortisone—after 10 gm.	9	1.83 — 2.13 = 0.30	0.54	1.87	0.1>P>0.05
After 1 gm.—after 3 gm.	8	1.29 — 1.54 = 0.28	0.35	2.25	0.1>P>0.05
After 1 gm.—after 10 gm.	5	1.46 — 2.14 = 0.68	0.35	4.43	0.02>P>0.01

After one week, the glucose assimilation is markedly inhibited. At the third week of treatment, however, there is a return to the normal value and after several weeks the glucose uptake is even better than before treatment. These changes can be considered differently according to the theory which is admitted concerning the action of cortisone on carbohydrate metabolism: either the theory of inhibition of glucose utilization or that of neoglucogenesis. Recent work of Stetten and coworkers[8] seems to indicate that cortisone acts by both mechanisms.

In the normal subject, the test used in this work certainly indicates the rate of glucose assimilation. Even if according to Levine,[9] cortisone administration induces marked gluconeogenesis, the disappearance of the extra glucose from the blood cannot be accounted for except by admitting that the glucose has finally passed from the extracellular fluids into the cells.

Thus, admittedly the changes in the "glucose assimilation coefficient" do not give information on the intimate mechanism of this underlying process. Nevertheless they measure alterations in the glucose uptake

by the tissues.

It may be of interest to note that similar changes have been observed in the insulin activity tested in 10 of the patients.[10] At the time of reduced glucose assimilation the insulin activity is also diminished; during protracted treatment increased glucose uptake is found together with enhanced insulin activity.

These observations suggest that usual therapeutic doses of cortisone induce definite but transitory alterations in the carbohydrate metabolism, together with changes in insulin activity. This would be in agreement with recent work (Drury and others,[12] Bouckaert and deDuve,[11] Levine,[9]) concerning the action of insulin as chiefly concerned with the assimilation of glucose by the tissues.

The observations showing improvement of carbohydrate tolerance and of insulin activity under protracted treatment might be explained either by reduction of the endogenous steroid secretion or by increased insulin activity. Whatever the explanation be, these observations further stress the importance of the physiological reactions of the subject who is treated with a diabetogenic steroid.

SUMMARY

In 18 patients with miscellaneous diseases, submitted to cortisone treatment, the glucose tolerance has been measured by the "glucose assimilation coefficient." Definite changes have been observed, showing reduction of tolerance in the initial stages of cortisone administration, improvement under protracted treatment.

ADDENDUM

Since the presentation of this paper (May 30, 1953), 15 additional cases have been studied. It has been found that with the use of smaller doses of cortisone, the inhibiting effect of the drug on glucose assimilation is of very short duration. After 10 days of therapy the glucose assimilation coefficient may begin to increase.

REFERENCES

1 Mason, H. L., Power, M. H., Rynearson, E. H., Ciaramelli, L. C., Li, C. H., and Evans, H. M.: Results of administration of anterior pituitary adrenocorticotropic hormone to a normal human subject. J. Clin. Endocrinol. *8*:1-14, January 1948.

2 Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of cortisone and pituitary ACTH in rheumatoid arthritis; rheumatic fever and other conditions: a study in clinical physiology. Arch. Int. Med. *85*:5454-666, April 1950.

3 Forsham, P. H., Thorn, G. W., Frawley, T. F., and Wilson, D. L.: Studies on carbohydrate metabolism in adrenal cortical hypersecretion. Abstract. 32' meeting. Assoc. Study Intern. Secret. J. Clin. Endocrinol. *10*:825-826, 1950.

4 Mach, R. S. Indications, contre-indications et dangers des traitements a l'ACTH et la cortisone. J. Suisse de Méd. (Schweiz. med. Wchnschr.) *81*:155, 1951.

5 Bookman, J. J., Drachman, S. R., Schafer, L. I., Aldersberg, D.: Steroid diabetes occurring during cortisone and adrenocorticotropin (ACTH) therapy (Abstract). J. Clin. Invest. *31*:619, 1952.

6 Conard, V., Franckson, J. R. M., Bastenie, P. A., Kestens, J., Kovacs, L.: Etude critique du triangle d'hyperglycémie intraveineux chez l'homme hormal et détermination d'un "coefficient d'assimilation glucidique." Arch. Internat. Pharmacodyn. *93*, 277-292, 1953.

7 Lozner, E. L., Winkler, A. W., Taylor, P.H.L., Peters, J. P.: The intravenous glucose tolerance test. J. Clin. Invest. *20*, 507, 1941.

8 Welt, I. D., Stetten, D., Jr., Ingle, D. J., Morley, E.H.: Effect of cortisone upon rates of glucose production and oxidation in the rat. J. Biol. Chem. *197*, 57-66, July 1952.

9 a) Levine, R. Personal communication, May 1953.

b) Cohn, Cl., Katz, B., Huddlestun, B., Kolinsky, M. and Levine, R.: Utilization of carbohydrate by extrahepatic tissues of the adrenalectomized dog. Am. J. Physiol. *170*, 87-93, July 1952.

10 Bastenie, P. A., Verbiest, M.: Hypoglycémie et sensibilité a l'insuline au cours des traitements par la cortisone. Semaine des Hôpitaux Paris, 1953.

11 Boeckaert, J. P., deDuve, Ch.: The action of insulin. Physiol. Rev. *27*, 39. June 1947.

12 Drury, D. R., Sherrill, J. W., Wick, A. N.: On the mechanism of action of insulin on glucose metabolism. 1st International Congress of International Diabetes Federation. Leyden, July 1952.

DISCUSSION

BENJAMIN JABLONS, M.D., (*New York, N. Y.*): We have been studying sugar tolerance tests in cases of rheumatoid arthritis and other conditions treated with ACTH. We have found, in common with others, three types of response.

In one group apparently normal physiologically, ACTH does not modify the sugar tolerance test. In another group, ACTH produces a definite change from a normal sugar tolerance curve to a diabetic sugar tolerance curve. In a third group, including cases in which there may be latent diabetes, or fully developed diabetes, the diabetic state becomes considerably aggravated after ACTH administration and the sugar tolerance curve becomes considerably worse.

This is apparently in keeping with the conclusions of Dr. Bastenie, that the physiologic status of the individual

determines, to a large extent, how the adrenal steroids act in regard to diabetogenesis.

E. H. RYNEARSON, M.D., (*Rochester, Minn.*): I am sure I am speaking on behalf of the American Diabetes Association in thanking Dr. Bastenie for this splendid talk. I am equally sure that most of us in this room are aware that in too many instances cortisone is being used even before aspirin! It is being used rather indiscriminately in an effort to bring relief to patients with indeterminate diagnoses. We are almost certain to see more disturbances of carbohydrate metabolism in patients so treated and the work of Dr. Bastenie and his associates should prove helpful in our understanding of this enlarging problem.

When Dr. Bastenie closes his discussion, I would be interested to ask whether he has made observations of the glucose assimilation coefficient in patients who have Addison's disease and whether he has found any marked changes in cases of Cushing's syndrome.

P. A. BASTENIE, M.D., (*Brussels*): We made these observations after several attempts to find a method which would enable us to know exactly if therapeutic doses of cortisone affected the carbohydrate metabolism. We found that the usual oral glucose test, the intravenous tolerance test and even repeated tests do not give good results. We felt that perhaps this test might be a more accurate tool.

We have had the opportunity to study this factor in one case of Addison's disease and found it highly increased, but we had no experience with Cushing's disease. When desoxycorticosterone is given, the fluids are increased: the administered glucose is diffused in a wider "glucose-space" but the glucose assimilation remains unchanged.

Fortified Foods

In the 1930's certain nutritional deficiencies were found to be prevalent in the United States. Alert food processors began adding synthetic vitamins to their products, but with little or no scientific guidance. In 1940 the Food and Nutrition Board of the National Research Council was organized. This board and the older Council on Foods and Nutrition of the American Medical Association have issued statements regarding the addition of specific nutrients to foods from time to time. In November 1953, they reconsidered past statements and issued a joint statement that, although in no way a directive, should serve as a valuable guide.

The report endorses in principle the addition of specific nutrients to certain staple foods provided (1) there is a clear indication that probable advantage will result from such an addition, (2) the food item concerned is an effective vehicle of distribution for the additive, and (3) such addition would not interfere with the achievement of a diet good in other respects. The report further stresses the desirability of meeting the nutritional needs of the people by the use of natural foods insofar as possible. It recommends that foods chosen as vehicles for the distribution of additives should be, when practicable, those that have lost nutrients through refining or other processing. It approves the addition of greater than natural levels of nutrients to foods that are suitable vehicles of distribution when other methods for affecting the desired distribution appear to be less practicable. It recommends considering the restoration of essential nutrients should future technological and economic developments lead to extensive reduction in the consumption of some staple articles of diets. The report approves the enrichment of flour, bread, degerminated corn meal, and corn grits with thiamine, riboflavin, and niacin; the nutritive improvement of whole grain corn meal and white rice; the retention or restoration of thiamine, niacin, and iron in processed food cereals; and the addition of vitamin D to milk, vitamin A to butter and margarine, and iodine to table salt.

It is necessary to set definite limits to the addition of nutrients to food products in order to protect the public from combinations that are irrational or even harmful. Most states have based their laws on the recommendations of the Food and Nutrition Board and the Council on Food and Nutrition. There is good evidence that the policies recommended have benefited the public and have encouraged sound nutritional practices.

From the editorial section
of *The Journal of the*
American Medical Association,
May 8, 1954.