dium chloride and glucose, 0.4% potassium (in the form of potassium acetate), the formation of both muscle and liver glycogen was completely suppressed, while the blood sugar level quickly rose over 100%. The administration of this amount of potassium (40 mg. per 100 gm. body weight) produced no visible toxic effects, and the rats when sacrificed were in as good condition as the controls. When half the quantity of potassium was injected (*i. e.,* 20 mg. per 100 gm.), the blood sugar and tissue glycogen values observed did not differ significantly from the control levels.

Other experiments performed on animals under somewhat different conditions (fully-fed; urea-injected, etc.) confirmed the conclusion that the administration of sub-toxic doses of potassium leads to a great increase in blood sugar and a diminution of the tissue glycogen levels; in other words, to glycogenolysis and hyperglycemia. It is pertinent in this connection to recall that MacQuarrie, *et al.,*[2] observed the administration of potassium salts to decrease the glucose tolerance of diabetic children. To contend, therefore, that the increased potassium level observed in adrenal insufficiency is the cause of the lowered blood-sugar levels characteristic of that condition is contrary to the above experimental facts. It is very significant that, in spite of the heightened serum potassium concentration, the blood sugar levels after adrenalectomy are found to be subnormal.

9529

Effect of Prolonged Insulin Therapy on Glucose Tolerance in Schizophrenic Patients.

J. M. LOONEY AND D. E. CAMERON.

From the Memorial Foundation for Neuro-Endocrine Research and the Research Service of the Worcester State Hospital.

The treatment of schizophrenic patients by the insulin hypoglycemia method of Sakel[1] has been carried on in this institution for the past year by Cameron and Hoskins.[2] In connection with this treatment a systematic investigation of the changes produced in

2 MacQuarrie, I., Thompson, W. H., and Anderson, J. A., *J. Nutrition,* 1936, **11**, 77.

1 Sakel, M., *Neue Behandlungsmethode der Schizophrenie,* Moritz Perles, Wien und Leipzig, 1935.

2 Cameron, D. E., and Hoskins, R. G., *J. A. M. A.,* in press.

various physiologic functions has been undertaken to determine, if possible, the mechanism by which amelioration of the schizophrenic process is brought about. Among these the glucose tolerance was determined before treatment was initiated and also after insulin had been given for a considerable period.

In all cases the blood sugar was estimated by the method of Folin and Wu after giving 100 gm. of glucose by mouth while the patient was in a fasting state. Blood samples were taken before the sugar was given and at one half hour, one hour, and 2 hours after its ingestion.

The results of the analyses are given in Table I for the 9 patients studied. The treatment was carried out approximately 6 days a week for the period indicated in the table before the second tolerance test was made.

TABLE I.
Blood Sugar Values after 100 gm. of Glucose, mg./100 cc.

Case	Date	Fasting	½ hr.	1 hr.	2 hr.	Treatment From	Treatment To
M.L.	1/22/37	110	146	152	123	1/26/37	5/19/37
♀	5/20/37	114	234	214	172		
E.B.	11/5/36	87	145	128	120	11/9/36	5/19/37
♂	5/20/37	96	161	140	135		
T.S.	9/22/36	70	106	136	91	11/2/36	12/23/36
♂	4/8/37	112	168	176	120	2/15/37	3/22/37
R.W.							
♂	2/4/37	108	204	260	158	6/29/36	2/3/37
M.B.	3/25/37	75	111	70	76	3/29/37	5/19/37
♀	5/20/37	93	102	238	178		
A.S.	11/25/36	89	109	82	86	2/1/37	2/3/37
♂	2/4/37	103	206	154	not collected		
S.Mc.	12/3/36	93	118	72	60	12/8/36	2/1/37
♂	2/2/37	89	150	145	102		
A.C.	1/14/37	90	150	116	77	1/18/37	4/13/37
♂	4/22/37	96	180	120	69		
J.C.	12/3/36	92	120	93	84	12/7/36	2/1/37
♂	2/2/37	113	147	145	123		

In all the cases but one there was a definite decrease in the glucose tolerance of the patients following the repeated injection of insulin. In this case (A.C.) the maximum value for the blood sugar obtained after the ingestion of the same amount of sugar was 30 mg. % higher in the second test than in the first, but the

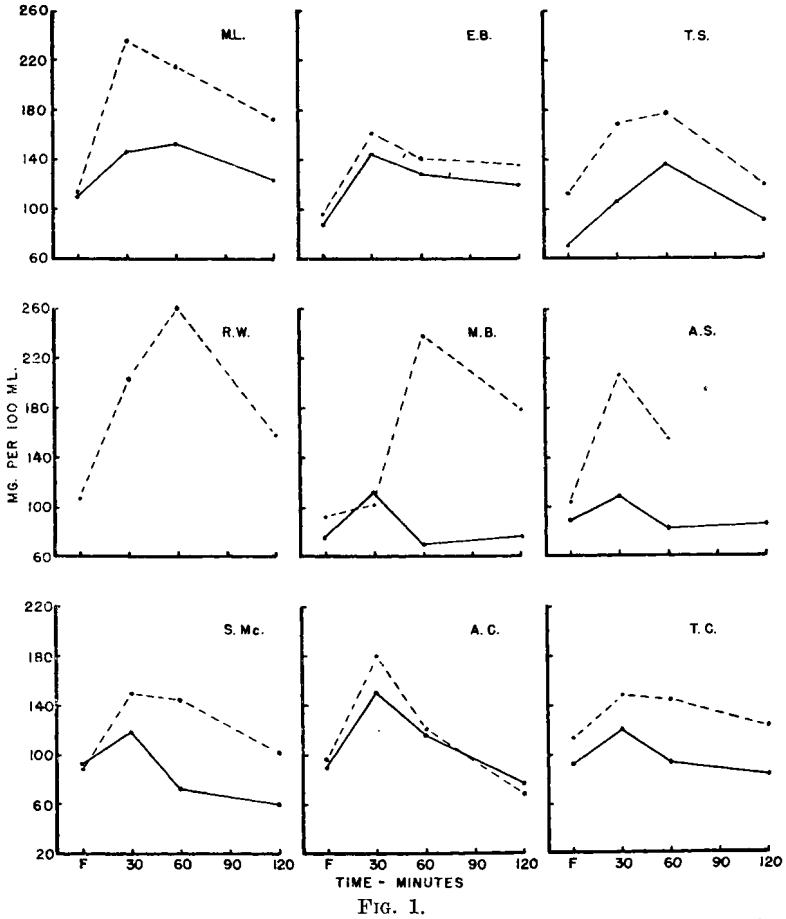

FIG. 1.

Blood sugar curves after the ingestion of 100 gm. of glucose. Solid line—Curve obtained before insulin therapy. Dotted line—Curve obtained after therapy.

height was not sustained as in the other cases. These changes are shown in Fig. 1. The curve for the patient (R.W.), who had been under treatment for the longest period showed the greatest elevation in blood sugar. Unfortunately no preliminary test was made in this case before treatment was instituted. However, no evidence that he was diabetic was found in routine examinations.

It is also to be noted that the initial fasting levels for the blood sugar were significantly higher in the majority of the cases at the second test over the values obtained in the first test.

The explanation for this change in the physiological response to sugar has not been determined. Two possibilities suggest themselves, first, that a stimulation of the pituitary has taken place so

that the insulin antagonistic factor is produced in greater amounts, and second, that a sensitization and stimulation of the adrenal-sympathetic system has occurred.

In view of the second possibility it is interesting to note that previous investigations from our laboratories have indicated that adrenal insufficiency may be a factor in the schizophrenic reaction, hence a change in the adrenal-sympathetic mechanism might correlate with the improved clinical status of the patients under insulin treatment. These patients have been noted by Hoskins and Jellinek[3] to be characterized by a sluggish sympathetic reactivity. The correlation between systolic and diastolic blood pressures is significantly higher in the schizophrenic than in the normal subject. This would indicate that in the schizophrenic patient the cardiovascular system operates more as a mechanical hydrostatic system and is less subject to homeostatic influences than that of the normal subjects. After injecting adrenalin there was a disappearance of the correlation, the patients acting more like the normal group. Furthermore, most schizophrenic patients react with an increase in blood pressure to the oral administration of glycerine extract of the adrenal cortex, whereas relatively few normal subjects are affected by this medication.[4]

The theory is offered that repeated injections of large amounts of insulin increase the antagonistic activity of the adrenal glands. When glucose is administered by mouth, the increased concentration in the blood provokes the liberation of insulin and this in turn elicits the adrenal response with the liberation of adrenalin. The adrenalin prevents the formation of glycogen in the liver and the blood sugar remains elevated because of a slowing down of its removal. This is in accord with the proposal of Soskin, *et al.*,[5] that the liver is the main homeostatic agent preventing the increase of blood sugar after the ingestion of glucose.

Summary. In 7 schizophrenic patients undergoing insulin therapy there was a significant decrease in sugar tolerance, the blood sugar levels after glucose administration attaining higher values and remaining elevated for longer periods than before treatment. In a ninth patient in whom a preliminary determination was lacking, the

[3] Hoskins, R. G., and Jellinek, E. M., *Proc. Assn. Research in Nervous and Mental Diseases*, 1933, **14**, 211.

[4] Hoskins, R. G., and Freeman, H., *Endocrinology*, 1933, **17**, 29; Freeman, H., Linder, F. E., and Hoskins, R. G., *Endocrinology*, 1933, **17**, 677; Freeman, H., and Hoskins, R. G., *Endocrinology*, 1934, **18**, 516.

[5] Soskin, S., Mirsky, I. A., Zimmerman, L. M., and Heller, R. C., *Am. J. Physiol.*, 1936, **114**, 648.

tolerance was notably low, also. This change may have been due to the stimulation and sensitization of the adrenal mechanism.

9530 P

Hyperplasia of Uterine Muscle, as Studied by the Colchicine Method.

EDGAR ALLEN, GEORGE M. SMITH AND SAMUEL R. M. REYNOLDS.*

From the Department of Anatomy, Yale University School of Medicine, and the Department of Physiology, Long Island College of Medicine.

Distention of the uterus is undoubtedly a factor in stimulating its growth during pregnancy.[1, 2, 3] The scarcity of mitotic figures in muscle during the enlargement of the pregnant uterus has led to the usual textbook statement that increase in size is due to hypertrophy rather than to hyperplasia of the muscle fibers. It is usually difficult to find dividing cells in uterine muscle even when the endometrium is undergoing marked hyperplasia in response to stimulation by ovarian follicular hormone.

The use of the drug, colchicine, which arrests mitoses in metaphase and thus accentuates hyperplasia[4, 5, 6] has made the search for cell division much more effective.

In a first series of short experiments (48 hours) with theelin and colchicine in adult ovariectomized mice, mitotic figures were abundant in the surface epithelium and glands of the uterus, but very scarce in the uterine muscle.[7, 8]

In later experiments, where injections of theelin, prephysin and pregnant mares' serum were made for longer periods in conjunction with colchicine (0.1 to 0.3 mg.) into puberal or young adult mice

* Fellow of the John Simon Guggenheim Memorial Foundation.

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