age found by the analyses of tissues from accident cases (Table I). In order to determine the effect of disease on the tissues the young pathological and accident cases were compared. Except for calcium, which was lower in the pathological tissues, there was a tendency toward changes in disease similar to those found in senescence. The magnitude of the changes in disease was less than in senescence, except in the case of magnesium. The present data do not warrant further comparisons. Extensive studies of tissue changes in selected diseases should be instructive. However, it is necessary to determine whether the differences found in tissues from patients dying of disease were produced progressivly with the advancement of the pathological condition or whether they arose in the terminal state preceding death.

These preliminary results are presented with no attempt to interpret their significance. Detailed analyses will be published after more data have been obtained. Only minor modifications of the average values for accident cases are to be expected as more tissues are analyzed. On the other hand, we do not claim that the analyses of pathological tissues are representative, but we feel that further work in that field would be profitable.

SUMMARY

Analyses of tissues from people over seventy years old who died from accidents were compared with analyses of tissues from thirty to forty-year-old people who also died from accidents. The old tissues contained more water, chloride, total base, sodium and calcium; and they contained less potassium, magnesium, phosphorus, nitrogen and ash than the younger tissue.

Tissues from pathological cases of the same two age groups showed the same changes after seventy years. Only part of these changes were found in tissues sixty-five to seventy years old.

Tissues from young pathological cases when compared with accident cases of the same age were found to have undergone changes similar to those found in senescence, but to a lesser degree. Calcium formed an exception.

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EFFECTS OF CARBOHYDRATE PLETHORA IN EXPERIMENTAL DIABETES

IN a recent study of carbohydrate metabolism[1] it was concluded that the depancreatized dog in the early stages of fasting was unable to oxidize administered glucose, since there was no fulfilment of the necessary criteria, *i.e.*, an elevation in respiratory quotient, a corresponding diminution in the amount of extra glucose excreted, a protein-sparing action and a ketolytic effect. Since the completion of that work Mirsky and co-workers reported that ketolytic[2] and nitrogen-sparing[3] effects were produced by injection of large amounts of glucose into depancreatized animals. The quantities administered were such as to lead one to expect glycogen formation, even in the absence of insulin,[4] although no data were reported on this point. Because of the suggestion that the deposition of glycogen in the depancreatized animal may result in oxidation of this material, we are reporting experiments on nephrectomized-depancreatized dogs conducted without anesthesia in order that respiratory metabolism, as well as blood constituents, could be studied.

Of nine operated animals, only three satisfactory preparations were obtained. In these, one kidney was removed and, ten days later, a loose tie was placed around the blood vessels of the remaining kidney at the time of pancreatectomy. Food and insulin[5] were administered to the animals until four days before the following experiment was conducted. A blood sample was drawn, functional nephrectomy was performed by tightening the kidney tie, and a basal metabolism period obtained for three to four hours. At the times noted in Table I blood was drawn and glucose injected

TABLE I

EFFECTS OF GLUCOSE INJECTED INTO NEPHRECTOMIZED-DEPANCREATIZED DOG

Time after nephrectomy	Glucose injected	R.Q.	Blood constituents				Air Acetone
			Sugar	Acetone bodies	Non-protein N	Lactic acid	
hr.	gm.		mg. per cent.				mg./hr.
0	0		345	43	38	22	
4	0	0.73	430	49	55	25	51
11	25	0.72	1250	41	71	32	36
16.5	25	0.74	1727	33	83	38	23
21.5	25	0.74	2000	19	91	42	18
26	0	0.74	2022	10	94	45	13

intravenously. In the intervening time the animal was replaced in the chamber for determinations of the respiratory metabolism. Table I summarizes the data obtained on a single, representative animal. The absence of any significant change in the respiratory

[1] S. B. Barker, W. H. Chambers and M. Dann, *Jour. Biol. Chem.*, 118: 177, 1937.

[2] I. A. Mirsky, J. D. Heiman and R. H. Broh-Kahn, *Amer. Jour. Physiol.*, 118: 290, 1937.

[3] I. A. Mirsky, J. D. Heiman and S. Swadesh, *Amer. Jour. Physiol.*, 119: 376, 1937.

[4] S. G. Major and F. C. Mann, *Amer. Jour. Physiol.*, 102: 409, 1932.

[5] We wish to express our appreciation of the generous amounts of insulin supplied by the Eli Lilly Company.

quotient shows no oxidation of the administered carbohydrate, despite pronounced ketone- and nitrogen-sparing effects.

Carbohydrate values of the tissues obtained after the last respiration periods on this dog are shown in Table II, which includes, as controls, average figures previously reported from this laboratory.[6] It is evident that the administration of glucose caused deposition of appreciable amounts of glycogen, both in muscle and in liver. From the carbohydrate values obtained on the tissues, calculations, although only approximate, indicate that all the injected sugar can be accounted for.

TABLE II

TISSUE CARBOHYDRATES OF DEPANCREATIZED DOGS

Animal	Tissue	Glycogen mg. per cent.	Total fermentable carbohydrate plus lactic acid mg. per cent.
Nephrectomized-depancreatized, after 75 gm. glucose intravenously	Muscle	416	938
	Liver	845	2,982
Fasting depancreatized[6]	Muscle	71	266
	Liver	79	454

Some explanation other than carbohydrate oxidation must, therefore, be advanced for the nitrogen-sparing and ketolytic effects observed. It should first be pointed out that decreased protein catabolism is judged in this type of experiment solely on the basis of changes in blood non-protein nitrogen; any unmeasured retention of urea in the liver or in the muscles would give a false picture. Secondly, since protein is ketogenic in pancreatic diabetes, any lowering of protein breakdown might account for some of the ketone sparing. In any case, these changes may be attributed fully as well to the high glucose concentrations produced as to glycogen deposited. These experiments indicate that neither formation of glycogen nor establishment of high tissue carbohydrate levels facilitates the oxidation of sugar by the depancreatized dog.

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BRAIN METABOLISM DURING THE HYPOGLYCEMIC TREATMENT OF SCHIZOPHRENIA[1]

THE most interesting and perhaps the most important advance in the treatment of mental disease in many years is Sakel's[2] new treatment of schizophrenia. The amelioration which occurs as a result of his insulin treatment must be ascribed to functional changes in the brain. It is therefore of fundamental importance to examine the physiological effects induced in the brain after the intramuscular injection of large doses of insulin.

The present communication presents data concerning these changes in patients with schizophrenia receiving the insulin treatment. Though the investigation is not yet completed, the observations made thus far are adequate to indicate a possible mechanism for the alleviation. Cerebral metabolism was studied by determining the glucose and oxygen contents of the blood traversing the brain, blood samples being collected practically simultaneously from the internal jugular vein and the femoral artery. It was thus demonstrated that the oxygen utilization of the brain and therefore its metabolic rate are decreased during severe hypoglycemia. The average utilization of oxygen before the injection of insulin was 7.09 vol. per cent. (eighteen observations). During hypoglycemic coma the average cerebral uptake was 2.46 vol. per cent. (eleven observations), a fall of approximately 65 per cent. The average glucose uptake simultaneously decreased from 13.0 to 2.2 mg per cent. Since the brain oxidizes only carbohydrate,[3] insulin, in reducing the blood sugar, deprives the brain of its foodstuff. A diminished oxygen utilization is therefore secondary to lack of substrate.

This partial deprivation of energy of the brain finally leads to hypoglycemic coma; in most instances a necessary phase in the alleviation of schizophrenia. In the course of the production of this coma abnormal reflexes such as the Babinski appear finally to be succeeded by complete areflexia. The present studies also reveal that the Babinski sign appears at the time when a definite decrease in the oxygen utilization is noted; a more prolonged period of diminished energy supply leads to complete areflexia.

It is true that the metabolism of the entire brain, and perhaps the cord as well, is depressed as a result of hypoglycemia. However, the oxidations of different parts of the brain proceed at varying rates and since the energy requirements of the cerebral hemispheres are greater than those of the brain stem, medulla or cord, a diminished supply of energy would first be manifested in the functions of the hemispheres with

[6] W. H. Chambers, M. A. Kennard, H. Pollack and M. Dann, *Jour. Biol. Chem.*, 97: 525, 1932.

[1] From the Department of Physiology and Pharmacology, Albany Medical College, Union University, and Bellevue Psychiatric Hospital, Department of Psychiatry, New York University Medical College. This investigation was made possible by a grant from the Child Neurology Research.

[2] K. T. Dussik and M. Sakel, *Zeit. f. d. ges. Neur. Psych.*, 155: 351, 1936.

[3] H. E. Himwich and L. H. Nahum, *Amer. Jour. Physiol.*, 101: 446, 1932.