in excess of its production. These differences suggest that the immediate hypoglycemia induced by administration of insulin, on the one hand, and of Orinase on the other, occurs via different mechanisms.

These results do not support the concept that the sulfonylurea compounds produce acute hypoglycemia by stimulating rapid release of endogenous insulin.

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Group Discussion

FRANCIS D. W. LUKENS, M.D., (*Philadelphia*): One question about Dr. Anderson's report. I just wonder whether one can compare the results obtained at your time interval of a few minutes with those obtained when the blood sugar is lowered maximally by this drug in two to four hours. I just wonder whether you should have done the same experiment two to four hours after giving the drug?

GEORGE E. ANDERSON, M.D., (*Brooklyn*): We have done that in animals. In other words we have carried out investigations not only hours but days later. In the latter instance there *is* a depression. The methodology of these acute experiments will be thoroughly expounded in a coming issue of the *Journal of Clinical Nutrition.*

THOMAS H. MCGAVACK, M.D., (*New York City*): Regarding Dr. Achelis' paper, on what dosage level or levels were his patients carried for two and a half years without signs of toxicity?

J. D. ACHELIS, PROF. DR. MED., (*Mannheim-Waldhof, Germany*): One to two tablets or 0.5 — 1 gm.

LAURANCE W. KINSELL, M.D., (*Oakland, California*): In terms of peripheral effects and mechanisms, as we have reported previously, studies have been carried out in which patients have been maintained on constant diet containing essentially only fat. The objective was to produce major hyperketonemia and then to determine the possibility of modifying the hyperketonemia with particular reference to its progression. In studies that we have previously done, such a diet in any patient, diabetic or nondiabetic, without other measures being used, will proceed to marked ketoacidosis, and has to be interrupted because of this. In two such patients the administration of therapeutic amounts of the sulfonamide, either BZ-55 or on short-term experiments Orinase, has resulted in apparent major modification of this progression in that patients could be maintained indefinitely although with significant hyperketonemia but without ketoacidosis. This raises the question as to mechanism since we could know the total carbohydrates being metabolized from the urinary nitrogen on the one hand, and on the basis of the known glycerol moiety of the fat administered on the other. The question arose whether we might be having an increased oxidation of acetate peripherally as a result of BZ-55 administration. Two studies have been done using tracer doses of C^{14} carboxyl labeled acetate and determining its rate of appearance in expired CO_2 under controlled conditions. Our expectation was that there might be an increased amount of the C^{14} appearing in a stated period of time. The reverse has been found to be true. That is as far as we have gone.

HOWARD F. ROOT, M.D., (*Boston*): I would also like to ask Prof. Achelis a question, having recently had experience with one or two patients seriously ill with jaundice and other evidences of liver damage, particularly the type described by Dr. Duff some years ago. Now that the series has become so large, there will of necessity be patients who will die of other causes who have been receiving sulfonamides. Do you know whether any such patients have been studied with particular reference to the well-known pathologic findings in sulfonamide intoxication; that is, will there be an attempt to analyze, or is there anywhere any chance of getting some results of that sort? Two or three hundred thousand cases ought to offer a good many opportunities.

DR. ACHELIS: We have never seen jaundice in connection with our use of BZ-55. There have been patients on the drug with obstruction of the bile ducts. But in our reports there has been no jaundice resulting from the treatment.

DR. ROOT: I misunderstood you, Dr. Achelis. I assume you are saying that there have been some cases who, while receiving sulfonamides, have had jaundice which have been dismissed as jaundice not due to the

drug. Is that right?

DR. ACHELIS: Yes, that is right.

DR. ROOT: Well, that is one thing I did not get clear in my mind.

DR. ACHELIS: No jaundice as a result of the treatment.

DR. ROOT: On what basis are you sure of that? Is that on pathologic evidence?

DR. ACHELIS: It is on pathologic evidence, yes.

DR. ROOT: Do you mean that there are autopsied cases who had jaundice and in whom the findings were completely explained by the pre-existing liver disease?

DR. ACHELIS: Yes, that is correct, cancer or infection.

JAMES B. FIELD, M.D., (*Bethesda, Maryland*): Could I ask Dr. Anderson a question by way of clarification? Did you say that you would not expect a patient who had a normal response to glucagon to respond to Orinase?

DR. ANDERSON: You are quite right. In the group of patients that we have been studying the ones who show a normal response to glucagon to a small dose, 10 to 20 mg., do not respond to the Orinase in a clinical sense, just as people who show an excess or response to insulin or a perfectly normal response to insulin, do not respond to the sulfonylureas. We have used this to determine which patients we shall put on the sulfonylureas even though they are of the obese-adult type of diabetic.

DR. FIELD: If that's the case, I wonder if you have an explanation for the fact that nondiabetic normals presumably respond in a normal fashion both to glucagon and to insulin.

DR. ANDERSON: I must say that I don't have an explanation except that in the normal dog we used excessive doses of the drug and so you can't gauge on that. I am referring to the straight clinical cases that we tested. I am not too sure that that is true in the normal.

DR. FIELD: Isn't it fairly well documented that normal humans when given this drug will have a hypoglycemic response?

DR. ANDERSON: Not all. Occasionally there are subjects without a hypoglycemic response.

STEFAN S. FAJANS, M.D., (*Ann Arbor*): In relation to that, 3 gm. of BZ-55 in four divided doses at six-hour intervals given to normal individuals keeps the blood sugar consistently around 60 mg. per cent although the control blood sugars would be around 85 mg. per cent. So in the therapeutic dose of 3 gm. given in divided doses, an effect in normal individuals can certainly be demonstrated.

GEORGE F. CAHILL, M.D., (*Boston*): Fall in blood pyruvate is the first definite biochemical differentiation, I believe. I asked Dr. Fajans whether he has measured blood lactate. The reason I ask that is because we know that the sulfonamides may be nonspecific inhibitors of many enzymes, e.g., glucose-6-phosphatase, cytochrome oxidase, etc. If by this mechanism the lactate dehydrogenase or some redox system is inhibited a fall in pyruvate might occur which means nothing in reference to metabolic pathways, unless a comparable fall in blood lactate was found.

DR. FAJANS: I am sorry we did not measure blood lactate. We realize that the fall in blood pyruvate could occur if pyruvates were removed simultaneously or independently with stimulation of insulin secretion. All we can say at the present time is that the difference in response of the blood pyruvate following the treatment with Orinase and insulin respectively does not support the concept that sulfonylureas work by causing stimulation of endogenous insulin secretion.

DR. FIELD: We have some information that might bear on Dr. Cahill's question. We have done some studies similar to Dr. Fajans' comparing the effect of insulin and Orinase on pyruvate levels. Our studies have been somewhat different from Dr. Fajans'. We've done these in diabetic subjects and we've given our insulin subcutaneously rather than intravenously. The reason I didn't comment on this before is because our results haven't been as consistent as his in showing in each case or almost each case a definite difference of the effect of insulin and Orinase, but we have also measured lactate and we haven't found any reciprocal change in pyruvate and lactate which might explain the pyruvate fall. In other words, we haven't observed a rise in lactate acid concomitant with the pyruvate fall or vice versa.

But what I would like to know is: Did the lactate fall parallel to the pyruvate? I'm not looking for the reciprocal change. But, if lactate acid falls parallel to the pyruvate then we can say there has been a completely altered C_3 metabolism which would be exceedingly important.

GARFIELD G. DUNCAN, M.D., (*Philadelphia*): I would like to come back to these patients with jaundice. Maybe I didn't get it quite clear, but I wonder if the patients with jaundice continued to receive the sulfonamide preparation and overcame their hepatic disturbance, or whether the drug was withdrawn and this disturbance cleared up and if so, was the drug reinstituted without a recurrence of hepatic trouble?

DR. ACHELIS: We had one clinic where they were

treating a case of cirrhosis with BZ-55 and there was no further damage of the liver. There was a bigger group of cases where it has been demonstrated at autopsy that there is no connection between the treatment and the jaundice since they had pathologic findings in the liver, such as cancer. In other cases, I know that the treatment was continued and the jaundice did not recur.

A. E. RENOLD, M.D., (*Boston*): Could I ask Dr. Achelis one more question? Is there some evidence which you know about which indicates that the carbutamide can have an effect in the absence of the beta cells of the pancreas? And also some action on the glucose uptake on the diaphragm? I just wonder whether you could elaborate a little on this point.

DR. ACHELIS: I think there is some action if the beta cells are not present, and if you combine the insulin with BZ-55, you will have lowering of the blood sugar in alloxan diabetes and in the depancreatized dogs. And, therefore, it is my feeling that the exclusive theory of the stimulation of the beta cells is not sufficient. Your second question was about the diaphragm. At first we observed no change in the glucose uptake by the diaphragm. We repeated this test and found an increase in glucose uptake but we have not shown an increased storage of glycogen. These investigations are completely negated using the diaphragm from an alloxanized rat. Therefore, it is my feeling that in this case there must be a combined effect of insulin and BZ-55.

HENRY T. RICKETTS, M.D., (*Chicago*): I want to clarify this point still further if I may. I'm not sure we're quite clear about it yet. Do you think that in the total absence of the pancreas or the beta cells the sulfonylurea drugs have any effect if insulin is not given?

DR. ACHELIS: No, they have no effect.

DR. ROOT: May I ask one more question? You spoke of an incidence of 1 to 2 per cent of skin rashes. Has the drug always been discontinued in the presence of skin rashes?

DR. ACHELIS: Not in all cases. In only about 50 per cent of the skin rashes is it necessary to discontinue treatment with the drug.

DR. ROOT: Skin rashes are a puzzle to us because we have seen a variety of skin lesions other than mere itching. I speak now about a variety of eruptions, elevations, small and large, and I mean very large. In your experience have these types subsided and have you been able to resume the use of the drug?

DR. ACHELIS: We have found this in some cases but not in all.

DR. STADIE: We have been very much interested in the effects of the different media on the effect of insulin upon glucose uptake of metabolism of glucose on the diaphragm. Dr. Achelis, you mentioned that you were able to demonstrate an effect when you changed the media. Would you oblige us by being a little more detailed?

DR. ACHELIS: I do not have the data with me. I think I can send it to you later.

Metabolic Effects of Carbutamide in Diabetes and Interrelations with Glucagon

A Preliminary Report

Joseph L. Izzo, M.D., with the assistance of Angela Roncone, B.S.,† Rochester, New York*

To elucidate the mechanism of the hypoglycemic action of certain sulfonamide derivatives, studies were undertaken to determine: a) effects of carbutamide on organic and inorganic metabolism in selected diabetic patients; and b) metabolic interrelationships of carbutamide and glucagon. The following daily measurements

From the Department of Medicine, University of Rochester, and Medical Clinic of Rochester Medical Center, Rochester.

* Assistant Professor of Medicine.

† Department of Medicine.

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