rather a reason to find out to which insulin the patient is allergic, and whether he is allergic to the added protein or to the insulin molecule itself. If he is allergic to regular insulin, by all means desensitize him so that, if acute complications occur, he will not be deprived of its use. To use Orinase in place of insulin and do nothing more about insulin allergy would mean avoidable exposure to future difficulties.

"In a patient who has a blood sugar relapse after several months of therapy when do you discontinue Orinase?"

Discontinue it as soon as you decide Orinase is having no effect.

"How do you persuade the patient it is necessary to stop Orinase?"

By pointing out that his regimen is not adequate to control the diabetes.

"In resuming insulin therapy after failure with an oral agent, do you encounter sensitization to insulin?"

We have not had this experience. Such cases must be exceedingly rare.

"Are there other difficulties to be anticipated in the resumption of insulin?"

There are no difficulties. If oral therapy is inadequate, the insulin taken previously by the patient can be resumed promptly.

DR. DOLGER: In the light of this morning's conference and this afternoon's presentation, is it not logical to assume that a drug whose disadvantage is supposed to be that it works only via endogenous insulin may be superior to exogenous insulin?

DR. COLWELL: We must close now. On behalf of Dr. Marble, the Chairman of the Program Committee, and of the audience, I would like to thank the panelists for their interesting comments, and on behalf of the panel, to thank the audience for their attention and interest.

# A Thirty-fifth Anniversary of Insulin Therapy and a Sixty-fifth Wedding Anniversary

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The January 1956 issue of DIABETES commemorated the thirty-fifth anniversary of the discovery of insulin. Appropriate tribute was paid to the discoverers of insulin in Toronto, Sir Frederick G. Banting and Prof. Charles H. Best, and to Leonard Thompson, the first patient to receive insulin in Canada. We would like to supplement that report this year by reporting the case of Charles E. Cowan of Anaheim, California, a patient of the late Dr. William D. Sansum. According to our information, he is the first patient in the United States to receive insulin made here, and in May 1957 he celebrated his thirty-fifth year of insulin therapy. Mr. and Mrs. Cowan celebrated their sixty-fifth wedding anniversary on April 12, 1957. Such a celebration was an event in itself, but of greater significance was the fact that Mr. Cowan had lived to make it possible.

Mr. Cowan came to the Potter Metabolic Clinic in Santa Barbara on Nov. 8, 1920, the same day that Dr. Sansum arrived from Chicago to be director of the clinic. A brief history of this clinic may be of interest. It was established in 1919 by Dr. Nathaniel Bowditch Potter of New York City for the purpose of studying metabolic disorders, particularly diabetes, from the research and clinical viewpoints. Dr. Potter was a diabetic patient himself. Because of failing health, he had come to Santa Barbara and was unable to return to New York. Contributions, including funds for the project from the Carnegie Corporation, were transferred to Santa Barbara. With the financial assistance of friends here the Potter Metabolic wing of the Cottage Hospital was built. Dr. Potter died in July 1919, before the building was completed. In 1928 the Potter Metabolic Clinic be-

came a part of the Cottage Hospital. However, between 1920 and 1928 it was the scene of historic events in the field of research and treatment of diabetes, a fitting memorial to Dr. Potter.

This clinic had the honor of being the first place in the United States where insulin was manufactured and successfully used. Experimental work on diabetes had been started along other lines in the clinic laboratories when insulin was discovered in Toronto in 1921. Because the Canadian reports published in February and March of 1922 offered greater promise of success, and because the clinic was fully equipped for the study of diabetes, work was started immediately on insulin extraction. In April, Dr. Sansum and his chief chemist, Dr. Norman R. Blatherwick, had succeeded in making a small amount of insulin. By May, they had sufficient insulin to start work on nine patients of whom Mr. Cowan was the first. A report of the work was sent to Prof. J. J. R. Macleod in Toronto in June, and exchange of information regarding insulin continued during the experimental years. Important contributions were made from this clinic, many of which were adopted by pharmaceutical houses later. By 1925 the manufacture of insulin was discontinued here, as an ample supply was available from Eli Lilly and Company. This company had been invited in May 1922 to assist Dr. Banting in the commercial manufacture of insulin and by August had produced a product that was very stable. The company had the privilege of making available the first commercial insulin in the world. Some of the methods of extraction and purification of insulin worked out in the laboratories of the Potter Metabolic Clinic were adopted by this pharmaceutical house, and the method devised in this laboratory of estimating the strength of the insulin units is still in use. The report of the first 100 patients treated with insulin manufactured here was published in 1923.[1]

Mr. Cowan had developed diabetes after a severe case of influenza in 1919, one and one-half years prior to coming to the clinic and three years before the discovery of insulin. He was fifty-one years of age, five feet eight inches in height, with a large frame and weighed 112 pounds. He was admitted with a severe case of diabetic acidosis and there was little hope for his life. However, he recovered from this acute condition and returned to the clinic in 1921 to remain for a number of years as a "human guinea pig." He received his first insulin in May 1922. At that time he weighed 95.5 pounds and had been existing on a diet of 844 calories, containing 24 gm. of carbohydrate, 34 gm. of protein, and 68 gm. of fat. The strength of the first insulin is not recorded but it must have been quite weak as he was given 3 cc. one hour before each meal at first and later 2 cc. When the first supply was exhausted the amount was reduced to 1 cc. before each meal, as it was stated that the next insulin obtained was twice as strong as the first. By July 15, 1923, he weighed 125 pounds on a diet of 2,993 calories, containing 91 gm. of carbohydrate, 79 gm. of protein, and 257 gm. of fat. On April 16, 1924, his weight was 153 pounds on a diet of 2,417 calories, containing 91 gm. of carbohydrate, 79 gm. of protein, and 193 gm. of fat.

During the period before the discovery of insulin, various forms of treatment and diet had been used on Mr. Cowan, ranging from yeast and bran to very high fat diets. In 1925, Dr. Sansum started experimental work with higher carbohydrate diets,[2,3] which made it possible to feed diabetic patients adequate diets for the first time in this country. As soon as possible Mr. Cowan was placed on a higher carbohydrate diet consisting of 2,334 calories, containing 235 gm. of carbohydrate, 83 gm. of protein, and 118 gm. of fat. He has continued with this type of diet to the present time. His weight has been maintained at approximately 148 pounds for several years.

Mr. Cowan continues to test his urine twice daily. He has very few insulin reactions and they are mild. His insulin dosage consists of 40 units of U80 NPH insulin daily before breakfast and occasionally 5 units of regular insulin when the need arises. This dosage has been essentially the same for several years.

He still retains useful vision as he is able to read ordinary print without the aid of glasses. There are lenticular opacities present, making examination of the eyegrounds unsatisfactory.

The only complaint is pain in his feet, especially when walking. He has had pernicious anemia since 1938, controlled by liver extract, discovered by Dr. G. R. Minot and Dr. W. P. Murphy. (Dr. Minot was a diabetic whose life was saved by insulin.) A recent blood count showed 16.6 gm. of hemoglobin, 4,500,000 red blood cells, and 8,300 white blood cells, of which 60 per cent were polymorphonuclear leukocytes and 40 per cent lymphocytes. The platelets were normal.

His general physical condition shows no great abnormalities except that the tendon reflexes of the knees and ankles are not obtainable. The pulsations in the dorsopedal and posterior tibial arteries are not palpable. There is no edema of the lower extremities. The chest is clear. The heart rate is 72 per minute, when he is resting in a chair, rhythm is normal and there are no murmurs. His blood pressure is 142/80.

Mr. Cowan is now eighty-nine and his wife eighty-four years of age. He is mentally alert and carries on a conversation concerning current events, as well as reminiscences regarding his long and interesting life. He has outlived his doctor and his allotted time of three score years and ten and credits his longevity to both insulin and an adequate diet. Mr. Cowan's life should be an inspiration to all diabetic patients and a great satisfaction to the people still living who worked so diligently on insulin in the early days. He and his wife give daily thanks to those who saved his life and made it possible for him to live a normal, happy life.

REFERENCES

[1] Sansum, W. D.; Blatherwick, N. R.; Smith, Florence H.; Long, M. Louisa; Maxwell, L. C.; Hill, Elsie; McCarty, Ray; and Cryst, J. H.: The treatment of diabetes with insulin. J. of Met. Res. Vol. 3, Nos. 5-6, May and June 1923.

[2] Sansum, W. D.; Blatherwick, N. R.; and Bowden, Ruth: The use of high carbohydrate diets in the treatment of diabetes mellitus. J. A. M. A. 86:178-81, Jan. 16, 1926.

[3] Blatherwick, N. R.; Sansum, W. D.; Bell, Marion; and Hill, Elsie: The insulin requirements of various diets. J. of Met. Res. Vols. 7-8, Nos. 1-6, Jan. 1925 and Dec. 1926.



# EDITORIALS

## IS THE METABOLISM OF PERIPHERAL TISSUES AFFECTED BY THE ARYLSULFONYLUREAS?

In this issue of the Journal a paper by Ashmore, Cahill, Earle and Zottu[1] reports experiments in which the actions of insulin and tolbutamide in one and the same experimental preparation are compared. This paper prompts a review of the experimental evidence reported in the recent literature on the effects of the arylsulfonylureas in experimental and clinical diabetes. The conclusion seems to be warranted that the main action of these drugs is pancreatropic, bringing about a release of insulin from the β-cells. This conclusion is based on the unequivocal evidence that in the absence of the pancreas and in instances of complete alloxanization, as well as in the Houssay animal, no hypoglycemic action of the drug is demonstrable. The insulin released from the pancreas by the action of the drug, through its effect upon the metabolism of the liver, brings about a diminished output of hepatic glucose resulting in hypoglycemia. However, it is impossible to rule out that the sulfonylureas, aside from the action of the released insulin itself, may have some direct action upon hepatic mechanisms through which the release of sugar is diminished. For example, evidence has been presented indicating that certain hepatic systems, particularly glucose-6-phosphatase, may be inhibited, thus increasing hepatic glucose retention.

One of the main obstacles in accepting this thesis as an exclusive hypothesis for the action of the sulfonylureas is the difficulty in excluding unequivocally the peripheral action of the drug. Endogenous insulin released in response to the pancreatropic action of the drug should be expected to reach the periphery and exert its customary effect there. However, experiments from many laboratories have failed to demonstrate an unquestionable insulin-like action in the periphery following the administration of these hypoglycemic agents. Indeed, the significance of the paper by Ashmore et al. lies in the demonstration that a direct comparison of the respective actions of tolbutamide and insulin upon peripheral tissues (muscle and fat) shows that they are quite different. In detail, the experiments of Ashmore et al. show that tolbutamide action brings about a cessation of hepatic glucose output. In contrast, insulin increases it. After isotopic glucose administration the hypoglycemia following tolbutamide does not increase the decay in blood glucose specific activity greater than that of a saline control, but following insulin administration it is markedly accelerated. Furthermore, when identical blood glucose changes are produced by tolbutamide and insulin the former has no significant effect upon the incorporation of $C^{14}$ from isotopic glucose in either peripheral glycogen or fatty acids, in sharp contrast to the significant effects which insulin produces in these two metabolic reactions. From the summation of their evidence Ashmore et al. conclude that the action of tolbutamide appears to be limited to the pancreas and the liver.

In general, these conclusions are in conformity with the experimental data published by others, but there is sufficient authoritative data leading to opposite conclu-