of diabetes, revealed by his many distinguished contributions, will be ideally complemented by Dr. Graef's background in pathology and his present activities in clinical medicine. This is a powerful team, and we have every confidence that under their leadership the Journal will continue to grow and prosper.

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ORAL ANTIDIABETIC SULFONAMIDES

In October 1955 three reports in the *Deutsche Medizinische Wochenschrift*[1-3] described a new sulfonamide derivative possessing the ability when given by mouth to reduce normal blood sugar values to subnormal, and elevated blood and urine sugar values in diabetes to normal. Reduction of normoglycemia had been shown with other sulfonamide derivatives as early as 1942,[4-8] but the application to therapy in diabetes mellitus was not made. The earlier compounds were p-amino-sulphonamido-alkyl-thiodiazoles: The current ones are aryl sulfonylureas. Those now under the most intensive investigation are N_1-sulfanilyl-N_2-n-butylcarbamide (BZ 55) and N_1-p-tolylsulfonyl-N_2-n-butylurea (U 2043 or D 860). More clinical evidence is available concerning the former than the latter: The laboratory evidence on glycemia with both is similar.

There is no doubt that these substances in single doses by mouth lower the blood sugar promptly and substantially in normal men, dogs and rabbits. Hypoglycemic effects are observed within an hour or two (earlier when given with alkali) and they persist for hours. Indeed, it was the hypoglycemic manifestations seen on administration to nondiabetics for antibacterial purposes which led to their trial in diabetes.[2]

There is no doubt, also, that abnormal glycosuria and hyperglycemia are reduced or eliminated by these compounds in many patients with mild and moderately severe diabetes mellitus. Franke and Fuchs[1] showed eight examples of this, and they claim similar results in 80 per cent of fifty diabetics treated in Berlin for periods up to one year. After seven months of study in Hamburg, Bertram, Bendfeldt, and Otto reported successful control of diabetes in 25 of 28 older, mild diabetics not using insulin and replacement of insulin in 28 of 38 patients using it.[3] In younger patients with severe forms of the disease the sulfonamide had no effect. In some cases it appears uncertain from their data whether restriction of food or the sulfonamide was responsible for the reduction in sugar, but the evidence in favor of the drug is convincing in some of the trials. Unpublished results comparable to these are being obtained by laboratories and clinical investigators in this country.

Toxic side effects appear to be negligible and LD 50 dosages in animals are high. Skin reactions have been encountered not infrequently, but hematologic, hepatic and renal effects have seldom been observed. Crystalluria seems less likely to occur than with other sulfonamides, especially when alkali is given concurrently. Therapeutically effective blood sulfonamide levels of 10 to 15 mg. per 100 ml. are obtained with about 1 gm. daily, following larger priming doses for the first day or two. Blood levels fall slowly for days after administration is stopped.

There is general agreement among all investigators that the compound is totally ineffective in "pancreatectomy diabetes" and relatively so in alloxan diabetes. Ferner[9] and others[5c,8,10] have seen damage to the alpha cells of the islets after its use. These considerations, together with the fact that in most diabetics with favorable responses glycosuria does not recur promptly on stopping the drug, have led to the favored hypothesis that it acts by suppressing glucagon secretion. Other mechanisms of action have not been eliminated, however, among them accelerated release of insulin from the pancreas, inhibition of insulinase, other hepatic effects, and suppression of pituitary or adrenal function. It must be borne in mind that hypoglycemia in normals and apparent improvement of diabetes in diabetics can be produced at will by administration of insulin, hepatectomy, hepatic damage, and reduction in pituitary or adrenal activity. The fact that diabetes can be ameliorated and normoglycemia reduced by artificial means does not prove that the fundamental defect in diabetes has been improved in a physiological manner. Indeed, the fact that acidosis and severe diabetes cannot be controlled with the new compounds suggests that it is not.

No agent of this type is on the market yet in this country, but supplies have recently been distributed by two pharmaceutical firms for appraisal in diabetic patients in selected clinics and laboratories. Controlled experiments are being conducted, mechanisms of action explored and the effects of long continued administration watched closely. Results are being compared freely in joint conferences. Investigators feel as great an obligation to protect the diabetic public from possible exploitation and harm as to recognize and adopt a long sought therapeutically effective oral agent. The record of dependable and rational therapy in diabetes has been kept remarkably free from abuse and there is every

indication that the present developments will be no exception, in this country at least.

Those who witnessed the transient enthusiasm regarding the guanidine compound Synthalin (which also originated and was marketed in Germany until lenticular, hepatic and renal damage were encountered after sustained use) will welcome long, well-controlled studies by earnest and experienced investigators. To yield to the pressure of healthy diabetics for an easier way than insulin might do more harm than good. It is apparent that the type of diabetes which responds best to the new oral agents is also the type which is easiest to control by diet restriction. Since convenience is the only thing at stake, all concerned should be patient until convincing evidence concerning indications, mechanism of action, and particularly dangers from continued use is available, probably by the end of this year at the latest.

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THIRTY-FIFTH ANNIVERSARY OF THE DISCOVERY OF INSULIN

This issue commemorates the thirty-fifth anniversary of the discovery of insulin. In it are recorded a personal recollection of Banting by Fulton, reminiscences of the work with Banting by Best, the clinical impact of the discovery as recalled by Joslin, and the printing in abridged form of the first report of the clinical use of the successful extract.

On the cover the first human subject to receive insulin, Leonard Thompson, is portrayed. He was fourteen years old when first treated, survived the vicissitudes of severe childhood diabetes and went on to live in good health until 1937 when he died of unrelated pneumonia. Had the precious antibiotics been available, they too might have brought even longer life to a human being who already owed most of his life to the work of two previously unknown but persistent and patient young investigators with an idea.

In considering the origin of their work it is apparent that the roots of their research stretch back almost timelessly into past medical and other scientific advances and experiments; the flower was the substance that consistently proved to be the hormone needed to make up the deficiency that characterizes experimental or human diabetes. Banting had surgical technic, a physiological and clinical appreciation of the possible role of a pancreatic extract which had to be obtained from the tiny endocrine islets imbedded in the mass of exocrine tissue. Best, a biochemically trained scientist, with unflagging energy, had the task of chemical separation and purification of the tissue extracts. Each needed the other and they were a model team for many others to copy.

Others before them, sensing the secret of the islets, had tried and failed to produce a consistently effective substance that was comparable to theirs. Readers of this Journal need no reminder that millions owe their lives directly or indirectly to the success of Banting and Best.

It is fitting therefore to commemorate on suitable anniversaries their achievement which, like so many medical discoveries, unites men of science by integrating knowledge and changing theory to fact or fancy. We grope towards the truth—limited by our own capacities—but discoveries like that of insulin give new minds the opportunity to retest old ideas or formulate