



## EDITORIALS

### *THE JOURNAL DIABETES IN RETROSPECT AND PROSPECT*

In an editorial entitled "DIABETES Looks Ahead" in the first issue of the Journal, the writer discussed the objectives of the publication. These were defined as fulfillment of the aims of the American Diabetes Association in respect to the dissemination of knowledge of diabetes, the promotion and maintenance of high standards of treatment, and the stimulation of investigation. It was planned that the contents of DIABETES would include material appealing to the widely-varying interests of the Association members and other subscribers including internists and specialists in various other fields of medicine, general practitioners and scientists. That these aims have been achieved with a substantial degree of success has been confirmed by the results of the "Reader Interest Survey" presented in the November-December issue.

The favorable comments received from the majority of readers have been appreciated by the Editors and Editorial Board. At the same time, it is realized that consideration must be given to the possibilities of improvement, to which attention has been directed. Readers can be assured that efforts to bring about continuing progress will be made by the new Editor and his Associate.

The major factor in the success of any scientific publication is the quality of the papers which it can present to its readers. Much of the material published in the Journal has been derived from the program of the Annual Meeting of the Association, and to some extent also, from the Postgraduate Course which has been presented each year since 1953. These programs are planned and organized by committees which thus render indirectly an important service to the Journal supplementing the Editorial Board in the procurement and selection of papers.

Unsolicited manuscripts are submitted to DIABETES in increasing numbers, but more papers written especially for the Journal are desired. Contributions are welcomed from any source in which reliable observations can be made and sound ideas can be developed,

whether in a university, a large medical center, or a small town, in the United States and Canada or elsewhere in the world. Each paper has been, and will be evaluated on its own merits. The Editors have available the advice of Board members possessing diversified interests and experience. No paper is arbitrarily rejected on the basis of a single adverse opinion, so that personal bias or disinterest can be eliminated as a factor in selection. Laboratory investigators and clinicians working in the field of diabetes can find that, in this Journal, their reports will come to the attention of the greatest number of readers whose dominant interest is concerned with this disorder and related endocrine and metabolic problems.

FRANK N. ALLAN, M.D., *Vice-Chairman*  
Editorial Board, DIABETES

### *THE EDITORSHIP OF DIABETES*

With this issue the Editorship of DIABETES passes from Frank N. Allan of Boston to William C. Stadie of Philadelphia, with Irving Graef of New York as Associate Editor. Dr. Graef will serve as Acting Editor until Dr. Stadie can assume full responsibility for his position in July 1956.

Dr. Allan's long service to the American Diabetes Association has earned him the gratitude and respect of its members, particularly of those who have worked closely with him. He had already proved himself a faithful worker and an able leader when in 1951, having been elected President of the Association, he consented to becoming as well the first Editor of its Journal. Either office would have taxed the energies of an ordinary man. Dr. Allan effectively and cheerfully filled both of them. Continuing as Editor after his presidency, he nurtured the new Journal not only with skill but also with a rare devotion born of love for his work and, more than a little, of a New England conscience with Canadian origins. This has been Dr. Allan's Journal, although he would be quick to deny it, and its manifest success is the success he has given it.

The Journal is extremely fortunate in its incoming Editors. Dr. Stadie's interest in the biochemical aspects

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.

HENRY T. RICKETTS, M.D., *President*  
American Diabetes Association

## ORAL ANTIDIABETIC SULFONAMIDES

In October 1955 three reports in the *Deutsche Medizinische Wochenschrift*<sup>1-3</sup> 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,<sup>4-8</sup> but the application to therapy in diabetes mellitus was not made. The earlier compounds were p-amino-sulphonamido-alkyl-thiadiazoles: The current ones are aryl sulfonylureas. Those now under the most intensive investigation are N<sub>1</sub>-sulfanilyl-N<sub>2</sub>-n-butylcarbamide (BZ 55) and N<sub>1</sub>-p-tolylsulfonyl-N<sub>2</sub>-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.<sup>2</sup>

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<sup>1</sup> 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.<sup>3</sup> 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<sup>9</sup> and others<sup>5,8,10</sup> 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