have been found in visceral granulomata in penicillin hypersensitivity in association with eosinophilic myocarditis.[10] Although this patient did receive one injection of penicillin four days before death, it seems likely that the changes were due to sulfonamide sensitivity. Eight days after beginning BZ-55 and seventeen days before the penicillin injection, a 6 per cent eosinophilia was present, contrasted with a maximum pretreatment value of 2 per cent. Chills, fever and back pain without apparent infection developed during treatment with BZ-55 and before penicillin was given.

The granulomatous changes in the liver, spleen and lymph node could conceivably have been produced by an infectious microbial agent, but multiple special stains did not demonstrate one.

Of the several possible causes of death in this case, hypoglycemia or arrhythmia seems most likely. However, hypoglycemic death is characteristically not sudden and Bertram[3] has not observed any instances of profound hypoglycemia in the course of clinical use of the sulfonylurea compounds. Of numerous blood sugars obtained in this patient, including one the day before death, none was in the hypoglycemic range. Since arrhythmias are not uncommon in association with myocarditis[13] this seems a more likely cause of death. The extensive myocardial infiltration by inflammatory cells and the severe pulmonary congestion and edema are consistent with this interpretation.

It thus appears that this sulfonamide derivative may be capable of producing some of the same toxic side effects as other sulfonamide compounds. Since these drugs are likely to be widely used, an awareness of this potentially fatal, toxic reaction is important.

SUMMARY

A case of sudden death in a diabetic patient receiving BZ-55 is reported. Chills, fever, neutropenia and eosinophilia were present shortly before death. Autopsy findings of interstitial myocarditis and focal miliary granulomata were similar to those previously reported in sulfonamide hypersensitivity.

ACKNOWLEDGMENT

We are indebted to Dr. Nicholas Leone of the National Institute of Dental Research for referring this patient for study and for his cooperation in her care.

REFERENCES

1 Franke, H., and Fuchs, J.: Ein neues antidiabetisches Prinzip. Deutsche med. Wchnschr. *80*:1449-52, Oct. 7, 1955.

2 Achelis, J. D., and Hardebeck, K.: Über eine neue blutzucker-senkende Substanz. Deutsche med. Wchnschr. *80*: 1452-55, Oct. 7, 1955.

3 Bertram, F., Bendfeldt, E., and Otto, H.: Über ein wirksames perorales Antidiabeticum (BZ-55). Deutsche med. Wchnschr. *80*:1455-60, Oct. 7, 1955.

4 Miller, M., and Craig, J. W.: Hypoglycemic effects of 1-butyl-3-p-toluene sulfonylurea given orally in human diabetic subjects. Metabolism *5*:162-64, March 1956.

5 Kirtley, W. R.: Personal communication.

6 Kinsell, L. W., Brown, F. J., Jr., Friskey, R. W., and Michaels, G. D.: Insulin-sparing sulfonamides. J. Clin. Endocrin. and Metab. *16*:821-27, June, 1956.

7 French, A. J., and Weller, C. V.: Interstitial myocarditis following the clinical and experimental use of sulfonamide drugs. Am. J. Path. *18*:109-22, January, 1942.

8 French, A. J.: Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy. Am. J. Path. *22*:679-702, July, 1946.

9 More, R. H., McMillan, G. C., and Duff, G. L.: The pathology of sulfonamide allergy in man. Am. J. Path. *22*:703-36, July, 1946.

10 Waugh, D.: Myocarditis, arteritis, and focal hepatic, splenic and renal granulomas apparently due to penicillin sensitivity. Am. J. Path. *28*:437-48, May-June, 1952.

11 Folin, O.: The micro-method for the determination of blood sugar. New England J. Med. *206*:727-29, April 7, 1932.

12 Benedict, S. R.: The detection and estimation of glucose in urine. J.A.M.A. *57*:1193-94, Oct. 7, 1911.

13 White, P. D.: Heart Disease. New York. The MacMillan Company, 1951, p. 659.

Effects of Carbutamide in the Diabetes Associated with Acromegaly

James B. Field, M.D., and Daniel D. Federman, M.D.,† Bethesda, Maryland*

In the course of our clinical investigation of carbutamide (BZ-55), we have had occasion to treat two patients who had both acromegaly and diabetes. In one of these patients, there was a prompt elimination of glycosuria and reduction in the fasting blood glucose without significant change in the two-hour postprandial

From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, United States Department of Health, Education and Welfare, Bethesda, Maryland.

* Senior Assistant Surgeon, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

† Senior Assistant Surgeon, United States Public Health Service.

blood glucose. The other patient showed no effect from 3 gm. of carbutamide daily and indeed, while on the drug developed acetonuria requiring resumption of insulin administration.

CASE REPORTS

Case One. A.L., a fifty-three-year-old woman, had had slowly progressive enlargement of the hands and feet for ten years and the diagnosis of acromegaly was made two and one-half years before admission to the Clinical Center. At that time she developed polyuria, polydipsia and burning of her eyes. Glycosuria and hyperglycemia were demonstrated, and the patient was given insulin. The dose was rapidly increased to 130 units per day, but glycosuria and acetonuria persisted, and the patient was hospitalized.

Large hands and feet, prognathism, enlargement of the sella turcica and hyperphosphatemia were found, and the patient was treated with thirty doses of x-radiation to the pituitary without appreciable amelioration of the diabetes. Since she was asymptomatic despite glycosuria and acetonuria, insulin was discontinued without incident.

At the time of her admission to the Clinical Center, she had noted no progression in the acromegalic symptoms. Despite constant glycosuria and acetonuria, she had no symptoms attributable to diabetes.

The main findings on physical examination were acromegalic features and healed choroiditis in the right eye. Urinalysis revealed a 4+ qualitative test for sugar and a positive test for acetone. Repeated determination of basal metabolic rate ranged from +1 to +19 per cent. Repeated serum phosphorus determinations varied from 2.9 mg. to 3.8 mg. per 100 ml. Other laboratory tests, including tests of liver function, were within normal limits. X-ray examination confirmed an enlarged sella turcica and acromegalic changes in the spine and digits.

The acetonuria disappeared within four days after she was given a 1,700 calorie diet. Her response to carbutamide therapy is shown in figure 1. Glycosuria, which averaged 17.4 gm. per day during the control period, rapidly disappeared while she was taking carbutamide. The control fasting blood glucose averaged 199 mg. per 100 ml. and fell to 149 mg. per 100 ml. during the period of carbutamide therapy. Postprandial blood glucose levels fell from an average of 248 mg. to 213 mg. per 100 ml. Because of comparatively low blood values of carbutamide the daily dose was increased to 2.5 gm. During the period of treatment there was no significant change in any of the laboratory examinations including urinary and blood corticoid levels. Before therapy, the protein bound iodine varied from 2.5 micrograms per cent to 5.1 micrograms per cent while during treatment it was 3.5 micrograms per cent. After eight days of carbutamide the drug was discontinued since it was not possible to follow the patient. Four days after omitting carbutamide, she was discharged from the hospital. At this time she was still aglycosuric but her fasting blood sugar values had begun to rise toward the pretreatment level.

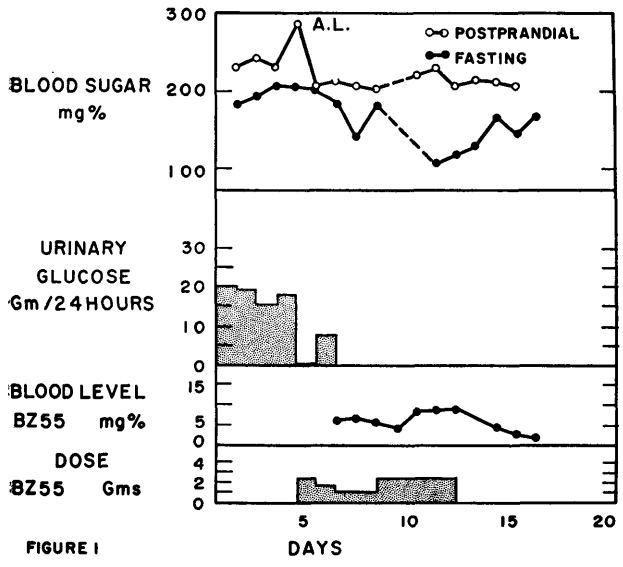

FIGURE 1

Case Two. B.G., a thirty-eight-year-old female, developed symptoms of diabetes eight years prior to admission to the Clinical Center. At that time the diagnosis of acromegaly was also made on the basis of her physical features and an enlarged sella turcica by x-ray examination. She was given a diet and 30 units of insulin daily, but after three months, the insulin was discontinued. However, after six months without insulin therapy, her glycosuria recurred and insulin was again administered. Over the next seven years her daily insulin dosage was increased to 120 units. Since her acromegaly was asymptomatic, she had not received any therapy for it. At the time of her admission to the Clinical Center she was asymptomatic except for occasional insulin reactions and moderate headache.

The positive findings on physical examination were blood pressure 170/100 mm. Hg, prognathism, enlargement of the hands and feet, and macroglossia. The thyroid was enlarged (estimated twice normal size) and the liver edge was felt one centimeter below the costal margin. Urinalysis revealed 2+ test for sugar, but was otherwise normal. The serum phosphorous ranged between 4.9 mg. and 3.9 mg. per 100 ml. Other laboratory examinations including tests of thyroid and adrenal function were within normal limits. X-ray examination disclosed an enlarged sella turcica and acromegalic changes of the hands and feet.

The patient was given an 1,800 calorie diet (carbohydrate, 200 gm.; protein, 60 gm.; fat, 85 gm.) and insulin was withdrawn for eight days preparatory to the administration of carbutamide. Figure 2 summarizes the response to carbutamide. Glycosuria averaged 110 gm. per day during the control period. Insulin was given for three days before the institution of carbutamide when the diabetic control began to deteriorate, but was then withheld for two days while carbutamide was given in doses of 3 gm. per day. During this time her glycosuria increased and acetonuria developed. There was a concomitant rise in her fasting blood sugar. Because of the deterioration of her diabetic control, insulin therapy was begun without changing her dose of carbutamide. Over several days her insulin dosage was stabilized at approximately 95 units of insulin with a marked reduction in her glycosuria and blood sugar values. Carbutamide was discontinued after sixteen days, without any apparent increase in her insulin

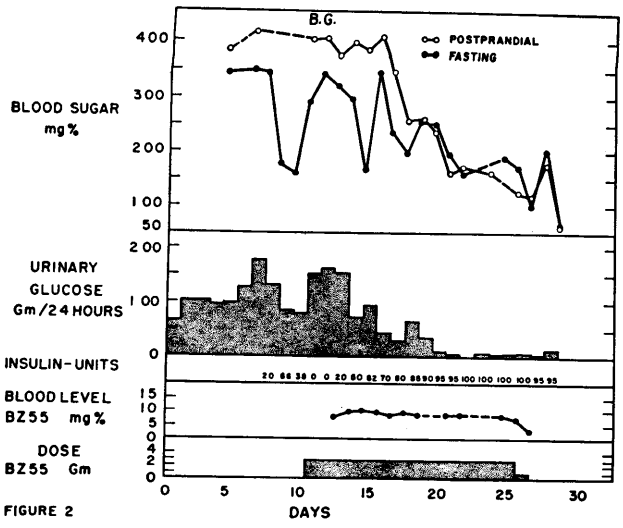

FIGURE 2

requirement. During treatment with carbutamide there was no significant change in any of the laboratory tests, renal, thyroid, adrenal and liver functions.

DISCUSSION

It is impossible to draw any conclusions from these contrasting cases regarding the efficacy of carbutamide in the diabetes which accompanies acromegaly, particularly since both such diabetes and the action(s) of the sulfonylurea drug are incompletely understood. The second patient, B.G., who did not respond, had developed diabetes at age of thirty, and developed ketonuria when insulin was withheld. Further, she had been treated with insulin for over eight years. These several factors have been shown to influence adversely the chances of success with the sulfonylurea agents. In the first patient, despite poor regulation with as much as 130 units of insulin previously, carbutamide was highly effective. She was able to do without insulin without developing acetonuria, but had been treated with insulin for a short time only. In addition to these differences, it is possible that the diabetes of acromegaly is influenced by extrapituitary factors. In this connection it is to be noted that there was no observed change in thyroid or adrenal function in these patients during carbutamide therapy.

SUMMARY

Two patients with diabetes and acromegaly were studied using carbutamide. One patient made a satisfactory response to the drug while the other one did not.

Occurrence of Sensitivity and Side Reactions Following Carbutamide

W. R. Kirtley, M.D., Indianapolis*

Toxicity has been an item of primary concern from the beginning of the clinical trial program with carbutamide. Knowing that as a class sulfonamide drugs cause side reactions of certain types, we were alerted to the possibility of complications developing and a request for information in this regard was included in the report sheets furnished to all investigators.

Upon receipt of information from the National Institutes of Health concerning the first fatal case, just reported by Field and Federman, it became apparent that this information must be supplied to all physicians who had been receiving the drug on clinical trial. This decision was reinforced by two additional fatal cases reported from New York City. Although the data were not clear-cut, there was at least some indication that the administration of carbutamide might have contributed to the deaths in these cases as well.

At the time the information was dispatched, a request for data as to the incidence of toxicity of any sort was included and a tabulation of the data received is shown in the following tables.

At the present time, carbutamide has been supplied to 2,900 physicians. It is assumed that the majority of this group now has experience with the drug in the treatment of diabetes. This report is derived from data which have been obtained from almost half of this group and the total sample includes over 7,000 patients. (The unfavorable reaction percentage has been determined to be a bit over 5 per cent.)

* Senior Physician, Lilly Laboratory for Clinical Research. Associate in Medicine, Indiana University Medical School, Indianapolis.