There was no correlation between clinical and radiological improvement in individual cases. The less severe the radiological changes before operation the more likely they were to improve. Radiological improvement occurred more often in patients with a pre-operative history of less than five years than in those with longer histories.

Failure was due to recurrence of achalasia in four cases and peptic stricture in one. In two cases the cause of failure was uncertain. Relapse may occur more than six years after cardiomyotomy.

In spite of its manifest imperfections cardiomyotomy remains the best available surgical operation for achalasia of the cardia.

We thank the surgeons of the Middlesex and Harefield Hospitals who permitted us to study their patients and report these findings.

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CARBUTAMIDE IN JUVENILE DIABETES

BY

J. M. SMELLIE, O.B.E., T.D., M.D., F.R.C.P.

Professor of Paediatrics and Child Health, University of Birmingham

In August, 1956, the *British Medical Journal* published six articles (Duncan *et al.*, 1956; Wolff *et al.*, 1956; Hunt *et al.*, 1956; McKenzie *et al.*, 1956; Walker *et al.*, 1956; Murray and Wang, 1956) reporting the observations of British workers who had been treating diabetic patients with the hypoglycaemic sulphonamide known as carbutamide (BZ 55). These studies confirmed that the type of patient responsive to this treatment is the middle-aged or elderly diabetic who has never had ketosis or who needs less than 30 units of insulin a day.

The original German reports stated that carbutamide effected no improvement in children suffering from diabetes, and the English literature deals almost exclusively with adults. Chute and Bain (1956) treated five children and found no evidence of a hypoglycaemic effect. Barta (1957) tested the drug in 16 patients between 6 and 13 years of age, and states that the blood-sugar level was not reduced by carbutamide even in full adult doses. On the other hand, Engleson and Lehmann (1956) consider that these preparations are of limited value in juvenile diabetes provided the dosage is very high, but that side-effects are likely to develop.

The mode of action of the so-called hypoglycaemic sulphonamides is still undetermined, but various possibilities have been advanced (Young, 1956; Best, 1956)—for example, stimulation of beta cells leading to increased insulin secretion, inhibition of activity of alpha

cells, depression of secretion of glucagon, inhibition of insulinase, and the possibility that this sulphonamide may depress an occult infection in the liver or elsewhere which is accelerating the breakdown of insulin. The metabolic investigations of Bastenie *et al.* (1957) would appear to indicate that sulphonamide treatment induces no increased uptake of glucose by the tissues and the improvement in the diabetes cannot be ascribed to an increase of either secretion or activity of insulin.

The desirability and advantages of a drug that can be given by mouth to control diabetes mellitus, particularly in children, needs no emphasis. Before any such substance can be recommended its efficacy, its safety, and its reliability must be established beyond doubt, it being appreciated in particular that therapy will be life-long. The authors of the papers in the *British Medical Journal* already referred to issued a warning that carbutamide should at present be used only under careful hospital supervision, in view of certain complications that were being reported in some cases.

The investigations herein recorded were undertaken to ascertain whether, with a careful selection of cases based on reported experiences with adult diabetics, this oral sulphonamide had any place in the treatment of children. In general the adults who have been treated have been diabetics of long standing, and presumably their beta cells are atrophied and their endogenous insulin-secretion negligible. If carbutamide acts, at least in part, by stimulation of the beta cells, then its antidiabetic action might perhaps be much greater in the young diabetic whose illness is of recent origin and who may therefore still have an appreciable secretion of endogenous insulin. Theoretically, however this substance may act, the recuperative potentialities of a child of 10 years should be many times greater than his adult counterpart of 50 or more, as he has not been subjected to the dietetic and other insults and indiscretions of the latter.

Case 1

A boy aged 7½ years developed symptoms of diabetes in June, 1956. On admission to hospital three weeks later the diagnosis was established and he was stabilized on a diet of 220 g. of carbohydrate (with unlimited protein and fat) and 14 units of insulin zinc suspension once daily. He remained well and returned to school.

He was readmitted in October. His diet was then fixed at 210 g. of carbohydrate, and insulin was omitted. A few days later a diurnal blood-sugar curve showed a fasting level of 127 mg./100 ml. with a rise to 510 mg./100 ml. later in the day, but his urine remained free from acetone. He was then treated with carbutamide for a period of nine days. Fig. 1 records his progress. This shows that, although his

FIG. 1.—Progress and treatment in Case 1.

fasting blood sugar appeared satisfactory for the first seven days, there was no diminution in his urinary sugar output. An increase in dosage to 25 mg./lb. (55 mg./kg.) daily caused a rise in his blood sulphonamide level, but his blood sugar also rose and his general clinical condition deteriorated, polyuria and polydipsia became increasingly troublesome, but his acidosis was negligible. On the ninth day he developed a mild erythematous rash—possibly indicative of sulphonamide poisoning—and treatment was abandoned. His total carbutamide dosage over the period of nine days was 8.5 g. At no time was there any leucopenia or thrombocytopenia. Thereafter insulin therapy was reinstituted, but there was some delay before he was satisfactorily re-stabilized.

Case 2

A boy aged 11 years 9 months was admitted to hospital in January, 1957, with a two-months history of polyuria and polydipsia. His urine contained a large amount of sugar, and his blood sugar was 352 mg./100 ml., but there was only a faint trace of acetonuria. He was placed on a diet of 220 g. of carbohydrate (and unlimited protein and fat) and was reasonably well controlled in a few days on a daily dose of 34 units of soluble insulin. Insulin was then omitted and a few days later he had no acidosis, and a diurnal blood-sugar curve showed levels varying from 137 to 264 mg./100 ml.

Carbutamide was then given for a period of 11 days, and Fig. 2 records his progress during that period. The dosage of carbutamide was high—25 mg./lb. (55 mg./kg.) a day

FIG. 2.—Progress and treatment in Case 2.

for nine days—and his blood sulphonamide level exceeded 25 mg./100 ml. His urinary sugar output fluctuated to a low level and the fasting blood-sugar levels were also satisfactory. Nevertheless his general clinical state slowly but progressively deteriorated and was associated with a gradually falling platelet and white-cell count from 210,000 to 175,000 and 6,500 to 3,000 respectively. Whilst he did not develop any features which could be definitely ascribed to sulphonamide intoxication, this was the clinical impression that led to a cessation of therapy. He had then received carbutamide for 11 days, the overall amount totalling 20 g. During the subsequent three weeks, without any insulin, his clinical condition showed material improvement and his glycosuria remained low for a long time. During most of this time he continued to excrete detectable amounts of sulphonamide in his urine; indeed, 10 days after his last dose of carbutamide his urine sulphonamide output over a 24-hour period was 13 mg. This may, in part at least, be the explanation for the control of the glycosuria and the blood-sugar levels. Soon all the features of diabetes returned and insulin had to be reintroduced.

Case 3

A boy aged 11 years was admitted to hospital in March, 1957, with diabetic symptoms of about two months' duration his acidosis was negligible. On a diet containing 220 g. of

carbohydrate (with unmeasured protein and fat) he was satisfactorily stabilized on 32 units of insulin zinc suspension.

Carbutamide therapy was then instituted, and in this instance the dosage was aimed at maintaining his fasting blood sulphonamide level at approximately 15 mg./100 ml. Fig. 3 records his progress. His fasting blood-sugar levels

FIG. 3.—Progress and treatment in Case 3.

were well controlled, but his urinary sugar output remained elevated. Here, too, gradual but progressive clinical deterioration set in despite a falling excretion of sugar in his urine, and carbutamide therapy was stopped after 27 days, by which time he had received a total of 19 g. Although his blood-sugar and urine output remained low his clinical state did not improve, and insulin therapy had to be reintroduced within two weeks. Thereafter progress was uneventful.

Summary

Three children whose diabetes was of very recent origin and who had little or no ketosis have been studied as in-patients.

The hypoglycaemic action of carbutamide has been demonstrated, and in two was associated with a reduction in the glycosuria. Such effects were achieved only with relatively high and potentially dangerous blood sulphonamide levels, and evidences of ill-health of a non-specific character, presumably due to sulphonamide intoxication, soon developed. These studies support the view of others that carbutamide has no place in the treatment of diabetes in childhood, even although the disease is of very recent origin and uncomplicated by ketosis. Attention was focused on these children on the assumption that they might still have some effective endogenous insulin (Wrenshall and Best, 1956), and whether the failure to respond to the drug signifies that this assumption is erroneous or that the action is in no way dependent on endogenous insulin remains unanswered. No investigations have been undertaken to ascertain whether carbutamide will reduce the exogenous insulin requirements, as it is considered that such properties would not have any practical advantages in the treatment of diabetes in this age group.

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OBSERVATIONS ON THE MEDICAL CONDITION OF MEN IN THE SEVENTH DECADE

BY

R. G. BROWN, B.A., Ph.D.

Lecturer in Social Medicine, University of Birmingham

THOMAS McKEOWN, M.D., D.Phil., M.R.C.P.

Professor of Social Medicine, University of Birmingham

AND

A. G. W. WHITFIELD, M.D., Ph.D., F.R.C.P.

Assistant Physician, United Birmingham Hospitals;

Lecturer in Medicine, University of Birmingham

Discussion of the age of retirement has hitherto been handicapped by lack of information about the extent to which the medical condition of individuals in the seventh decade restricts or prohibits their employment. Our knowledge of morbidity in the elderly is derived chiefly from inquiries which have had much wider objectives, and the numbers in the appropriate age group were inevitably small (Sheldon, 1948; Hobson and Pember-ton, 1955; Richardson, 1956). If medical evidence is to assist retirement policy it is evidently required in sufficient detail to show the changes in physical capacity from year to year. Accordingly we have attempted to complete a medical examination of approximately the standard required for life insurance purposes in a group of representative men aged 60-69. The material is presented in two parts. Part I is concerned with the incidence of disease and its variation according to age and social class. Part II examines the effect of disease upon fitness for employment, and considers the significance of the results in relation to the broad question of retirement policy.

I. DISEASE INCIDENCE

It was thought that the most satisfactory means of obtaining a full medical examination of representative persons was to invite the co-operation of a number of general practitioners. Eleven Birmingham doctors consented to examine all men on their lists who were aged 60-69. It was estimated that there would be a little over 1,000—approximately 100 in each year of age—and, as it was not possible to increase the total substantially above this figure, it was thought better to restrict the inquiry to males rather than to obtain a much smaller number of examinations for both sexes. The doctors were chosen because of the representative character of their practices and because of their interest and experience in research; several of them are active members of the research panel of the College of General Practitioners.

There were 1,243 men in the appropriate age group, of whom 1,062 were examined (Table I). Of the remainder, 21 had died, 58 were untraced, and 102 were not examined

for other reasons. As the doctors made a serious attempt to see all individuals in their own homes or in their surgeries, we are satisfied that no serious bias has been introduced. Perhaps the most satisfactory test of the representativeness of the sample is its distribution according to age and social class (based on occupation). The 1951 Census has provided recent information about the composition of the total male population in the decade, and the distributions are compared in Tables II and III. The sample is evidently representative by age, and in respect of social class differs only by a small deficiency of men in class IV.

TABLE I.—Number of Men Aged 60-69 on the Lists of 11 General Practitioners

	No.	%
Men examined	1,062	85.4
Men not examined	21	1.7
{ Dead	21	1.7
{ Untraced ..	58	4.7
{ Other	102	8.2
Total	1,243	100.0

TABLE II.—Age Distribution

Age (Years):	60	61	62	63	64	65	66	67	68	69	Total
Birmingham { No. (sample) %	115 10.8	140 13.2	130 12.2	108 10.2	111 10.5	103 9.7	96 9.0	79 7.4	91 8.6	89 8.4	1,062 100.0
England and Wales* %	11.7	10.9	11.0	10.7	10.3	10.0	9.4	8.9	8.7	8.4	100.0

* From 1951 Census.

TABLE III.—Social Class Distribution

Social Class	Birmingham (sample)		England and Wales* (Men Aged 60-69) %	Birmingham County Borough* (Men Aged 15 and Over) %
	No.	%		
I	28	2.6	3.5	2.2
II	159	15.0	17.5	11.5
III	614	57.8	43.4	59.0
IV	108	10.2	17.1	14.3
V	153	14.4	18.5	13.0
Total	1,062	100.0	100.0	100.0

* From 1951 Census.

The information recorded in the inquiry was as follows.

(a) *Medical Data.*—The medical examinations were of "life insurance" type. In most cases they included a chest radiograph, and, whenever necessary, appropriate specialist investigation. Coronary disease was the subject of a separate inquiry, and all men with suggestive signs or symptoms were referred to one of us (A. G. W. W.) at a hospital clinic for full cardiological assessment.

(b) *Smoking Habits and Physical and Mental Demands of Occupation.*—The inquiry provided an opportunity to explore further the possible significance of these variables in relation to disease, particularly coronary disease. The method used in recording amounts smoked was that employed in other inquiries (Doll and Hill, 1950). A man was regarded as a smoker if at any time he had smoked 1 cigarette a day (or $\frac{1}{2}$ oz.—14 g.—of tobacco a week) for a year. Smokers were asked at what age they started, how much they were smoking at the time of inquiry, or, if they had given up smoking, the age at which they stopped and the amount smoked immediately before. The method of assessment of the physical and mental strain imposed by an occupation has been described elsewhere (Brown, Davidson, McKeown, and Whitfield, 1957).

(c) *Employment and Fitness for Employment.*—Doctors recorded information about each individual's occupation, and attempted to assess fitness for employment at the time of examination. These subjects are discussed in Part II, where the methods are described.