Halsted, J. A., Adams, W. S., Sloan, S., Walters, R. L., and Bassett, S. H. (1951a). *Proceedings of the Second Clinical A.C.T.H. Conference*, 2, 489. Churchill, London.
—— —— —— —— —— (1951b). *Gastroenterology*, 19, 698.
Hillemand, P., and Gilbrin, E. (1951). *Arch. Mal. Appar. dig.*, 40, 1328.
Kirsner, J. B., and Palmer, W. L. (1951). *J. Amer. med. Ass.*, 147, 541.
—— —— and Klotz, A. P. (1950). *J. Lab. clin. Med.*, 36, 846.
Machella, T. E., and Hollan, O. R. (1951). *Amer. J. med. Sci.*, 221, 501.
Redish, M. H. (1951). *Gastroenterology*, 18, 179.
Tulin, M., Kern, F., and Almy, T. P. (1952). *J. Amer. med. Ass.*, 150, 559
Wilson, D. A. W., and Roth, D. (1953). Ibid., 152, 230.
Wirts, C. W., and Carroll, J. L. (1952). *Rev. Gastroent.*, 19, 13.
—— Rehfuss, M. E., and Yantes, H. A. (1954). *J. Amer. med. Ass.*, 154, 36.

ARE DIABETIC DEGENERATIVE COMPLICATIONS PREVENTABLE?*

BY

D. M. DUNLOP, M.D., F.R.C.P.

Professor of Therapeutics and Clinical Medicine, University of Edinburgh

There are few diseases about which we are so knowledgeable and yet so ignorant as diabetes mellitus. We realize how the metabolic disturbance conflicts with physiological integrity, and how by taking even a little thought and modest action the diabetic can avoid the immediate lethal effects of the disease, which were so formidable in the pre-insulin era, and can live a life, for a considerable time at any rate, which is not far short in well-being from that enjoyed by normal people. Nevertheless the diabetic state itself is so far incurable, and we are largely ignorant not only of its aetiology but also of the cause of most of its complications.

When I was a student and young doctor we were entirely occupied, so far as diabetes was concerned, with endeavouring to keep the patient alive for a while, and, apart from gangrene, we were taught little of its ultimate complications, for relatively few patients had by then lived long enough to develop them. To-day the problem is not so much that of the acute disease as exemplified by diabetic coma, for we know or ought to know how to avoid that disaster, as it is of a chronic disorder with a considerable expectation of life which involves a prolonged effort to avoid the degenerative complications which so commonly ensue. These are most distressing when they occur in relatively young patients in the third or fourth decade—when, if they were not diabetic, they might expect to be in the prime of life—and are particularly tragic when they involve blindness. Are these complications to be regarded fatalistically as being due to something inherent in the diabetic process, like the large babies of diabetic and pre-diabetic mothers—the inevitable sequel in a shorter or longer time, of the diabetic state? Or can they be prevented by care and trouble directed to the control of the metabolic disturbance?

Two Points of View

In my younger days I had no doubts on this point. If you were a good diabetic and kept the commandments you not only remained well so far as good nutrition and the avoidance of ketosis were concerned but you avoided the later complications of the disorder; whereas if you were bad you reaped the harvest of tares. I think it was the study of diabetic pregnancy and the high foetal loss rate which occurred in the pre-diabetic obstetrical history of the mothers which introduced doubt into my simple faith and ushered in a period of agnosticism, during which time I flirted with the use of the so-called "free diets" in treatment. In this system hyperglycaemia and glycosuria were largely disregarded and the criteria adopted to govern insulin dosage were freedom from hunger, thirst, nocturia, and ketosis, and the maintenance of weight and energy on the one hand; and the avoidance of hypoglycaemia on the other. It did not matter very much how great the quantity of sugar lost in the urine so long as enough insulin was administered to ensure an efficient carbohydrate utilization from the abundant intake.

The advocates of this system—and there were and still are many—claim that patients benefit psychologically from this form of treatment through freedom from irksome restrictions imposed upon their daily life; that "each meal which should be an elegant satisfaction of appetite is not turned into a problem in arithmetic and a trial of self-abnegation"; that patients are better nourished and therefore more resistant to infections, including tuberculosis; that in children growth and sexual development are satisfactory; and that in women the incidence of pregnancy is high. Lichtenstein (1945), who followed up a group of patients so treated for ten years, claimed that the incidence of degenerative complications in them was not unduly high. Dolger (1947), who observed 200 diabetics over a period of 20 years, found that vascular disease occurred neither sooner nor more frequently in those with persistent glycosuria than in those kept relatively sugar-free. A similar conclusion was reached by Goodof (1945) in relation to the nephropathy of diabetes. As for diabetic retinopathy, Ballantyne (1946) stated: "The outstanding paradox is the lack of any apparent relation between the severity of diabetes, the control of the condition by treatment, and the presence or absence of retinal changes." Goadby (1950) and Hunt (1951) are both sceptical of the value of careful dietetics in the prevention of the vascular complications. Finally, there is Mirsky's (1946) profoundly pessimistic profession of therapeutic nihilism, which also contains a statement of the obvious: "It makes little difference how the diabetic is treated; if he lives long enough, he will develop one or another form of vascular disease."

Opposed to this point of view are those who believe that every effort should be made to restore physiological conditions, including freedom from glycosuria and a normal blood-sugar concentration so far as this is possible. Joslin, with his vast experience of diabetes, has thundered against the *laisser faire* heresy in its treatment with a puritanical evangelistic fervour. Good diabetic control, he maintains, can be reached only along the thorny path of scrupulous dietetics, and the sin of diabetics who reject this commandment is sure to find them out in a shorter or longer time (Joslin *et al.*, 1952). During the last five years several surveys have been made by other workers (Whittaker, 1949; Jackson *et al.*, 1950; Root *et al.*, 1950; Wilson *et al.*, 1951a, 1951b, 1951c; Spoont *et al.*, 1951; Beaser, 1951; Hall, 1952; Keiding *et al.*; 1952) which have suggested that there is an undoubted correlation between the control of the disease and the incidence of its complications.

The "Free Diet"

Some years ago we (Forsyth, Kinnear, and Dunlop, 1951) published the result of our observations on 50 diabetics treated with a "free diet" for five years. During that time seven patients—all of them young—showed a progressive worsening of their diabetic state and had to revert to controlled diets. The change was also necessary for two patients who suffered from frequent insulin reactions, and for two others who became obese and developed pruritus. The results, however, were satisfactory in the remaining 39 patients in whom episodes of ketosis or hypoglycaemia were not more numerous than in other patients treated on more conventional lines, and their general health and happiness seemed in some respects to be superior. It was fortunate that we stressed the fact that five years was much too short a time on which to base conclusions regarding the

*Extract from the Lumleian Lectures on the "Complications of Diabetes" delivered at the Royal College of Physicians on April 6 and 8, 1954.

TABLE I.—50 *Diabetics Treated with a "Free" Diet*

1945–50:		
Progressive deterioration in sugar tolerance	7	
Frequent severe hypoglycaemia	2	11
Obesity and pruritus	2	
1950–4:		
Obesity and pruritus	3	
Tuberculosis (all forms)	9	
Retinopathy, neuropathy, etc.	14	30
Cardiovascular deaths	4	
Satisfactory		9

desirability of the regime. For, as can be seen from Table I, the results in this group of patients during the succeeding four years have been disastrous, particularly as regards the incidence of tuberculosis. Only 9 of the original 50 patients are still in good shape at the end of nine years. The series is small but nevertheless suggestive. No random selection of groups of 50 diabetics on controlled diets has shown such unfavourable results over the same period.

Diabetic Control in Presence of Complications

In preparation for this lecture I have, during the last few months, personally examined 167 patients who have attended our dietetic department for periods of time varying from 15 to 31 years, and have attempted to correlate the degree of control of their diabetes with the incidence of tuberculosis, neuropathy, and degenerative complications. None of the patients were very mild diabetics in that they had all required at least 20 units of insulin a day during the many years of their attendance, but they were otherwise unselected. I awarded marks to each patient according to the number and severity of the five main complications present—tuberculosis, retinopathy, cardiovascular disease, nephropathy, and neuropathy—three marks being given for severe, two for moderate, and one for slight involvement in each case. Thus a severely tuberculous, blind, hypertensive, gangrenous diabetic with advanced nephropathy and neuropathy would score the possible—15; while a patient with no complications at all, to whom Joslin would give a gold medal, would score 0.

From the records which we keep in our department I attempted to separate the degree of diabetic control achieved in each case into three main classes—good, fair, and poor. This was not easy to do. The treatment of most diabetics viewed in retrospect constitutes a record of success and failure, of discipline and licence. The requirements I adopted before classifying a patient in the good class, were, however, very stringent. Any long period of significant glycosuria or even a short one of severe ketosis disqualified the patient from that class. The out-patient case sheets of the patients accepted for the good class thus disclosed year after year a record of sugar-free tests when they reported, or only occasional and moderate glycosuria. It has to be realized, however, that the diabetic condition of no patient requiring a significant amount of insulin is perfectly controlled over 15 to 31 years' time, in the sense that the urine is *always* sugar-free and the blood *always* normoglycaemic. One deals perforce with individuals whose diabetes has been under varying degrees of inadequate control and one speaks of the best of them as having good control. Nevertheless, I think rough justice was done in the classification.

Table II shows the results. Of the 167 patients, 75 (45%) had to be classified as having been under poor control because during their 15 to 31 years of diabetes hyperglycaemia and glycosuria had been very common and incidents of ketosis not infrequent; 53 (32%) had been much better controlled though their records were by no means unblemished; and there were 39 patients who were accepted for the class of good control according to the rather stringent qualifications already outlined. The patients in the three classes were not dissimilar in the number of old or young in each, and they were all, as has been said, taking over 20 units of insulin a day. It will be seen, however, that the marks allotted to them for complications were strikingly different—the complication index in the poor control group being three times that in the good-control group.

TABLE II

Control	No. of Patients	Total Score	Average per Patient
Good	39 (23%)	66	1·7
Fair	53 (32%)	149	2·8
Poor	75 (45%)	382	5·1

Of the 167 patients, only 27 (16%) seemed to be entirely free from complications and achieved in consequence 0 marks. Again it will be seen (Table III) that such patients were four to five times more common in the good than in the poor group.

TABLE III.—*Incidence of Complications*

	Good	Fair	Poor	Total
No. of patients	39 (23%)	53 (32%)	75 (45%)	167 (100%)
No. without complications	13 (33%)	9 (17%)	5 (7%)	27 (16%)
No. with retinopathy	17 (44%) **1·6**	25 (47%) **1·7**	59 (79%) **2·0**	101 (60%)
No. with C.V.S. complications	18 (46%) **1·2**	33 (62%) **1·5**	54 (72%) **1·6**	105 (63%)
No. with nephropathy	2 (5%) **2·0**	4 (8%) **2·0**	26 (35%) **2·1**	32 (19%)
No. with tuberculosis	2 (5%) **1·5**	3 (6%) **1·7**	6 (8%) **2·2**	11 (6%)
No. with neuropathy	9 (23%) **1·0**	28 (53%) **1·5**	61 (81%) **1·7**	98 (59%)

Bold figures give the average severity index: maximum 3.

When the incidence and the severity of individual complications are examined similar trends are obvious and invariable. Out of the 167 patients, 101 (60%) had ophthalmic complications. These were more numerous and severe in the poorly controlled group in comparison with those well controlled—those with fair control occupying an intermediate position (Table III).

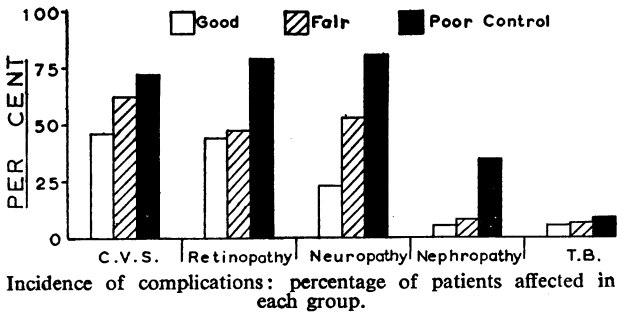
Cardiovascular complications, as evidenced by hypertension, coronary disease, defective pulsation in the dorsalis pedis and posterior tibial arteries, calcification of arteries, or gangrene, were present in 63% of the patients—the incidence and severity showing the same trends as before in the three groups (Table III).

Nephropathy was present in 19% of the patients, being very much more common in the poorly controlled group (Table III).

Six per cent. of the patients were tuberculous. Though the trend is the same, the figures are too small to be significant (Table III).

Neuropathy was present in 98 (59%) of the patients, and of all the complications its incidence and severity presented the most striking correlation with the degree of control achieved (Table III). Diabetic retinopathy, nephropathy, and neuropathy are all, in some as yet ill-understood way, the result of the metabolic disorder, but whereas the incidence of the two former is considerably affected by the duration of the diabetes the incidence of neuropathy is determined almost entirely by neglect of diabetic control.

These figures, which are summarized in the Chart, are not unlike those obtained from similar recent surveys by other workers, and particularly the extensive studies of Wilson



Incidence of complications: percentage of patients affected in each group.

et al. (1951a, 1951b, 1951c). As the result of this and my experience of "free diets" I have returned to my original simple diabetic faith. I believe that whatever specific aetiological factors may be causing diabetic degenerative lesions—endocrine, infective, or metabolic—the careful control and

aggressive treatment of the disorder over the years is a most important factor in their prevention or postponement. I believe that to obtain good control diabetic diets should not usually contain much more than 200 g. of carbohydrate; that patients should be initially trained in the hard school of food-weighing, for it is only in that way that they learn to appreciate quantities; and that they should report regularly to a diabetic clinic to be assessed as regards symptoms, weight, glycosuria, and occasionally blood-sugar concentration, and, depending on the findings, to have their insulin dosage and diet suitably altered, for it is most exceptional to encounter a well-controlled diabetic who has been made entirely responsible for his own treatment.

REFERENCES

Ballantyne, A. J. (1946). *Trans. Ophthal. Soc. U.K.*, **66**, 503.
Beaser, S. B. (1951). *New Engl. J. Med.*, **244**, 714.
Dolger, H. (1947). *J. Amer. med. Ass.*, **134**, 1289.
Forsyth, C. C., Kinnear, T. W. G., and Dunlop, D. M. (1951). *British Medical Journal*, **1**, 1095.
Goadby, H. K. (1950). *St Thom. Hosp. Rep.*, **6**, 5.
Goodof, I. I. (1945). *Ann. intern. Med.*, **22**, 373.
Hall, G. F. M. (1952). *Quart. J. Med.*, **21**, 385.
Hunt, B. (1951). *Med. J. Aust.*, **1**, 114.
Jackson, R. L., Hardin, R. C., Walker, G. L., Hendricks, A. B., and Kelly, H. G. (1950). *Pediatrics*, **5**, 959.
Joslin, E. P., Root, H. F., White, P., and Marble, A. (1952). *The Treatment of Diabetes Mellitus*, 9th ed. London.
Keiding, N. R., Root, H. F., and Marble, A. (1952). *J. Amer. med. Ass.*, **150**, 964.
Lichtenstein, A. (1945). *Acta Pediat., Stockh.*, **32**, 556.
Mirsky, I. A. (1946). *Diabetes Abstr.*, **5**, 71.
Root, H. F., Sinden, R. H., and Zanca, R. (1950). *Amer. J. digest. Dis.*, **17**, 179.
Spoont, S., Dyer, W. W., Day, R., and Blazer, H. (1951). *Amer. J. med. Sci.*, **221**, 490.
Whittaker, H. (1949). *Practitioner*, **163**, 413.
Wilson, J. L., Root, H. F., and Marble, A. (1951a). *New Engl. J. Med.*, **245**, 513.
——, —— —— (1951b). *Amer. J. med. Sci.*, **221**, 479.
—— —— —— (1951c). *J. Amer. med. Ass.*, **147**, 1526.

SULPHONAMIDE PROPHYLAXIS IN CHRONIC BRONCHITIS

A CLINICAL TRIAL

BY

G. S. KILPATRICK, M.B., M.R.C.P.Ed.

AND

P. D. OLDHAM, M.A.

(From the Pneumoconiosis Research Unit of the Medical Research Council, Llandough Hospital, near Cardiff)

A clinical trial was carried out to determine whether the continuous administration of small doses of one of the sulphonamide drugs through the winter months would reduce the frequency and severity of the attacks of "winter bronchitis" which are common in cases of pneumoconiosis, emphysema, and "chronic bronchitis." The seriousness of the problem in general practice has been emphasized by Pemberton (1949) and Fry (1953, 1954), while Goodman *et al.* (1953) have stressed its importance as a cause of morbidity and mortality in the country. Energetic treatment by means of penicillin and streptomycin (Mulder *et al.*, 1952) is usually effective in an established attack, but if prophylaxis were possible much disability might be prevented and economy of hospital facilities achieved.

Plan of Investigation

Strict criteria for the suitability of a subject for inclusion in the trial were laid down initially. Subjects were included only if they gave a clear-cut history of having had an attack of increased cough and purulent sputum, necessitating their going to bed or being off work for more than one day, in each of the two previous winters. Those with conditions such as rheumatic or hypertensive heart disease, cor pulmonale, rheumatoid arthritis, or pulmonary tuberculosis, which might lead to periods of illness unassociated with bronchitis, were excluded. A medical and industrial history was taken from each subject, followed by a clinical examination and a chest radiograph. The appearance of the sputum was noted, but no bacteriological examinations were made.

Methods of Assessment.—Previous experience suggested that all attacks of "bronchitis" were not similar and that a satisfactory classification and method of assessment would not be easy. This difficulty has been noted by Lister (1949), Oswald *et al.* (1953), and Fry (1954). We paid particular attention to the subject's history of the types of attack experienced, which were classified as follows:

Type A1.—A typical unmodified attack of winter bronchitis as severe as any previous one, with increased cough and purulent sputum causing the subject to stay off work and usually retire to bed.

Type A2.—A less severe variant of A1, the subject not having to stay off work, there being less cough, and the sputum being less in both amount and purulence.

Type B.—An attack of tightness of the chest or bronchial spasm without any change in cough or sputum.

Type C.—A typical "head cold" or influenza without involvement of the lower respiratory tract.

It was decided that the attacks should be assessed by one person, and, although some difficulty in classification was occasionally encountered, on the whole the system worked well.

The investigation took place in two stages, while the subjects fell into three separate groups.

Stage I

Group 1.—In the winter of 1951–2 35 subjects were selected from men with pneumoconiosis (simple or complicated) who had attended the Pneumoconiosis Research Unit and from men with emphysema and "chronic bronchitis" who were under the care of general practitioners near Llandough Hospital. It had been hoped that a much larger number of suitable subjects would be found: the trial was begun in November, and extra subjects were included, as they became available, until the beginning of January, when it was decided that further additions should cease. As they were selected, subjects were allocated to either a "treated" or a "control" group on a random basis in such a way that neither they nor the medical assessor knew to which group they had been assigned.

The treated group were given one tablet of sulphadimidine (0.5 g.) three times a day (on waking, at mid-day, and before retiring), and the control group an indistinguishable but inert tablet at the same times. The purpose of the trial was explained to each subject's own doctor in a letter, and each subject was issued with one week's supply of tablets at a time, with written instructions on when to take them; it was explained that they must report any sore throat or skin rash. The majority of subjects started taking the tablets in November, and the remainder had begun by the beginning of January; all stopped at the end of April. Information on the date and duration of any illness or absence from work was obtained weekly, and a clinical examination was carried out monthly. Frequent interviewing is considered very important, as people with chronic cough and sputum often have difficulty in establishing the precise date of onset of an attack of bronchitis.

When the results of this first small experiment had been evaluated it was found that differences suggestive of a benecial effect of the drug had occurred. It was therefore decided to start a subsequent trial rather earlier in the autumn and increase the number of subjects. Accordingly, Stage II of the trial was planned for the winter of 1952–3, this time using two groups of subjects chosen in exactly the same way.

Stage II

Group 2.—This group comprised 30 men from a factory in a South Wales valley employing a large proportion of ex-coal-miners with pneumoconiosis.