Proc. Nutr. Soc. (1973), **32**, 199

Diabetes mellitus and obesity

By JOYCE D. BAIRD, *Department of Medicine, University of Edinburgh, Western General Hospital, Edinburgh*

It has been shown that in the population as a whole, both the amount of fat in the body and the concentration of glucose in the blood are distributed as a continuum in which there is no clear division into normal and abnormal sub-groups (Sharp, Butterfield & Keen, 1964). The application of fixed criteria in the diagnosis of both obesity and diabetes has therefore been arbitrary, and the incidence and prevalence of these conditions has depended not only on the methods used to detect and measure them, but also on the diagnostic criteria set. These difficulties have emphasized the need for a different approach, and recently the possibility of relating blood glucose concentration and body-weight to any adverse consequences, and of reducing these effects by treatment, have been explored. In this approach, diagnostic criteria used are those which will select persons needing treatment.

Association of diabetes and obesity with vascular disease

Life insurance statistics have consistently shown that: significantly higher mortality is found among subjects having greater than average body-weight than subjects of average and less than average body-weight; the greater the degree of over-weight, the greater the excess mortality; the excess mortality can be diminished by reducing body-weight (Society of Actuaries, 1959; Clark & Preston, 1965). Thus body-weight can be used as an index of body fat, in the clinical context.

Over the past decade, it has been established that there is a relationship between the concentration of glucose in the blood and arterial disease. The evidence for this has come from various sources (Sharp, *et al.* 1964; Epstein, Ostrander, Johnson, Payne, Hayner, Keller & Francis, 1965; Hayward & Lucena, 1965; Kannel, Castelli & McNamara, 1967; Pell & D'Alonzo, 1970).

The question of whether treatment can diminish this risk remains open (Wilson, Martin & Hartcroft, 1969; Keen, 1970; Paasikivi, 1970; University Group Diabetes Programme, 1970). It has been suggested that increased risk of death from coronary artery disease results from treatment with sulphonyl-ureas (University Group Diabetes Programme, 1970). Nevertheless there is some justification for regarding glucose intolerance, defined according to classical criteria, as a quantitative risk factor in relation to arterial disease and, therefore, as a valid clinical entity.

Incidence and prevalence of obesity and diabetes

Montegriffo (1971) has recently estimated that in the United Kingdom, 47% of persons between the ages of 25–70 years weigh more than the desirable (based on

mortality statistics) body-weight and has also provided evidence that the incidence of obesity has increased significantly in this country over the past 20–30 years.

Using urine testing as a screening procedure followed by a glucose tolerance test in those with glycosuria, and applying diagnostic criteria similar to those recommended by a WHO Committee on diabetes (WHO, 1965), it has been shown with remarkable consistency in several population surveys in the sixties, that the over-all prevalence of diabetes in this country was about 1% of the population (Redhead, 1960; Walker & Kerridge, 1961; College of General Practitioners, 1962; Harkness, 1962; Butterfield, 1964). However, when glucose tolerance tests are performed on the whole population, without regard to the presence or absence of glycosuria, the incidence of abnormal glucose tolerance tests is much higher, probably about 6% over-all (College of General Practitioners, 1962). There is a clinical impression that the incidence of clinical diabetes is rising in this country and it is thought that this may be related to the increasing incidence of obesity.

West and Kalbfleisch (1971) have related the prevalence of hyperglycaemia to such variables as socio-economic status, diet, obesity and race in several populations. The most impressive and consistent association observed was between prevalence of diabetes and obesity. Both within and among countries and races, this association was marked. Inter-racial differences in the prevalence of diabetes were small when racial groups were matched for adiposity.

Association of diabetes and obesity

On the basis of chance, it would not be surprising that two such common conditions should co-exist not infrequently, and in a recent study, it was found that 58% of all new cases of diabetes mellitus, occuring within a defined geographical area over a 2-year period, could be classified as obese at diagnosis (Baird, 1973).

However, it was suggested many years ago that it was not by chance that there was an association between diabetes and obesity (John, 1929). One of the earliest studies to provide valid statistical evidence of this was done by Pyke & Please (1957). Further evidence of the association of adult-onset diabetes and obesity has been provided by population surveys (College of General Practitioners, 1962; Fowler, Butterfield & Acheson, 1970) and by studies of sibships in which the *propositi* were diabetic patients aged 45–65 years (Baird, 1973).

Nature of the association between diabetes and obesity

Although there can be little doubt that there is a close association between adult-onset diabetes and obesity, the nature of the relationship between them is doubtful. On the one hand, it is considered that obesity is an integral part of the diabetic state, the result of, rather than the cause of, the diabetes, and, on the other hand, that obesity acts as a diabetogenic factor in those genetically predisposed to develop diabetes.

The first possibility was originally suggested by Vallance-Owen's work with the 'syn-albumin antagonist', a circulating insulin antagonist more antagonistic to the action of insulin on muscle than on fat (Vallance-Owen, 1964). However, this work

has been much criticized, and subsequently the main support for this view has been derived by analogy from the obese hyperglycaemic syndromes found in several species of small laboratory animals (Stauffacher, Orci, Cameron, Burr & Renold, 1971) and by the observations of for example Galton (1966), Feldman, Sender & Siegelaub (1969), Galton & Wilson (1970), and Atkinson & Randle (1972) which suggest that specific abnormalities in enzymatic and hormonal activity may be found in obese diabetic subjects.

The latter is based on the fact that 'simple' obesity is characterized by insulin resistance (Rabinowitz & Zierler, 1961), particularly in muscle (Butterfield & Whichelow, 1968) and hyperinsulinaemia (Karam, Grodsky & Forsham, 1963). Although the mechanisms which induce increased secretion of insulin and resistance to its action in obesity, and the sequence of events which occur in their development are still being investigated (Perley & Kipnis, 1966; Salans, Knittle & Hirsch, 1968; Felig, Marliss & Cahill, 1969; Mahler & Szabo, 1971), it is clear that obesity constitutes a stress on the endocrine pancreas (Ogilvie, 1964). It is postulated that genetically poorly endowed beta cells may be unable to meet the stress of obesity, and that when obesity and an inherited liability to develop diabetes coincide, clinical diabetes results.

Estimates of plasma immuno-reactive insulin (IRI) levels in newly-diagnosed, untreated diabetic subjects support this concept. Although early work with the immunoassay for insulin suggested that maturity-onset diabetes was characterized by hyperinsulinaemia, (Yalow & Berson, 1961), it is now generally agreed that, as a group, newly-diagnosed, untreated, obese diabetic subjects presenting spontaneously because of symptoms of diabetes, show some degree of insulin deficiency in comparison with both non-obese and more particularly with obese non-diabetic subjects (Perley & Kipnis, 1966; Seltzer, Allen, Herron & Brennan, 1967; Baird, 1973). In general, the more severe the degree of impaired carbohydrate tolerance in obese diabetic subjects, the more deficient the insulin response to various stimuli (Crockford, Hazzard & Williams, 1969; McKiddie, Buchanan & Hunter, 1969).

In keeping with their hypoinsulinaemia, obese diabetic subjects have higher fasting plasma non-esterified fatty acid (NEFA) levels and a smaller reduction in plasma NEFA in response to an oral glucose load than obese non-diabetic subjects, but the two groups resemble each other in showing an abnormally low plasma concentration of growth hormone (HGH) in the post-absorptive period (Baird, 1973). In both groups of obese subjects, loss of weight restores the metabolism to normal (Kalkoff, Kim, Cerletty & Ferrou, 1971; Baird, Hunter & Smith, 1973); the post-absorptive HGH peak reappears and in obese non-diabetic subjects the plasma IRI concentration decreases, while in obese diabetic subjects it increases. This would tend to support the view that obesity is not an integral part of the diabetic syndrome, although it certainly does not prove it. Indeed, it has been shown that dietary restriction, not necessarily accompanied by loss of weight, is also associated with improved secretion of insulin in men (Rudnick & Taylor, 1965), and, even when obesity is apparently an integral part of an inherited syndrome, as in the obese hyperglycaemic strains of laboratory animals, dietary restriction or

reduction of body-weight or both may also restore the metabolism to normal, (Batt & Mialhe, 1966; Cahill, Jones, Lauris, Steinke & Soeldner, 1967; Chlouverakis & White, 1969; Dulin & Wyse, 1970; Wyse & Dulin, 1970; Abraham & Beloff-Chain, 1971; York, Steinke & Bray, 1972; Larkins, 1973). Also, when obesity is induced experimentally in animals (Hales & Kennedy, 1964; Farrant, Neville & Stewart, 1969; Larkins, 1973) by injecting gold thioglucose to induce a hypothalamic lesion resulting in hyperphagia, the metabolic abnormalities found are precisely the same as those shown by mice of the obese-hyperglycaemic strain. It seems clear, therefore, that over-eating–obesity can induce marked abnormalities in enzyme and hormonal activity.

Interaction of heredity and environment in the aetiology of maturity-onset diabetes

Attempts have been made to study the interaction of the 'inherited liability to diabetes' (Falconer, 1967) and obesity. In a study of the factors affecting glucose tolerance in obese subjects, Medley (1965) found that the presence of a positive family history of diabetes or a history of big babies was more important in determining abnormal glucose tolerance than either the degree or duration of obesity. Similarly, Chiumello, del Guercio, Carnelutti & Bidone (1969) assessed the influence of obesity in the evolution of diabetes in a group of Italian children. There was no positive relationship between obesity and impaired glucose tolerance curves, except in children with a strong family history of diabetes.

The interactions of obesity and a genetic predisposition to diabetes in the development of clinical diabetes mellitus have been demonstrated also in studies of diabetic sibships and the offspring of diabetic parents (Baird, 1973). In the former studies, three groups of subjects were tested for diabetes and compared in various respects: diabetic subjects aged 45–65 years, the non-diabetic brothers and sisters of these diabetic subjects, and the non-diabetic brothers and sisters of control subjects. It was found that in this group of diabetic subjects, it was possible to distinguish a subgroup with a strong familial tendency from the majority with a relatively weak genetic tendency simply on the basis of their body-weight. Therefore, over-all, 10% of the siblings of diabetic subjects were found to be diabetic, compared with 3·8% of the siblings of control subjects, but while there was no significant difference in the percentage of diabetic subjects between siblings of obese and non-obese control subjects (4·1% and 3·4% respectively), 15% of the siblings of non-obese diabetic subjects were found to be diabetic compared with 7·3% of the siblings of obese diabetic subjects. Furthermore, although the percentage of those found to be diabetic was, over-all, three times higher among the obese subjects compared with the non-obese subjects in both groups of siblings, the diabetogenic effect of obesity was most marked in families where there was a strong genetic tendency to develop diabetes, i.e. among the siblings of non-obese diabetic subjects. Therefore, although only 27% of the siblings of non-obese diabetic subjects were obese compared with 50% of the siblings of obese diabetic subjects, as many as 30% of those who were obese in the former sibships were diabetic. It is difficult to interpret these

results other than by suggesting that obesity acts as a diabetogenic factor in those genetically susceptible.

Summary

Although an inherited liability to develop diabetes is probably the most important single factor leading to the development of clinical diabetes, obesity, acting as a diabetogenic factor, is probably a critical factor in the appearance of diabetes in many instances. Avoidance of over-eating and obesity may prevent the appearance of the clinical syndrome of adult-onset diabetes in many instances.

Obesity and diabetes are separate and distinct risk factors for ischaemic heart disease, and their combined presence in the obese diabetic person may be particularly lethal. Most diabetic patients die from ischaemic heart disease. It is uncertain whether the risk of death from ischaemic heart disease can be reduced by treatment with either insulin or oral hypoglycaemic agents. The risk of death from ischaemic heart disease can however certainly be diminished by reducing body-weight, and this should be the over-riding aim in treating obese diabetic subjects.

REFERENCES

Abraham, R. R. & Beloff-Chain, A. (1971). *Diabetes* **20**, 522.
Atkinson, J. N. C. & Randle, P. J. (1972). *Diabetologia* **8**, 371.
Baird, J. D. (1973). *Publs R. Coll. Physns Edinb.* No. 42, p. 83.
Baird, J. D., Hunter, W. M. & Smith, A. W. M. (1973). *Post-grad. med. J.* **49**, 132.
Batt, R. & Mialhe, P. (1966). *Nature, Lond.* **212**, 289.
Butterfield, W. J. H. (1964). *Proc. R. Soc. Med.* **57**, 196.
Butterfield, W. J. H. & Whichelow, M. J. (1968). *Lancet* ii, 785.
Cahill, G. F. Jr, Jones, E. E., Lauris, V., Steinke, J. & Soeldner, J. S. (1967). *Diabetologia* **3**, 171.
Chiumello, G., del Guercio, M. J., Carnelutti, M. & Bidone, G. (1969). *Diabetes* **18**, 238.
Chlouverakis, C. & White, P. A. (1969). *Metabolism* **18**, 998.
Clarke, R. D. & Preston, T. W. (1965). *Trans. Fac. Actu., Edinb.* **29**, 251.
College of General Practitioners (1962). *Br. med. J.* **1**, 1497.
Crockford, P. M., Hazzard, W. R. & Williams, R. H. (1969). *Diabetes* **18**, 216.
Dulin, W. E. & Wyse, B. M. (1970). *Diabetologia* **6**, 317.
Epstein, F. H., Ostrander, L. D. Jr, Johnson, B. C., Payne, M. W., Hayner, N. S., Keller, J. B. & Francis, T. Jr (1965). *Ann. intern. Med.* **62**, 1170.
Falconer, D. S. (1967). *Ann. hum. Genet.* **31**, 1.
Farrant, P. C., Neville, R. W. J. & Stewart, G. A. (1969). *Diabetologia* **5**, 198.
Feldman, R., Sender, A. J. & Siegelaub, A. B. (1969). *Diabetes* **18**, 478.
Felig, P., Marliss, E. & Cahill, G. F. Jr (1969). *New Engl. J. Med.* **281**, 811.
Fowler, G., Butterfield, W. J. H. & Acheson, R. M. (1970). *Guy's Hosp. Rep.* **119**, 297.
Galton, D. J. (1966). *Br. med. J.* **2**, 1498.
Galton, D. J. & Wilson, J. P. D. (1970). *Br. med. J.* **3**, 444.
Hales, C. N. & Kennedy, G. C. (1964). *Biochem. J.* **90**, 620.
Harkness, J. (1962). *Br. med. J.* **1**, 1503.
Hayward, R. E. & Lucena, B. C. (1965). *J. Inst. Actu.* **91**, 286.
John, H. (1929). *Endocrinology* **13**, 388.
Kalkoff, R. K., Kim, H. J., Cerletty, J. & Ferrou, C. A. (1971). *Diabetes* **20**, 83.
Kannel, W. B., Castelli, W. P. & McNamara, P. M. (1967). *J. occup. Med.* **9**, 611.
Karam, J. H., Grodsky, G. M. & Forsham, P. H. (1963). *Diabetes* **12**, 197.
Keen, H. (1970). *Early Diabetes* p. 437. New York: Academic Press.
Larkins, R. G. (1973). *Diabetes* **22**, 251.
McKiddie, M. T., Buchanan, K. D. & Hunter, I. A. (1969). *Q. Jl Med.* **38**, 445.
Mahler, R. J. & Szabo, O. (1971). *Diabetes* **20**, 336.
Medley, D. R. K. (1965). *Q. Jl Med.* **34**, 111.
Montegriffo, V. M. (1971). *Post-grad. med. J.* **47**, suppl. 418.
Ogilvie, R. F. (1964). *Ciba Fdn Colloq. Endocr.* **15**, 45.
Paasikivi, J. (1970). *Acta med. scand.* Suppl. 507.

Pell, S. & D'Alonzo, C. A. (1970). *J. Am. med. Ass.* **214**, 1833.
Perley, M. & Kipnis, D. M. (1966). *New Engl. J. Med.* **274**, 1237.
Pyke, D. & Please, N. W. (1957). *J. Endocr.* **15**, 26.
Rabinowitz, D. & Zierler, K. L. (1961). *Lancet* ii, 690.
Redhead, I. H. (1960). *Br. med. J.* **1**, 695.
Rudnick, P. A. & Taylor, K. W. (1965). *Br. med. J.* **1**, 1225.
Salans, L. B., Knittle, J. L. & Hirsch, J. (1968). *J. clin. Invest.* **47**, 153.
Seltzer, H. S., Allen, E. W., Herron, A. L. Jr & Brennan, M. L. (1967). *J. clin. Invest.* **46**, 323.
Sharp, C. L., Butterfield, W. J. A. & Keen, H. (1964). *Proc. R. Soc. Med.* **57**, 193.
Society of Actuaries (1959). *Build and Blood Pressure Study*. Chicago: Society of Actuaries.
Stauffacher, W., Orci, L., Cameron, D. P., Burr, I. M. & Renold, A. E. (1971). *Recent Prog. Horm. Res.* **27**, 41.
University Group Diabetes Programme (1970). *Diabetes* **19**, Suppl. 2.
Vallance-Owen, J. (1964). *Ciba Fdn Colloq. Endocr.* **15**, 217.
Walker, J. B. & Kerridge, D. (1961). *Diabetes in an English Community*. Leicester: Leicester University Press.
West, K. M. & Kalbfleisch, J. M. (1971). *Diabetes* **20**, 99.
WHO (1965). *Tech. Rep. Ser. Wld Hlth Org.* No. 310.
Wilson, R. B., Martin, J. M. & Hartcroft, W. S. (1969). *Diabetes* **18**, 225.
Wyse, B. M. & Dulin, B. M. (1960). *Diabetologia* **6**, 268.
Yalow, R. S. & Berson, S. A. (1961). *Diabetes* **10**, 339.
York, D. A., Steinke, J. & Bray, G. A. (1972). *Metabolism* **21**, 277.

Printed in Great Britain