AETIOLOGICAL FACTORS IN DIABETES

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The aetiology of diabetes is not understood. Many facts are known but they have not been put together to form a satisfactory theory.

It is generally agreed that some factors, such as inheritance, obesity and pregnancy, are important and that others, such as hormonal oversecretion, are less important although sometimes significant.

Diabetes can be caused by injury, tumour or inflammation of the pancreas and is invariably caused by its removal. But diabetes due to these disorders is rare, its cause is obvious and it is, for this discussion, unimportant.

The ways in which the various causative factors have their effects—by slowing insulin production, destroying it too quickly or causing the body to become resistant to insulin—are not considered in this discussion.

Age and Sex Incidence

Fig. 1 shows the age and sex distribution of 953 diabetics attending the Radcliffe Infirmary. Among the younger patients there are a few more men than women, but after the age of about forty, women heavily outnumber men. A survey of family doctors in and around Oxford revealed that about 80 to 90 per cent. of their diabetic patients attended this clinic, so these figures are likely to be representative of known cases of diabetes in this area. They are similar to others reported from Britain and North America.

There is some evidence that the sex ratio has changed in this century and that 50 years ago men and women diabetics were about equal in number (Harris and McArthur, 1952).

Inheritance

There has been much discussion and little agreement on how diabetes is inherited. It has long been observed that a larger number of relatives of diabetics than of normal people have diabetes. Among diabetics attending the Radcliffe Infirmary a relative was known to be affected in 30 per cent.—in 10 per cent. a parent, in 10 per cent. a sibling and in 10 per cent. another relative. Among all the parents and siblings of their diabetic patients Pincus and White (1934a) found 6.7 per cent. to be

FIG. 1.—The age and sex distribution of 953 diabetics.

diabetic (9 per cent. of the parents and 5.5 per cent. of the siblings) as compared with 1.2 per cent. of the parents and siblings of a non-diabetic control group.

Harris (1949a) found that 4 per cent. of the siblings of 1,241 diabetics had the disease. This is probably at least five times the number to be expected among the general population. Two striking trends emerged in his study: (a) the siblings tended to develop diabetes at the same age as the probandi. Of 158 siblings 112 developed the disease within 10 years (younger or older) of the probandi. The age at onset was not correlated in parents and offspring. (b) The affected siblings tended to be of the same sex as the probandi, especially among females.

The Effect of Age

The proportion of diabetics with a positive family history of the disease is higher among young than among older patients. Among the Radcliffe Infirmary cases 33 per cent. of diabetics under the age of 45 knew of an affected relative as compared with 30 per cent. over that age, and other series have shown larger differences (Munro, Eaton and Glen, 1949; Watson and Thompson, 1951).

The average age at diagnosis is lower in patients with a family history of diabetes than in those without. Thompson, Laakso and Watson (1950) found that where there was no relative known to

have the disease the average age at diagnosis was 53.8, where the family history was 'positive' it was 47.3, and where a family history was present on both sides of the family 33.1 years.

A family history is found more often among women diabetics than among men. Munro, Eaton and Glen (1949) found that 24 per cent. of the men and 36 per cent. of the women patients under the age of 40 were known to have an affected relative; over 40 the figures fell to 17 per cent. and 23 per cent. respectively. Among the Radcliffe Infirmary series a family history of diabetes was found among 28.6 per cent. of the men and 32.5 per cent. of the women.

In twins, when one has diabetes the other is affected in about 50 per cent. of cases if they are identical, 30 per cent. if non-identical.

There appears to be no relation between birth rank and the tendency to develop diabetes.

Parental Consanguinity

An incidence of parental consanguinity above that to be expected was found by Harris (1949b) among younger diabetics but not among those developing the disease over the age of 30. The difference was slight (in 1,241 cases there were 18 cases of consanguineous marriage instead of the 10 expected) but was considered to be probably significant. If the difference is true it suggests a separate mode of inheritance for the young-onset and old-onset types.

Pincus and White (1934b) found that when both parents were diabetic a quarter of the children were, at the time of the enquiry, known to have diabetes.

If diabetes is a genetically determined disease one might expect that its frequency would be declining, since those affected before or during the reproductive epoch would be likely to have a reduced fertility. Some would die (before the introduction of insulin nearly all did), others would presumably have a lower fertility than normal. Yet, as far as can be judged, diabetes is not declining in frequency. It is more probable that it is increasing (although it is doubtful if accurate figures of incidence exist). This could be due to an unusually high mutation rate, an increase in environmental factors favouring the development of diabetes or to those bearing the genes which might lead to the early appearance of diabetes in their children but not in themselves bearing more children than the rest of the population. The observation that women who develop diabetes in later life have had more children on average than normal women does not, as at first sight it may seem to, support the last suggestion, since the effect of parity seems to be merely to reveal a tendency to diabetes (Pyke, 1956). There is nothing to suggest that the 'pre-

diabetic state' leads to the bearing of more children. It seems improbable that a woman who in 30 years time will develop diabetes will, because of this fact, be more fertile than otherwise.

Genetic Hypotheses

The most popular explanation of the pattern of diabetic inheritance is still that it is caused by a single recessive gene (Pincus and White, 1933). Harris (1949a) suggested that the young-onset type were homozygous, the older-onset type heterozygous. The simple concept of recessive gene inheritance is inadequate to explain all the facts. The proponents of this theory point out that many cases of diabetes are not diagnosed. Steinberg (1958) suggests that 60 to 90 per cent. of those genetically liable to diabetes are not recognized and advocates more vigorous efforts at detection. It seems more probable, however, that there is no simple explanation for the inheritance of diabetes.

The difficulty in defining and diagnosing may be due not only to the inadequacy of our investigating techniques but to there being no clear-cut dividing line between diabetes and normality. It seems probable that the disease is a graded effect and inherited in a similar way to, say, height. This is suggested by the finding of Keen (1957) that 2 per cent. of the first-degree relatives of diabetics had glycosuria one hour after consuming 50 g. of glucose but only 15 per cent. of control relatives did so. The distribution of blood sugar levels in the relatives in the two groups showed no natural division between values regarded as normal and abnormal.

Weight

There are four important criticisms of most of the published work on obesity and diabetes.

(1) No distinction is drawn between fatness and excess of weight. There has been no study of the amount of subcutaneous fat in diabetics—data on 'obesity' have been based on measurements of weight and height or on clinical assessment. They provide poor grounds for judging a patient's fatness, since physique varies greatly from one patient to another.

(2) It is important to standardize the stage in the disease at which the observations are made. The appearance of diabetes is often associated with changes in weight—up or down—and so is the dietary treatment. Thus data collected after treatment has been begun or at the time of diagnosis are not comparable with the greatest weight which the patient has ever reached or recollects reaching, observations quoted by some authors.

(3) Many studies have classified patients as 'obese' without further defining the term either

in pounds or as a percentage above expected weight.

(4) Those studies in which comparison is made with control data have usually had to rely on figures collected by the Association of Life Insurance Directors and Actuarial Society of America. These were collected from candidates for life insurance in New York half a century ago and are not a reliable comparison for figures collected in Britain now.

More satisfactory control data are those of Kemsley (1950, 1952). They are presented in such a way that the *distribution* of weights is given or can be calculated. Most studies of the weights of diabetics have expressed the frequency of excessive weight—usually taken as 10 per cent. or more than the 'expected' weight for the same sex, age and height—without saying how many non-diabetic people might be expected to exceed the mean by this amount.

The conclusions which seem to be warranted concerning the weights of diabetics are (Pyke and Please, 1957):

(1) Diabetics are heavier than non-diabetics (the weight of the diabetics being that recorded at the time when the diagnosis was first made, the data for normal people being those of Kemsley).

(2) Young diabetics are not heavier than non-diabetics. It is not until about the age of 40, rather earlier in women than in men, that newly-diagnosed diabetics are, on average, appreciably heavier than normal people. The mean excess of weight is about 12 per cent. in each sex.

(3) Apart from the slight sex difference mentioned in the previous paragraph there is very little difference in the relative weights of men and women diabetics, contrary to the general clinical impression that women diabetics are fatter than men. The reason for this erroneous impression is probably that normal women are heavier than normal men, especially in middle age which is the time of life when diabetes chiefly occurs. After the age of 40, 27 per cent. of normal women exceed the mean weight for their age and height by at least 10 per cent., whereas only 21 per cent. of men do so.

(4) Weight increases with parity among diabetic women. It is not known whether this increase is greater than among normal women, since satisfactory figures for normal women do not exist. Diabetic women over the age of 45 who have borne two children are, on average, about 12 per cent. heavier than those who have had none, whose average weight is normal; with increasing parity beyond two there is little further increase.

(5) If the weights of a group of diabetics, expressed as a percentage of 'normal' weight, is plotted as a frequency distribution curve (Fig. 2) a

FIG. 2.—The weights of 946 diabetics each expressed as a percentage of 'normal' weight. The frequency distribution curve shows a fairly smooth pattern which does not suggest that there are two types of diabetes distinguishable from each other in terms of weight.

curve is obtained which appears to be fairly smooth. There is no suggestion of a double peak, which one would expect if there were two distinct types of diabetes distinguishable on grounds of weight (which is the basis of most classifications of diabetes into two groups).

There is little doubt that excessive weight plays some part in the aetiology of diabetes in some patients. This is shown by the figures quoted above and by insurance figures (Dublin, 1930) which show a rise of mortality from diabetes of at least fourfold with increasing weight. Those who are under the average weight have a lower mortality than those of average weight. Still more strikingly, reduction of weight may convert a diabetic glucose-tolerance curve to a normal one (Himsworth, 1949a). It is usual for weight reduction to improve carbohydrate tolerance in diabetics who are fat.

The incidence of diabetes in the second half of life seems to decline when food supplies are restricted, as in wartime (Himsworth, 1949b).

Pregnancy

Women diabetics outnumber men in the second half of life.

Various explanations have been put forward to explain the sex difference, in particular that it might be due to more women than men being fat or to the effects of the menopause. However, it was first noticed 25 years ago that the excess of women was confined to married women (Mosenthal and Bolduan, 1933). Munro, Eaton and Glen (1949) suggested that pregnancy might be an important factor, as they found that a higher proportion of their diabetic patients than of normal controls had large families.

Several other authors who have investigated the histories of their diabetic patients in order to determine the frequency of obstetric complications have reported levels of fertility which, although not usually compared with data for normal women, have been suggestively high. In two series control data have been given: Kriss and Futcher (1948) reported that 100 diabetic women had borne 360 children before the disease was diagnosed, whereas 100 women in a control group of similar age had borne only 315. Tomblinson (1954) reported 142 women and 101 men diabetics whose average numbers of children were 3.2 and 2.5 respectively.

That the excess of women diabetics appears to be confined to those who have borne children was shown by Pyke (1956). He found that among a group of 953 diabetics there were no more nulliparous women than might be expected by calculation from the number of men, but that with rising parity the number of women found exceeded the number expected by an increasing margin. Although his estimate of the influence of parity in increasing susceptibility to diabetes was exaggerated it seems likely that women who have borne five or more children are at least twice as liable to develop diabetes as those who have borne none.

The effect of parity is not due to an association with obesity, since women diabetics over the age of 45 outnumber men among those who are underweight and of normal weight as well as among those who are overweight.

It is curious that although multiparous women are more likely to develop diabetes than nulliparous they do not do so any earlier. Pyke (1956) found that the average age at diagnosis among women over the age of 45 was about 60 years, regardless of their parity. If pregnancy has a diabetogenic influence one would expect the disease to appear earlier in those who have had several children than in those who have had none.

The Menopause

The pattern of the curve for age and sex distribution of diabetes suggests that the menopause is an important aetiological factor; but since there appears to be no excess of diabetes among nulliparous women it cannot explain the difference in sex incidence. But it may affect the time of appearance of diabetes.

The Effect of Pregnancy upon a Carbohydrate Tolerance

Studies of the effect of pregnancy upon carbohydrate tolerance have given conflicting results. In one series of 158 normal pregnant women there were no changes in the glucose-tolerance curve as

pregnancy progressed (Cobley and Lancaster, 1955). Intravenous glucose-tolerance tests were similar in 20 pregnant and 11 non-pregnant women (Johnson and Bonsnes, 1948). But Hurwitz and Jensen (1946), who did oral glucose tolerance tests on 25 women in each trimester of pregnancy and one week post-partum, found deterioration in some as pregnancy progressed, with improvement afterwards.

In some women in whom there is suggestive evidence of diabetes—such as a family history of the disease, glycosuria or a history of having borne very heavy babies—there is often evidence of a deterioration of carbohydrate tolerance with pregnancy (Hoet, 1954; Jackson, 1955). Jackson has followed some of these women and has reported that a number have developed diabetes within a few years of a pregnancy or during a subsequent pregnancy. This observation is difficult to reconcile with the finding, mentioned above, that diabetes does not appear earlier in multiparae than in nulliparae.

Thus, although it seems to be true that parity is an aetiological factor in diabetes, it is far from clear how pregnancy predisposes to the disease and what, if any, is the role of the menopause.

Race and Geography

Knowledge of the effects of race upon the incidence and manifestations of diabetes is very imprecise. Joslin's view (1952) is that diabetes is 'universal' and that race is not important in its aetiology. But Hugh-Jones (1955) has reported striking differences between the disease in Jamaica and in Britain and has described cases (6 per cent. of his series) of young, thin diabetics who are persistently resistant to insulin yet have little tendency to become ketotic—an unusual combination of features in this country.

In Trinidad women diabetics outnumber men but the difference appears in the thirties instead of in the forties as in this country. Relatively few young diabetics are found in Trinidad although the general population is younger there than in Britain. Only 2½ per cent. of the patients are under 30 as compared with 7½ per cent. under that age in this country (Hugh-Jones and Pyke, 1958).

Parity is higher in Trinidad than in Britain and is completed earlier. This, one might think, would explain the earlier appearance of the female preponderance but, as in Britain, there appears to be no connection between parity and age at diagnosis. Although diabetic women in Trinidad have borne more children than non-diabetic, those with many children do not develop the disease earlier than those with few (Pyke and Wattle, 1958). In Trinidad there is an excess of diabetic women even among the nulliparae. Parity is not, therefore,

the only explanation of the large excess of women diabetics.

The weight distribution of Trinidad diabetics is different from that in Britain. In Trinidad the young diabetics are heavier and the older ones lighter than in Britain.

In Durban diabetes among patients admitted to hospital was found over 30 times more often among Indians than among Africans (Cosnett, 1957). The female preponderance appeared about 15 years earlier than in this country.

In West and East Africa crude hospital admission rates show diabetes to be commoner among men than among women, but little reliance can be placed upon these results since hospital data are probably not a true reflection of the prevalence of diseases in those areas (Hugh-Jones and Pyke, 1958).

In India the evidence that men diabetics outnumber women is stronger. In a series of 3,500 cases Bose (quoted by Hugh-Jones and Pyke, 1958) found that men diabetics outnumbered women by 3:1 after the age of 25. Other figures from Ceylon (De Zoysa, 1951; World Health Organization, 1955) and Japan (Segi, 1956) also suggest a male preponderance. Segi's figures show an age and sex distribution almost exactly the reverse of the British pattern.

Hormonal Factors

It is tempting to attribute diabetes to the effects of pituitary growth or diabetogenic hormone. This might explain the tendency of diabetic women to produce large babies. But there is nothing to support this suggestion. (1) Acromegals do not always develop diabetes, indeed they do so relatively seldom. (2) The foetuses of acromegals, although probably bigger than normal at birth on average (Jackson, 1955), are not as big as those of diabetic mothers. (3) There is, as a rule, no clinical sign of acromegaly in diabetics. (4) Experimental attempts to produce large foetuses in animals by injecting growth hormone into the mother during pregnancy have been inconclusive (Barns and Swyer, 1952).

In the majority of cases of human diabetes there is no clinical evidence of overactivity of the anterior pituitary. Nor is enough known about glucagon to assign to it any role in the aetiology of diabetes.

Hyperglycaemia and glycosuria may appear temporarily after burns and head injury.

In cases of adrenal cortical overactivity and of steroid administration diabetes may develop. This is more likely to be the case when the patient is predisposed to the disease, for example by inherited tendency (Jackson, 1955). Diabetes associated with steroid administration is uncommon,

it is not permanent and it does not closely resemble the usual clinical picture, in that there is little tendency to ketosis, nor is the condition usually responsive to insulin. Thus, although adrenal steroids can produce a diabetic state, there is no evidence that they are responsible for the ordinary syndrome of diabetes.

Steroids have been used in association with glucose-tolerance tests in order to reveal a tendency to diabetes. In normal people the glucose-tolerance curve is not altered by moderate doses of steroids; in those with known diabetes or with suggestive features of the disease the same dose of steroids may cause a deterioration of carbohydrate tolerance (Duncan, 1956). There is no evidence that this technique has revealed a sharp, natural division between diabetes and normality.

Summary

1. Diabetes is in part genetically determined. Thirty per cent. of diabetics have a relative affected. The mode of inheritance is unknown. Probably no single gene is responsible, the disease being inherited as a graded characteristic.

2. After the age of 40, diabetics tend to be overweight. This is equally true for men and women. Weight reduction usually improves carbohydrate tolerance. There is no evidence of a division of diabetes into two distinct types in terms of weight.

3. The excess of women among diabetics in this country is confined to those who have borne children. With rising parity the liability to diabetes increases. Parity does not, however, lead to the earlier appearance of the disease.

4. The role of the menopause in the aetiology of diabetes is unknown.

5. There appear to be differences in clinical features, age and sex incidence, weight and parity of diabetics in different countries and races.

6. In the great majority of cases of diabetes there is no evidence of disorder of the anterior pituitary or the adrenal cortex.

BIBLIOGRAPHY

- BARNES, H. H. F., and SWYER, G. I. M. (1952), *Brit. med. J.*, **2**, 914.
 COBLEY, J. F. C. C., and LANCASTER, H. O. (1955), *Med. J. Aust.*, **1**, 171.
 COSNETT, J. E. (1957), *South Afr. med. J.*, **31**, 1109.
 DE ZOYSA, V. P. (1951), *Ann. imm. Med.*, **88**, 812.
 DUBLIN, L. I. (1930), *Hum. Biol.*, **2**, 159.
 DUNCAN, L. J. P. (1956), *Quart. J. exp. Physiol.*, **41**, 453.
 HARRIS, H. (1949a), *Proc. roy. Soc. Med.*, **42**, 326.
 HARRIS, H. (1949b), *Ann. Eugen. (Lond.)*, **15**, 95.
 HARRIS, H., and MCARTHUR, N. (1952), *Ibid.*, **16**, 109.
 HIMSWORTH, H. P. (1949a), *Lancet*, **1**, 465.
 HIMSWORTH, H. P. (1949b), *Proc. roy. Soc. Med.*, **42**, 323.
 HOET, J. P. (1954), *Diabetes*, **3**, 1.
 HUGH-JONES, P. (1955), *Lancet*, **ii**, 891.
 HUGH-JONES, P., and PYKE, D. A. (1958), Paper read to the third congress of the International Diabetes Federation, Dusseldorf. Proceedings to be published.

Bibliography continued on page 286.

personal service offered to the old. Undoubtedly the State does much for old people in providing what material comfort it can, and sometimes the personal touch creeps in: but it is obviously difficult for the machinery of State to provide this touch, and it is to local and voluntary efforts that we must turn. Branches and clubs may well be the means of contributing very largely to the relief of distress in the aged diabetic.

Old age can be a time of great unhappiness or of calm and contentment. These states are not entirely dependent on physical health but may often be due to the withholding or giving of loving care. We must do all we can to help from the material angle but, and this is important, we must also give that extra loving kindness which will do so much to ensure a peaceful Indian summer for the aged diabetic.

Bibliography continued from page 265—D. A. Pyke, M.D., M.R.C.P.

- HURWITZ, D., and JENSEN, D. (1946), *New England J. Med.*, **234**, 327.
 JACKSON, W. P. U. (1955), *Lancet*, **ii**, 625.
 JOHNSON, D. G., and BONSNES, R. W. (1948), *J. clin. Invest.*, **27**, 145.
 JOSLIN, E. P. (1952), in 'The Treatment of Diabetes,' London.
 KEEN, H. (1957), Paper read to Banting Memorial Meeting of the British Diabetic Association, Oxford.
 KEMSLEY, W. F. F. (1950), *Ann. Eugen. (Lond.)*, **15**, 161.
 KEMSLEY, W. F. F. (1952), *Ibid.*, **16**, 316.
 KRISS, J. P., and FUTCHER, P. H. (1948), *J. clin. Endocr.*, **8**, 380.
 MOSENTHAL, H. O., and BOLDUAN, C. (1933), *Amer. J. med. Sci.*, **186**, 605.
 MUNRO, H. N., EATON, J. C., and GLEN, A. (1949), *J. clin. Endocr.*, **9**, 48.
 PINCUS, G., and WHITE, P. (1933), *Amer. J. med. Sci.*, **186**, 1.

- PINCUS, G., and WHITE, P. (1934a), *Ibid.*, **188**, 159.
 PINCUS, G., and WHITE, P. (1934b), *Ibid.*, **188**, 782.
 PYKE, D. A. (1956), *Lancet*, **i**, 818.
 PYKE, D. A., and PLEASE, N. W. (1957), *J. Endocr.*, **15**, xxv.
 PYKE, D. A., and WATTLE, G. H. (1958), unpublished observations.
 SEGI, M. (1956), 'Statistical Report on Patients in Tohoku University Hospital, 1953-54,' Sendai, Japan.
 STEINBERG, A. G. (1958), *Diabetes*, **7**, 244.
 THOMPSON, M. W., LAAKSO, L. E., and WATSON, E. M. (1950), *Canadian med. Ass. J.*, **63**, 556.
 TOMBLESON, S. B. (1954), *N.Z. med. J.*, **53**, 230.
 WATSON, E. M., and THOMPSON, M. W. (1951), *Amer. dig. Dis.*, **18**, 326.
 World Health Organization (W.H.O.) (1955), 'Annual Epidemiological and Vital Statistics, 1952.'

Bibliography continued from page 280—Harry Keen, M.B., M.R.C.P.

- HAND, B. H., and PATEY, D. H. (1953), *Brit. J. Surg.*, **41**, 161.
 HANDELSMAN, M. B., LEVITT, L. M., and CONRAD, H. (1952), *Amer. J. med. Sci.*, **224**, 34.
 HICKAM, J. B., and PRYOR, W. W. (1951), *J. clin. Invest.*, **30**, 401.
 HIRSON, C., FEINMANN, E. L., and WADE, H. J. (1953), *Brit. med. J.*, **i**, 1408.
 HODGES, F. R., RUNDLES, R. W., and HANELIN, J. (1947), *Radiology*, **49**, 659.
 JANOWITZ, H. D., and GROSSMAN, M. I. (1950), *J. invest. Derm.*, **14**, 453.
 JEFFERS, W. A., MONTGOMERY, H., and BURTON, A. C. (1941), *Amer. J. med. Sci.*, **202**, 1.
 JORDAN, W. R. (1936), *Arch. intern. Med.*, **57**, 307.
 JORDAN, W. R., and CRABTREE, H. H. (1935), *Ibid.*, **55**, 17.
 KASSANDER, P. (1953), *Ann. intern. Med.*, **48**, 797.
 KEEN, H., FIELD, J. B., and JACKSON, D., to be published.
 KERSLAKE, D. McK., and COOPER, K. E. (1950), *Clin. Sci.*, **9**, 31.
 LEARMONTH, J. R. (1931), *Brain*, **54**, 147.
 LEWIS, T. (1933), *Clin. Sci.*, **1**, 175.
 LISTER, J., and MAUDSLEY, R. H. (1951), *Lancet*, **ii**, 1,110.
 MACLEAN, E. R., and ALLEN, E. V. (1940), *J. Amer. Med. Ass.*, **115**, 2,162.
 MALINS, J. M., and FRENCH, J. M. (1957), *Quart. J. Med.*, **26**, 467.
 MARBLE, A. (1940), in 'Treatment of Diabetes Mellitus,' 7th Ed., Lea and Febiger, Philadelphia.
 MARBLE, A. (1952), *Ibid.*, 9th Ed.
 MARTIN, M. M. (1952), 'M.D. Thesis,' Univ., Durham.
 MARTIN, M. M. (1953), *Lancet*, **i**, 560.
 MARTIN, M. M. (1953), *Brain*, **76**, 594.
 MEGIBOW, R. S., MEGIBOW, S. J., POLLACK, H., BOOKMAN, J. J., and OSSERMAN, K. (1953), *Amer. J. Med.*, **15**, 322.
 MENDLOWITZ, M., GROSSMAN, E. B., and ALPERT, S. (1953), *Ibid.*, **15**, 316.
 MURI, J. W. (1953), *Acta med. scand.*, **146**, 143.
 NAUNY, B. N. (1906), in 'Der Diabetes Mellitus,' 2nd Ed., Holder, Vienna.

- OAKLEY, W. G. (1949), *Trans. med. Soc. Lond.*, **66**, 270 (discussion).
 OAKLEY, W., CATTERALL, R. C. F., and MARTIN, M. M. (1956), *Lancet*, **ii**, 953.
 ODEL, H. M., ROTH, G. M., and KEATING, F. R. (1955), *Diabetes*, **4**, 92.
 PARSONS, H., and NORTON, W. S. (1951), *New Engl. J. Med.*, **244**, 935.
 PAVY, W. F. (1885), *Lancet*, **ii**, 1,033 and 1,085.
 PICKERING, Sir G. W. (1958), *Ibid.*, **i**, 1 and 59.
 ROOT, H. F., and KENNY, A. J. (1952), in 'Treatment of Diabetes Mellitus,' 9th Ed., Lea and Febiger, Philadelphia.
 RUBIN, A., and BABBOTT, D. (1958), *J. Amer. med. Ass.*, **166**, 498.
 RUDY, A., and MUELLNER, R. S. (1941), *J. Urol (Baltimore)*, **45**, 844.
 RUNDLES, R. W. (1945), *Medicine (Baltimore)*, **24**, 111.
 RUNDLES, R. W. (1950), *Bull. N.Y. Acad. Med.*, **26**, 598.
 SHEPPE, W. M. (1953), *Ann. intern. Med.*, **39**, 625.
 SHERIDAN, E. P., and BAILEY, C. C. (1946), *J. Amer. med. Ass.*, **130**, 623.
 SHUMACKER, H. B. (1942), *Bull. Johns Hopk. Hosp.*, **71**, 1.
 SHUMAN, C. R., and GILPIN, S. F. (1954), *Amer. J. med. Sci.*, **227**, 612.
 SIMPSON, S. L. (1950), *Brit. med. J.*, **i**, 692.
 SMIRK, F. H. (1957), 'High Arterial Pressure,' Blackwell Scientific Publications, Oxford.
 SMITH, H. W. (1951), 'The Kidney,' Oxford University Press.
 SMITH, M. D. (1949), *Glasg. med. J.*, **30**, 181.
 SPRING, M., and HYMES, J. (1953), *Diabetes*, **2**, 199.
 STRAUSS, E. B. (1950), *Brit. med. J.*, **i**, 697.
 SWARTS, J. M., and STINE, L. A. (1948), *Amer. J. Med.*, **5**, 61.
 VEREL, D. (1951), *Brit. Heart J.*, **13**, 61.
 WAYTE, J. H., and BEETHAM, W. P. (1935), *New Engl. J. Med.*, **212**, 367, 429.
 WHITE, J. C., and SMITHWICK, R. H. (1944), 'The Autonomic Nervous System,' 2nd Ed., Kimpton, London.
 WILKINS, R. W., NEWMAN, H. W., and DOUPE, J. (1938), *Brain*, **61**, 290.
 WOLTMAN, H. W., and WILDER, R. M. (1929), *Arch. intern. Med.*, **44**, 576.