Diabetes Mellitus and Cancer

In theory it should be a fairly easy matter to see whether there is any difference between diabetic and non-diabetic persons in their risk of developing cancers of various sites. In theory, also, differences one way or the other might be expected in view of Otto Warburg's[1] observation that normal and tumour tissues differ in the way they metabolize glucose. In practice there are considerable difficulties. Criteria for the diagnosis both of diabetes and of cancer have to be defined, and in retrospective epidemiological studies it may be difficult to know whether or not particular criteria have been fulfilled and, if so, the ages at which they were first fulfilled in individual patients.

The fact that cancer and diabetes may occur together in the same patient has never been in serious doubt,[2] and for many years an association between diabetes and cancer of the pancreas has been evident. A. Marble,[3] as long ago as 1934, reported the coincidence of cancer and diabetes in 256 out of 10,000 diabetics. Of the 256 cancers, 33 (13%) were of the pancreas, a proportion that is much higher than seen in non-diabetics. An obvious explanation of an association between pancreatic cancer and diabetes would be destruction of islet cells by tumour, but experienced surgeons, such as Rodney Smith,[4] regard diabetes mellitus as a rare complication of destruction of pancreas by tumour, for "even an extremely small amount of normal pancreas remaining will avoid this complication."

This was broadly the state of knowledge before the recent publication of Irving I. Kessler's study.[5] Kessler ascertained the cancer mortality until 1959 among 21,447 patients registered at the large Joslin clinic for diabetes in Boston during the 26 years from 1930 to 1956. Before June 1939 the diagnosis of diabetes was established by a venous blood sugar (Folin-Wu) of 130 mg. or more per 100 ml. blood (fasting) or 170 mg. or more per 100 ml. (after a meal), in association with glucosuria which was plainly related to diet. After June 1939 the critical fasting blood-sugar level was 140 mg. per 100 ml. The criteria for death from cancers and other causes were the entries on death certificates, coded according to the International List.[6 7] Only patients who survived for at least one year after the first diagnosis of diabetes were included in the survey. The observed number of deaths from each cause was compared with the expected number, calculated from age- and sex-specific death-rate data published in the *Annual Reports* of the *Vital Statistics of Massachusetts.*

Among men with diabetes, death from cancer of all types occurred less frequently than expected. Deficiencies in deaths from cancers of the respiratory tract and of the rectum were partly responsible for this difference, the rest of which was mainly due to an increased risk of other causes of death, particularly diabetes itself and coronary heart disease. Despite the overall deficiency of cancer deaths in the male diabetics they experienced the expected excess risk of death from pancreatic cancer.

Among women with diabetes, deaths from cancers of all types were only slightly, and not significantly, more numerous than expected. However, this overall comparison hides a significantly increased risk of pancreatic cancer and a significantly decreased risk of cancer of the uterus, both of the body and of the cervix.

The interpretation of the diminished risk of respiratory cancer in diabetic males in Kessler's survey is complicated by the fact that 17% of them were Jews as compared with only 5% of the control population. The genetic constitution of the Jew, which is known to favour the development of diabetes, might protect against respiratory carcinogens. Alternatively, cigarette smoking might have been more prevalent among the control population either because of its lower proportion of Jews or for some other reason. In any event, the low risk of cancer of the uterine body in the diabetic females cannot be due to an excessive representation of Jews since this form of cancer is more common in Jewish than in gentile women.

The elucidation of most of the complex problems raised by Kessler's findings must await the results of further studies. Only in the case of the positive association between diabetes and pancreatic cancer, which is unequivocal in both sexes, is it reasonable to proceed to the next level of inquiry—namely, a consideration of the mechanisms involved. The requirement that patients could be included in the survey only if they survived for more than one year after the diagnosis of diabetes reduced the likelihood of cancer of the pancreas being the antecedent disease. However, this possibility is not eliminated as a partial explanation, since in 11 out of the 78 cases the cancer was diagnosed within one year of the first diagnosis of diabetes. The observation[8] of progressive pancreatic duct hyperplasia in diabetes is compatible with the operation of common aetiological factors, genetic or environmental or both. On the other hand there is no evidence to support the hypothesis that bovine or porcine insulin, which have been shown to be both antigenic and teratogenic,[9] are also carcinogenic for the pancreas in man.

[1] Warburg, O., *The Metabolism of Tumours.* London, Constable, 1930.
[2] Schäfer, O., *Carcinom und Diabetes.* Augsburg, Rösler, 1934.
[3] Marble, A., *New England Journal of Medicine,* 1934, **211**, 339.
[4] Smith, R., in *Cancer,* ed. R. W. Raven, Vol. 2, p. 186. London, Butterworths, 1958.
[5] Kessler, I. I., *Journal of the National Cancer Institute,* 1970, **44**, 673.
[6] U.S. Bureau of the Census, *Manual of the International List of Causes of Death,* 5th revision. Washington, D.C., U.S. Government Printing Office, 1938.
[7] World Health Organization, *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death,* 7th revision. Geneva, World Health Organization, 1957.
[8] Sommers, S. C., Murphy, S. A., and Warren, S., *Gastroenterology,* 1954, **27**, 629.
[9] Ingle, D. J., *Diabetes,* 1965, **14**, 93.

The Nation's Health

Though 1969 produced the lowest infant mortality and stillbirth rates ever recorded in England and Wales, some other indices of health give reason for disquiet.

In his latest annual report[1] the Chief Medical Officer of the Department of Health and Social Security records the expectation of life at 1 year old in 32 countries. The figures are mostly based on experience in the first half of the 1960s. In contrast to what is generally believed, England and Wales makes a remarkably poor showing. In no fewer than 17 countries males have a longer expectation of life. Among them are the Irish Republic, the Scandinavian countries, Switzerland, Spain, Bulgaria, East Germany, and Poland. For females five countries offer a longer expectation of life. They are France, Iceland, Netherlands, Norway, and Sweden. Prominent among the variety of reasons for British males' relatively low life expectancy must be the large number of deaths due to lung cancer from smoking of cigarettes. No doubt there are others—and in any case the figures for all the countries

[1] Chief Medical Officer of the Department of Health and Social Security, *Annual Report for the Year 1969, On the State of the Public Health.* London, H.M.S.O., 1970.