

CANCER OF THE UTERUS (BODY AND CERVIX) AND GLUCOSE TOLERANCE

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In the world-wide search for the cause of cancer innumerable avenues have been explored and metabolic factors have been extensively studied. In 1934 Marble⁵² reviewed 256 cases of malignant disease of all types in which diabetes was known to be present. After a careful analysis of these cases, she came to the conclusion that diabetes does not predispose to cancer, nor cancer to diabetes, but that 'both diseases occurred more commonly in the aged'. However, in 1948, Jacobson⁴⁰ studied all the cancers that occurred among a very large series of diabetics, and he concluded that the incidence of all cancers 'is somewhat higher among diabetics than among non-diabetic individuals'.

These 2 workers based their conclusions on a study of cancers generally and not on any specific type of cancer. However, in the 2 decades that followed their publications increasing evidence appeared to show that the association of endometrial cancer and diabetes mellitus was much more significant. Many articles were published supporting this contention,^{80, 57, 21, 48} but as many refuted it.^{68, 78, 26, 65, 59} This controversy is still raging in the gynaecological literature and the present investigation was carried out in an attempt to establish, if possible, whether a definite association exists or not.

THE CONTROVERSY

The evidence in favour of a high incidence of diabetes in cases of endometrial cancer is appreciable (Table I). Figures which have received much attention in the English literature are those of Stanley Way.⁸⁰ In 1954 he reported that as many as 29% of 106 patients with cancer of the endometrium had unquestionable diabetes, and a further 43% had 'a pre-diabetic type of glucose-tolerance curve'. This remarkably high incidence of frank diabetes was found by other investigators as well; Moss⁵⁷ found 39% of diabetics among 23 patients with cancer of the endometrium, Garnet²¹ demonstrated that 33% of 50 consecutive cases suffered from diabetes, and Louw⁴⁸ found a high incidence of 38% as well.

All these figures are impressive, but there have been as many publications showing that the incidence of diabetes is not increased in cases of endometrial cancer (Table I). Smith⁶⁸ found only 4% of diabetics among 307 of his cases, Vander⁷⁸ only 5.6%; Hertig and Somers,²⁶ 9%; Scheffey *et al.*,⁶⁵ 11%; and Palmer *et al.*,⁵⁹ 16.9%.

Why are these reports so contradictory? The discrepancy in the results is considerable. If the methods by which the various authors arrived at the diagnosis of diabetes are carefully analysed, one obvious reason for the different findings becomes apparent.

Table I shows how the diagnosis was made, and gives the results obtained. It is obvious that whenever the cases were fully investigated by glucose-tolerance tests, a high

TABLE I. INCIDENCE OF DIABETES MELLITUS AND OF MILDLY IMPAIRED GLUCOSE TOLERANCE IN CASES OF CANCER OF THE ENDOMETRIUM

	No. of cases	Impaired glucose tolerance			How diabetes was diagnosed
		Diabetic	Not frank diabetic	Total	
		%	%	%	
Moss ⁵⁷	23	39	26	65	Glucose-tolerance tests.
Garnet ²¹	50	33	33	66	Glucose-tolerance tests.
Way ⁸⁰	106	29	43	72	Glucose-tolerance tests.
Louw ⁴⁸	60	38			Glucose-tolerance tests.
Present series	50	28	24	52	Glucose-tolerance tests.
Smith ⁶⁸	307	4			Clinically diabetic.
Vander ⁷⁸	483	5.6			Glycosuria; and then only fasting blood sugar.
Hertig and Somers ²⁶	500	9			Clinically diabetic.
Scheffey <i>et al.</i> ⁶⁵		11			Clinically diabetic.
Palmer <i>et al.</i> ⁵⁹	165	16.9			Raised fasting blood sugar.

incidence of diabetes mellitus was found. In each and every series where the incidence of diabetes was lower, routine glucose-tolerance tests had not been done. The disease had been diagnosed only when the patient was a gross or obvious diabetic (e.g. where there was clinical evidence of diabetes, glycosuria, or raised fasting-blood sugar). In the series showing a low incidence of diabetes, therefore, only the most severe diabetics were discovered (and then probably not all of them), while many of the less severe cases, as well as all cases of mildly impaired glucose tolerance, were missed. This closer analysis of the literature as well as the present investigation show that there is no doubt of the high incidence of diabetes and of mildly impaired glucose tolerance in cancer of the endometrium, provided glucose-tolerance tests are carried out.

Even these proved high figures, however, are not significant unless they are compared with suitable control subjects who do not suffer from cancer of the endometrium. Obviously they also have no meaning unless the difference between the control and cancer groups is statistically significant.

An exploration of the literature does not reveal any control group that is suitable for comparison. Several diabetes-detection drives have been carried out to determine the incidence of diabetes mellitus in the general population.^{3-5, 7, 19, 20, 22, 41, 42, 44, 50, 62, 67, 73, 79, 82, 83}

Such bulk population surveys are well exemplified by the United States Public Health Service investigation.⁵² A survey was carried out in the town of Oxford, Massachusetts, which has a population of about 5,000. The survey included 2,468 women, and the incidence of diabetes in the whole group, i.e. women of all ages, was only 1.8%. But it was found that age had an important influence, and in the group over 45 years of age (the age group where cancer of the endometrium is most common), the incidence was between 4 and 7%. But how was this population investigated? Obviously glucose-tolerance tests could not be carried out on each person. The only tests that were made were those on a blood sample and a specimen of urine taken 1 hour after a meal. So this was a most inexact method of determining the glucose tolerance, and such a group is quite unsuitable as a control for cancer cases, where a full glucose-tolerance test should be done on each patient. But this survey showed the rising incidence of diabetes with age, especially after the age of 45 years, a finding confirmed by practically all workers in this field.^{1,11,8,61,66,69-72} The many other diabetes-detection drives reported in the literature were carried out in a similar way and the findings were similar; these, too, cannot serve as control series.

INVESTIGATION

It became necessary, therefore, to investigate our own control groups, as well as our cancer patients. The controls had to be strictly comparable with the cancer cases; they had to be of the same age groups, the conditions of the study had to be similar, and the subjects had to be drawn from the same population.

Each subject in the control and cancer group was submitted to the same glucose-tolerance test (the 'standard' 50 g. oral glucose test). As is well known, many exogenous factors may influence the glucose-tolerance curve.^{2,6,9,10,13,17,18,23-25,27-31,33-35,45,47,51,52,54-56,58,63,64,74-77,81} Accordingly, in each case an unrestricted carbohydrate diet was allowed for several days before the test, and as far as was known, the subjects were not suffering from any infection, hepatic disease, or any of the numerous other factors which may influence the curve. The same method of taking and examining the blood samples was applied to every subject, capillary blood being tested by the Hagedorn-Jensen method. In the majority of cases the test was repeated after an interval of at least a week to eliminate any errors, technical or otherwise.

The same standard of interpretation was placed on the results, the curves being divided into the 3 generally accepted groups: (1) A normal glucose-tolerance curve (the normal curve was regarded as one where the fasting level was below 120 mg., the highest level below 200 mg., and the 2-hour level below 120 mg. or at the most 140 mg. per 100 ml.); (2) unquestionable diabetes (this was shown by a curve where the fasting blood sugar was above 120 mg. per 100 ml., and where the 2-hour level was greatly elevated); and (3) a mildly impaired glucose-tolerance curve (also called the 'pre-diabetic' or 'mildly diabetic' curve by various authors^{15,16,32,36-38,43,48}). Group 3 included cases where the fasting level was below 120 mg. per 100 ml., but where the 2-hour level was elevated above 120 mg. and especially above 140 mg. per 100 ml.;

or where the 1-hour level was above 200 mg. per 100 ml. The importance of these minor aberrations in the curve has been stressed and has been generally accepted in recent years.^{12,14-16,32,36-39,41,43,46,49}

Control Group

Glucose-tolerance tests were carried out on 100 random gynaecological patients of 45 years of age and over, who were not suffering from cancer of the endometrium or cervix. These patients were drawn from the same population as the cancer groups. They all had pelvic pathology and abnormal vaginal bleeding—similar conditions to those pertaining in the cancer patients, and conditions which themselves might possibly alter the sensitive glucose-tolerance curve. In every case the endometrium was examined histologically, and was shown to be normal. The results are tabulated in Table II. Seventy-eight% had normal glucose-tolerance curves; 13% had diabetic curves and 9% mildly impaired curves. This incidence of 13% diabetics was much higher than that found in any of the diabetes-detection drives for the same age groups (4-7%). This showed that the glucose-tolerance test is a strict criterion of carbohydrate metabolism, and that a great many patients with impaired glucose tolerance are not detected unless full glucose-tolerance tests are done.

Cancer of the Cervix

The second control group consisted of 50 consecutive patients with cancer of the cervix, of 45 years of age and over. These patients were drawn from the same population as the endometrial cancer group. It was considered that this group would act as a most suitable control—the subjects were of the same ages, were drawn from the same population, and also suffered from uterine cancer (of a different form). The findings, shown in Table II, indicated that there was no appreciable difference in glucose tolerance between patients suffering from cervical cancer and those in the non-cancer control group.

Endometrial Cancer

Having thus obtained 2 suitable control series, we were in a position to compare these with the patients we investigated who had cancer of the endometrium, again of the same age groups, and drawn from the same population. The results are seen in Table II. Abnormal glucose-tolerance curves were present in 52% (28% had frankly diabetic curves, and 24% less severely impaired curves). This incidence of 52%, compared with 22% and 20% in the control groups, is high, and when analysed, is statistically significant.

TABLE II. GLUCOSE-TOLERANCE CURVES IN CONTROL SERIES, IN CASES OF CANCER OF THE CERVIX, AND IN CASES WITH ENDOMETRIAL CANCER

	Normal curves	Abnormal curves		
		Diabetes	Mildly impaired glucose tolerance	Total
Controls (100)	78%	13%	9%	22%
Cancer of the cervix (50)	80%	12%	8%	20%
Cancer of the endometrium (50)	48%	28%	24%	52%

DISCUSSION

All this confirms conclusively the significantly high incidence of diabetes mellitus and lesser grades of impaired glucose tolerance in patients with endometrial cancer. On the other hand it also indicates that in cancer of the cervix the incidence of diabetes and 'pre-diabetes' is not raised.

It is not the purpose of this article to consider the importance of this finding. The implications may be far-reaching, and may, for example, help to throw light on the cause of cancer of the body of the uterus. It may also help to explain certain clinical observations. For example, among Japanese women cancer of the cervix is very common but cancer of the endometrium is practically unknown,⁶⁰ and diabetes mellitus is rare in Japan;⁶⁰ among Jewesses cancer of the cervix is very rare, whereas endometrial cancer and diabetes are both commonly found in the Jewish race.⁶⁰ The main reason for this investigation was to establish whether this high incidence of disturbed glucose tolerance is factual or not. Otherwise attempts to explain this phenomenon, or research studies following on it, may have been based on a false premise. The literature to date has been singularly contradictory and it is difficult or impossible to assess the true state of affairs from it. It is submitted that our findings settle the issue conclusively.

SUMMARY AND CONCLUSIONS

1. In the literature of the past 20 years there have been highly conflicting views on whether diabetes mellitus is more common among patients with endometrial cancer than among women who do not suffer from this disease. The present investigation was made in an attempt to resolve the controversy.

2. The reasons for these contradictory reports are analysed.

3. Studies were made of 2 suitable control series as well as of a group of patients with endometrial cancer. A distinctly raised incidence of impaired glucose tolerance was found in the latter group, and this incidence, on analysis, is statistically significant.

4. The incidence of disturbed glucose tolerance in cancer of the cervix was not raised when compared with a suitable control group.

5. It is submitted that our findings confirm conclusively that there is a significant association between endometrial cancer and diabetes mellitus. No such association was found in patients with cancer of the cervix uteri.

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