intestinal absorption through obstruction of the lacteals by mesenteric lymph nodes is also a possible contributory factor.

The explanation of the unusual haematological findings in Case 2 is not easy. In this case, in addition to macrocytosis and an increased reticulocyte count, there were numerous nucleated red cells, mainly with pyknotic nuclei, Howell-Jolly bodies, Pappenheimer bodies, and a number of Heinz bodies in the peripheral blood; the bone-marrow contained a smaller number of intermediate megaloblasts. Such findings occur sometimes in idiopathic steatorrhoea with atrophy of the spleen, which in turn is thought to be due to folic-acid deficiency (Nieweg and Arends, 1953). In this case the red-cell anomalies could have been due to the small and pathological spleen. In view of the patient's condition it was impossible to carry out tests confirming the presence of folic-acid deficiency.

Macrocytic anaemia with Howell-Jolly bodies and target cells was observed in a further case of febrile subacute Hodgkin's disease in which Reed-Sternberg cells were found in the bone-marrow and the spleen was small and atrophic.

Summary

Two cases of unusual presentation of Hodgkin's disease are reported: one appeared to be an acute abdomen, the other a possible case of steatorrhoea. No lymphadenopathy was demonstrable clinically or radiologically in either case and the spleen was if anything atrophic. In the first, a case of acute Hodgkin's disease, Reed-Sternberg cells were circulating in the blood, and their discovery in the blood smears led to the diagnosis. In the second case the diagnosis was reached from the sternal puncture carried out for the purpose of investigating a macrocytic anaemia.

Both patients had macrocytic anaemia, leucopenia, and thrombocytopenia. The haematological findings are discussed.

It is suggested that cases of pyrexia of unknown origin presenting with the above haematological picture be carefully scrutinized for the presence of sternal tenderness.

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C

GLUCOSE TOLERANCE IN DYSFUNCTIONAL UTERINE BLEEDING AND IN CARCINOMA OF ENDOMETRIUM

A PRELIMINARY REPORT

BY

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"and now remains
That we find out the cause of this effect,
Or rather say, the cause of this defect,
For this effect defective comes by cause."

Hamlet, II, ii.

Investigations have been carried out in the gynaecology department of the Groote Schuur Hospital, Capetown, to determine the value of glucose-tolerance studies in cases of abnormal uterine bleeding of both benign and malignant origin. Studies were made of patients at the climacteric as well as in other age-groups. The results have been correlated in each case with the histological picture of the endometrium. Some interesting and significant findings have come to light, so that, though the work is still in a preparatory stage, it is considered that a preliminary report is warranted.

Several investigators have found that the incidence of diabetes mellitus and of impaired glucose tolerance is high in cases of carcinoma of the body of the uterus. Way (1954) reported that 29% of such patients had frank diabetes mellitus, and a further 43% showed a "pre-diabetic type of glucose-tolerance curve." Similar figures were found by Garnet (1958), and the findings of many other writers confirmed this abnormality, though most figures are not as striking as those of Way and of Garnet (Hertig and Sommers, 1940; Scheffey *et al.*, 1943; Moss, 1947; Palmer *et al.*, 1949; Louw, 1958; Noble and Attwood, 1958). Other workers, however, have failed to find a positive association between diabetes mellitus and carcinoma of the endometrium. Such reports include those of Marble (1934), Smith (1941), Jacobson (1948), and a recent one from Vander (1959); the latter found an incidence of 5.6% of diabetics, which is not higher than the incidence of diabetes in the general population of the same age and sex. The conflicting reports must in part, at least, be due to the lack of careful and adequate controls in the same age-groups; and few of these cases had been fully investigated by glucose-tolerance tests.

In view of the divergent reports, we first investigated patients with carcinoma of the body of the uterus, together with control subjects of the same age-groups. The work was then extended to embrace all cases with abnormal uterine bleeding, and especially those with benign glandular hyperplasia of the endometrium. So far the following groups have been studied by carrying out glucose-tolerance tests in each case and by correlating the results with the histological picture of the endometrium: (1) One hundred random women of 45 years of age and over who were not suffering from cancer of the endometrium or benign glandular hyperplasia. (2) Fifty cases of cancer of the endometrium. (3) Fifty patients who were proved by histological examination of the endometrium to have benign glandular hyperplasia.

On account of the recognized effect of age on glucose tolerance it was considered essential that the various groups should all be of the same ages.

Choice of Glucose-tolerance Test

Duncan (1952) states that the standard oral glucose-tolerance test is the most exacting test and, when properly assessed, the test of choice for determining, in doubtful cases, the presence or absence of diabetes mellitus. There is fairly general agreement about this in the literature, and the "standard one-dose (50 g.) oral glucose test" is probably the most satisfactory (Moyer and Womack, 1950; Jackson, 1952).

Accordingly, the following criteria formed the basis of the glucose-tolerance tests used in this investigation.

(1) An unrestricted carbohydrate diet was allowed for several days before the test, the subjects not suffering from any infection or known hepatic disease. (2) The blood was taken half-hourly, beginning with a fasting specimen and continuing at least up to two hours. Fasting and hourly urine specimens were also taken. (3) Capillary blood was used. It is easier to obtain and does not miss the "lag type of curve" (Jackson, 1952). Capillary blood gives the same fasting reading as venous, but after glucose it is higher to a variable degree (up to 50 mg.). (4) The Hagedorn-Jensen method of estimating glucose was used.

Interpretation of Glucose-tolerance Tests

According to Duncan (1952), curves are considered indicative of diabetes if the fasting blood-sugar level exceeds 120 mg./100 ml., or if the two-hour value exceeds 130 mg./100 ml.; when the diabetes is of a mild nature the fasting blood-sugar may be normal, while the two-hour specimen is elevated. Jackson (1952) adduced evidence to show that values above 140 mg. at two hours and above 130 mg. at two and a half hours in the oral glucose-tolerance test were highly suggestive, if not pathognomonic, of pre-diabetes; in a larger series Jackson (1953) later confirmed this view. Similar tolerance curves and similar conclusions have since been reported by Kritzer (1952), Lund and Weese (1953), and Hoest and Lukens (1954). At first the *British Medical Journal* (1952) doubted the significance of such small aberrations in the glucose-tolerance curve, but later (1959) it stated that "in Britain particular attention is paid to the two-hour value, figures in excess of 100 mg. 'true' glucose per 100 ml. being regarded with suspicion." Lawrence (1947) was quoted in support of this statement.

Peak values above 180 mg./100 ml. are attributed to rapid intestinal absorption if the two-hour figure is near normal, but Joslin *et al.* (1952) do not recognize this "lag" type of curve as a separate entity and regard the height of the peak, rather than a two-hour value, as evidence of potential abnormality. Kritzer (1952) regarded a "positive" glucose-tolerance curve as one which showed a value of 200 mg./100 ml. or greater in the first hour, above 150 mg. in the second hour, and over 125 mg. in the third hour. Jackson (1957), having followed up 10 patients with "pre-diabetes," found that every patient yielded a more definite abnormality after at least three years. He stated that these results demonstrate clearly the significance of the minor aberrations in the glucose-tolerance test which he labelled "pre-diabetic."

In view of the conclusions drawn from all these studies, the following interpretation was placed on the

glucose-tolerance results obtained in this investigation: (1) A normal glucose-tolerance curve: the normal curve was regarded as one where the fasting level is below 120 mg., the highest level is below 200 mg., and the two-hour level is below 120 mg. or at most 140 mg. (2) Unquestionable and possibly severe diabetes: a fasting level above 120 mg. and a two-hour level which is greatly elevated. (3) The third group is the most difficult to classify, and, as stated above, has been labelled "pre-diabetic" or "mildly diabetic." We have preferred to label this group "mildly impaired glucose tolerance." This group includes cases where the fasting level is below 120 mg. but the two-hour level is above 140 mg., or the peak, after half an hour, is above 200 mg.

Results

Using the glucose-tolerance test aforementioned on each subject investigated, and placing the same standard of interpretation on the results, the following groups were studied. In view of the known effect of age on glucose tolerance, this factor was constantly taken into consideration.

1. Women Who Acted as Control Subjects

One hundred consecutive women of 45 years of age and over who were not suffering from cancer of the endometrium or benign glandular hyperplasia were submitted to glucose-tolerance tests. These were in-patients and out-patients attending the Groote Schuur Hospital who were seen because of unrelated diseases, such as prolapse, fibroids, leucorrhoea, backache, cervical pathology, etc. In each case the endometrium was examined histologically, the specimen having been obtained by endometrial biopsy, curettage, or hysterectomy. If the endometrium was found to be hyperplastic or carcinomatous the case was excluded. All these women therefore had a normal endometrium—an endometrium which either was proliferative or secretory or was physiologically atrophic owing to the menopause.

This group was unselected in that it consisted of random consecutive gynaecological patients of 45 years of age and over. The majority of them, however, did have vaginal bleeding of varying degree and pelvic disease. It was therefore thought that this was the best type of control group for comparison with cases of cancer of the endometrium and benign glandular hyperplasia; for here we have a most comparable group of the same ages, and usually with pelvic disease as well—a condition similar to that which pertained in the other two groups.

The results are shown in the accompanying Table.

Glucose Tolerance in Control Subjects, in Cases of Cancer of the Endometrium, and in Patients with Benign Glandular Hyperplasia

Group Investigated	Normal Curves	Abnormal Curves		
		Diabetes	Mildly Impaired Glucose Tolerance	Total
100 control subjects	78%	13%	9%	22%
50 cases with cancer of endometrium	48%	28%	24%	52%
50 cases with benign glandular hyperplasia	16%	20%	64%	84%

2. Cases With Cancer of the Endometrium

Under the same conditions, 50 consecutive cases of cancer of the endometrium were investigated by glucose-tolerance tests. In order to compare this group with the

100 controls, only those who were 45 years of age and over were included. The results are summarized in the Table.

3. Cases With Benign Glandular Hyperplasia

So far 50 consecutive patients who were proved by histological examination of the endometrium to be suffering from benign glandular hyperplasia have been investigated along the same lines for glucose tolerance. Again the results are shown in the Table, and the curves of the first 25 consecutive cases are reproduced in the accompanying Figure.

The most striking findings were those obtained in the cases of benign glandular hyperplasia. In this group it was found that as many as 84% of the curves were abnormal. Most of the aberrations in the curves were not gross—22% were diabetic-type curves, and 62% showed less severely impaired glucose tolerance. This figure is considerably higher than that found in the control group (84% compared with 22%) and is statistically most significant; it is also appreciably higher than that obtained in cases of cancer of the endometrium (52%).

There is another reason why the findings in this group are most significant. The increasing incidence of diabetes with age is well known. All the control subjects, as well as the patients with cancer of the endometrium, were 45 years and over, and many were old women. But in this series with benign glandular hyperplasia the average age was low: 6 were under 35 years, 7 were between 35 and 44, 22 between 45 and 54, and 15 between 55 and 64 (the oldest patient was 63 years of age).

The number of cases is not large, but in view of the remarkable and statistically very significant findings this investigation is proceeding, and every case of abnormal endometrial bleeding that is encountered at this age is being investigated for glucose tolerance so as to obtain a much larger series.

Glucose-tolerance curves in 25 patients with benign glandular hyperplasia: Nos. 1-6, unquestionable diabetes; Nos. 7-22, impaired glucose tolerance; Nos. 23-25, normal glucose tolerance.

Discussion

This is preliminary report—a much larger number of cases are being and will be investigated. With the aid of careful controls the association of impaired glucose tolerance and cancer of the endometrium has been confirmed. The most striking result of the investigation, however, is even higher incidence (84%) of impaired glucose tolerance in patients with benign glandular hyperplasia. In spite of the relatively small number of cases, both these figures are found, on analysis, to be most significant statistically. The abnormality of carbohydrate metabolism was so frequent in cases with a hyperplastic endometrium and so relatively unusual where the endometrium is normal or atrophic that further studies are being carried out in a larger series. The glucose-tolerance test has become a more or less routine investigation in our department for such cases. An attempt is also being made to find the cause of this association by (a) endocrine assays of gonadotrophic hormones, (b) the administration of oestrogens, progesterone, and gonadotrophic hormones in suitable subjects, preceded and followed by glucose-tolerance tests.

The finding of this common factor (disturbance in glucose tolerance) lends more weight to the argument that benign glandular hyperplasia and endometrial cancer seem to be related. The association of the two conditions has often been reported (Novak and Yui, 1936; Strachan, 1936; Mazzola, 1938; Novak and Richardson, 1941; Purdie, 1945; Hertig and Sommers, 1949; Speert, 1949; Orrahood and Wyatt, 1953; Hunter *et al.*, 1954; Way, 1954; Barr and Charteris, 1955; Turnbull, 1956); and McBride (1955) reported the frequent association of "retrogressive hyperplasia or cystic atrophy" and carcinoma of the endometrium. Benign glandular hyperplasia (cystic and non-cystic) may be found in conjunction with frank cancer, and all gradations may occur, just as all degrees of atypical hyperplasia may precede the development of endometrial carcinoma (Novak and Novak, 1958).

What is the cause of the endometrial hyperplasia? And what is the factor that determines the development of carcinoma? Excessive or prolonged oestrogen activity has been suggested, because: (1) an increasing number of cases are being reported with a history of prolonged oestrogen therapy and later development of uterine cancer (Novak and Novak, 1958); (2) it is thought that there is a high incidence of endometrial carcinoma in feminizing mesenchymal ovarian tumours (Novak and Novak, 1958); and (3) endometrial hyperplasia is due to abnormal oestrogen activity (Brown *et al.*, 1959).

However, oestrogens alone do not explain the malignant development. (1) McBride (1955) showed that in post-menopausal women with endometrial carcinoma there was no evidence of continuing abnormal oestrogen activity. (2) Jones and Brewer (1941) reported on a group of young menstruating women whose endometria showed cancer in conjunction with a progestational endometrium—there is no question that this occurs, but as the exception to the usual picture of post-menopausal adenocarcinoma. (3) Cirrhotic subjects were thought to be more prone to develop endometrial cancer because of hepatic inability to detoxify oestrogen, but Brewer and Foley (1953) seemed to have disproved this fairly conclusively.

There appears, however, to be a factor common to both diseases—an aberration of carbohydrate metabolism. This finding may pave the way towards determining the missing factor which results in the development of malignancy. Such disturbances in carbohydrate metabolism may be the cause or result of benign glandular hyperplasia and may render the patient more liable to develop carcinoma, in a way similar to that whereby diabetes predisposes to certain infections. Underlying pituitary or adrenocortical dysfunction may be involved.

Summary

Studies in glucose tolerance have been extended to embrace all cases with abnormal uterine bleeding at the time of the climacteric, both benign and malignant. Similar investigations are proceeding in other age-groups. The results have been correlated with the histological appearances of the endometrium.

Conflicting reports have appeared in recent years with regard to the incidence of abnormal glucose tolerance in patients with carcinoma of the body of the uterus. Such cases were therefore investigated by glucose-tolerance tests and compared with control subjects of the same age-group (it is known that age has an important bearing on glucose tolerance). 52% of patients with cancer of the endometrium showed impaired glucose tolerance, compared with 22% in the control group. These figures, on analysis, are most significant statistically.

Patients with proved benign glandular hyperplasia were similarly investigated and compared with controls (both normal subjects and patients with uterine bleeding due to other causes). The incidence of abnormal glucose tolerance (84%) in cases of benign glandular hyperplasia was found to be striking and much higher than in the two control groups and higher than in cases of cancer of the endometrium. These figures are very significant statistically.

The possible significance of these findings is discussed.

It is submitted that further research along these lines is warranted. Such studies may throw more light on problems such as (a) the alleged association between benign glandular hyperplasia and cancer of the endometrium, and (b) the unknown factors that determine the onset of benign hyperplasia and the development of malignancy in some of these cases.

I am indebted to Professor J. T. Louw, professor of obstetrics and gynaecology, University of Capetown, at whose instigation this investigation is being carried out, for his invaluable advice and helpful criticism. Professor J. E. Kench and his department of chemical pathology, University of Capetown, carried out the biochemical investigation, and we gratefully acknowledge this work. Thanks are due to the Department of Pathology, University of Capetown, for the histological reports. Mrs. A. M. Strydom (M. Soc. Science, U.C.T.) carried out the statistical analyses, and I am grateful to her for doing this.

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HYDATID DISEASE IN NORTH WALES

BY

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This paper presents certain epidemiological and surgical aspects of hydatid disease as seen during recent years in North Wales; it does not give a detailed account of the life-cycle of the parasite or pathology of the disease, since authors from countries where the disease is far commoner have contributed to a voluminous literature on these aspects of the subject.

In 1937 Professor Lambert Rogers drew the attention of the Welsh Board of Health to the relatively high incidence of hydatid disease in South Wales. Howell (1938), reporting the results of the inquiry, showed that 144 cases were admitted to hospitals in Wales during the period 1927–36. Most of these patients came from the industrial areas of Glamorgan and Monmouth. Wolfe (1943) reported another 34 cases treated in the Cardiff Royal Infirmary between 1926 and 1938. I was prompted to conduct this further survey of what appears to be a continuing prevalence of the disease after personal observation of several cases in South Wales and later in North Wales. Data concerning 44 cases, hitherto unpublished, treated in hospitals serving the North Wales area during January, 1948, to December, 1957, have been collected. It is probable that the number of patients treated is larger, since many hospital records only extend back over a five-year period.