Afr. J. med. Sci. (1970) **1**, 67–77.

Cancer of the Uterus in the Western State of Nigeria

G. M. EDINGTON

Department of Pathology, University of Ibadan, Ibadan, Nigeria

(*Received* 24 *June* 1969)

Summary. The problem of uterine cancer in Western Nigeria and its differing pattern from that seen in temperate climates is discussed in the light of a recently completed 6-year survey in which 4502 malignant tumours were classified by site, age and sex.

The survey demonstrated that circumcision in the male and a low incidence of penile cancer does not prevent a high ratio frequency of cancer of the cervix, thus confirming previous conclusions that there is no relationship between the incidence of carcinoma of the penis or circumcisional habits in the male and cancer of the cervix in Africa South of the Sahara. Irrespective of the exact incidence of cervical cancer the lack of sophisticated medical centres capable of undertaking some form of therapy throws a tremendous burden on the few that exist as they may be, by referrals, responsible for a population of many million. To add to the problem, the majority of patients present at a late stage of the disease, radiotherapy is not available, and for many there is no possibility of cure or even palliative therapy. The need for prevention is manifest and the possibility of instituting such a programme is discussed in the light of conditions pertaining in Western Nigeria.

In addition to cervical cancer malignant disease of the trophoblast is also a problem of magnitude in Ibadan. The aetiology of this condition is discussed and the possibility of multiple infections and infestations especially malaria being factors in its pathogenesis considered.

Endometrial cancer occurs in low incidence and this finding is in keeping with previous reports from Ibadan and other areas of tropical Africa.

Résumé. Le problème du cancer de l'utérus dans le Nigéria Occidental et des différences qu'il présente avec le modèle des pays tempérés est discuté à la lumière d'une enquête de 6 ans récemment achevée et au cours de laquelle 4502 tumeurs malignes ont été classées selon la localisation, l'âge et le sexe.

L'enquête a montré que la circoncision chez le mâle et une faible incidence du cancer du pénis n'empêchent pas un taux élevé de cancer du cervix, ce qui confirme les conclusions antérieures qui ne voyaient aucun rapport entre le carcinome du pénis ou la circoncision masculine et le cancer du cervix en Afrique Sub-Saharienne. Indépendamment de l'incidence exacte du cancer cervical, l'absence de centres

Correspondence: Professor G. M. Edington, Department of Pathology, University of Ibadan, Ibadan, Nigeria.

médicaux modernes capables d'entreprendre une thérapeutique grève le petit nombre de ceux qui existent d'une charge écrasante, car ils peuvent être responsables d'une population de plusieurs millions à la suite des cas qui leur sont référés. Le problème s'aggrave encore du fait que le plupart des malades se présentent à un stade avancé de la maladie, que la radiothérapie n'est pas disponible et que pour beaucoup il n'y a aucune possibilité de guérison ou même de traitement palliatif. La nécessité de la prévention est évidente et la possibilité d'instituer un programme en ce sens est envisagée à la lumière des conditions existant au Nigéria Occidental.

Outre le cancer cervical, l'affection maligne du trophoblaste est également un problème d'importance à Ibadan. L'étiologie de cet état est discutée et la possibilité que les infections et infestations multiples (surtout la malaria) soient des facteurs de sa pathogénie est considérée.

Le cancer de l'endomètre se rencontres à faible incidence, conclusion qui recoupe les rapports antérieurs d'Ibadan et d'autres régions de l'Afrique tropicale.

A Cancer Registry was established in the University College Hospital, Ibadan, on 1 April 1960 and a report of its activities 1960–63 has been published (Edington & Maclean, 1965). Official census figures were not available at the time of the report and an unofficial provisional figure for the population had to be employed. A sample survey of the population in age and sex groups reported by the World Health Organization was applied to the estimated Ibadan population in order that age specific rate incidences could be calculated. The Federal Nigerian Census of 1963 has now been published and has made available, in 5-year age and sex groups, the urban population of Ibadan from which more accurate rate incidences of various types of cancer can be calculated. In addition to utilizing this defined population, the Registry also records all cases of malignant disease diagnosed in the Department of Pathology in the University College Hospital which serves as a referral centre for most of the rural hospitals in the Western State and a few in other States in Nigeria. From this combined material ratio frequencies can be calculated.

It should be noted, however, that the city of Ibadan is unusual as it is not truly urban in the Western sense. It resembles rather a large village. Many of its inhabitants are farmers who tend their land in the surrounding countryside. Eighty per cent of the population are Yorubas the predominant tribe in the Western State and approximately 60% are Moslems and 40% Christians. The staples are yams, cassava and plantain. Meat and fish are available but expensive. Multiple infestations and infections are common and the pattern of malaria is stable. A somewhat similar pattern of disease therefore pertains in urban and rural areas and the discrepancies between the rate incidences of cancer in the Ibadan population and the ratio frequencies which include malignancies diagnosed in rural populations are less than might be expected in urban and rural populations in other parts of the world. The details of the methodology employed in the Cancer Registry were described in the publication mentioned above and are not repeated in this paper except to emphasize that the one major specialty which is lacking in the medical armamentorium is that of radiotherapy—as it is throughout most of Tropical Africa.

An analysis of the 1960–66 figures available in the Cancer Registry is at present being completed (Edington & Hendrickse, 1969) and it is from this material that the problem of cancer of the uterus in the Western State of Nigeria is discussed. During the 6 years of the study, 4503 malignant tumours were diagnosed, 2266 in males and 2236 in females. The

sex was not recorded in one instance. The ratio frequencies of cancers of the uterus are shown in Table 1.

TABLE 1. Number of uterine malignancies diagnosed and their ratio frequencies (R.F.) in Ibadan and non-Ibadan patients, 1960–66

Classification	Ibadan		Non-Ibadan		Total	
	No.	R.F.	No.	R.F.	No.	R.F.
Tumours, all types	718	—	1518	—	2236	—
Cervix uteri	122	17·0	323	21·3	445	19·9
Corpus uteri	10	1·4	13	0·9	23	1·0
Other parts	2	—	3	—	5	—
Chorioncarcinoma	45	6·3	93	6·1	138	6·1

From this table, it will be seen that the ratio frequencies differed little in Ibadan and non-Ibadan patients, the overall figures being: carcinoma of the cervix 19·9%; chorion carcinoma 6·1%; and endometrial cancer 1%.

Four sarcomas of the uterus and one of the cervix were also diagnosed, and are shown separately, confirming the finding that although uterine fibroids are very common in Ibadan, malignant change is unusual.

CARCINOMA OF THE CERVIX

Incidence

In previous studies in Ibadan (1960–63) although the ratio frequencies of carcinoma of the cervix were 17·9 and 18·3% in Ibadan and non-Ibadan patients respectively with an overall ratio of 18·1%, the 3-year rate incidence study utilizing the method of indirect standardization showed that the number of cancers seen was almost 50% less than that expected in the United States white population and 25% of that expected in the United States non-white (Edington & Maclean, 1965). The 1960–66 study has shown almost similar ratio frequency values (see Table 1), but age specific rate incidence figures show a somewhat different pattern to that reported in 1960–63 and are shown in Fig. 1.

From this figure it will be seen that the age specific rate incidence of carcinoma of the cervix in Ibadan is higher than that recorded in the State of New York (Handy & Burnett, 1966) and has a somewhat similar incidence to that recorded in the Kyadondo in Uganda (Davies & Knowelden, 1966) but is much lower than that recorded in the South African Bantu (Higginson & Oettle, 1966). The figures for Ibadan should, however, still be accepted with caution, as Table 2 illustrates that the recording of one or two cancers in the older age groups may cause drastic differences in the age specific rate incidences and chance may play a part—this in spite of the fact that in the 6-year study a female population of 1·6 million was at risk. These findings favour the proposal of Doll & Cook (1967) that in areas where population figures in the older age groups are small, the incidence rates of epithelial tumours for comparative purposes should be compared in the 5-year age groups 35–64 on the premise that, below the age of 35, the rate incidences are low and that over the

age of 64 years numerous complicating factors arise—the most important in tropical areas being the yet unexplained low incidence of cancer in the older age groups (Edington & Gilles, 1969). It is believed that a more realistic picture of the problem of cancer of the cervix in Ibadan would have emerged if this suggestion had been followed in the 1960–63 study. It should be remembered, however, that there is always the possibility that epithelial tumours may occur in younger age groups in the tropics and this should not be ignored in any analysis of age specific rate incidence figures.

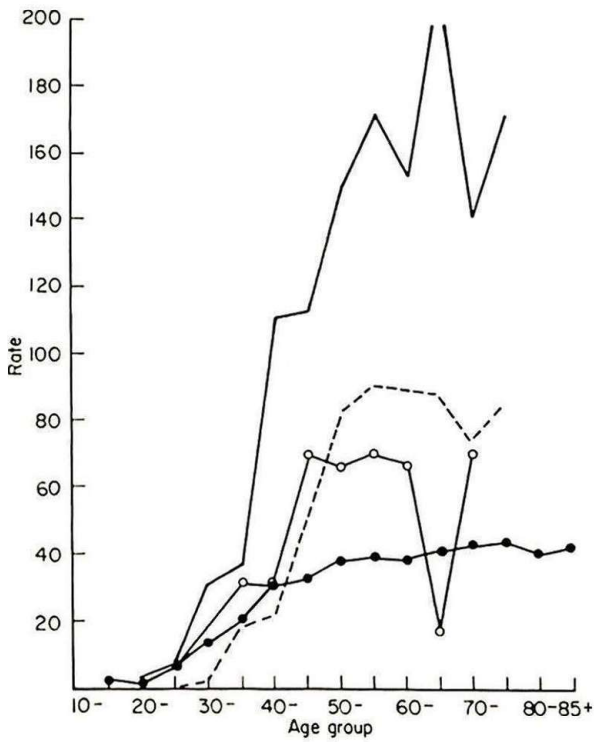

FIG. 1. Age specific rates of cancer of the cervix in the South African Bantu (——: Higginson & Oettle, 1966), Ibadan (– – – –: Edington & Hendrickse, 1966), Kyando, Uganda (○: Davies & Knowelden, 1966) and New York (●: Handy & Burnett, 1966).

There is evidence to suggest that cancer of the cervix may also be more common in East Africa than previously suspected as shown by Trussell, Hutt & Ziegler (1968) in Uganda. Cytological examination of cervical smears obtained from 10 965 patients attending gynaecological, antenatal and family planning clinics showed that 3·5% of patients required biopsy for definitive diagnosis. In addition, 43% of smears showed the presence of trichomonas infection and monilia infection was present in 11%. It is of interest that a figure of 5·5% was obtained in Barbados (Vaillant, Cummins & Richart, 1968) which is further evidence that carcinoma of the cervix is common in tropical areas. A similar investigation in Britain in which 10 000 gynaecological and antenatal out-patients were screened showed that only 1·4% of patients required biopsy (McLaren, 1963). The ratio frequency of cancer of the cervix in Uganda is high but rate incidences have been considered similar to that seen in the white population of the U.S.A. (Davies, Knowelden & Wilson, 1965). The

findings of Trussell *et al.* (1968) would suggest that the incidence of carcinoma of the cervix in Uganda may well be higher than that reported in rate surveys and more in keeping with the high ratio frequency figures. It is expected that a cytological survey in Ibadan will also probably reveal a high index of positive smears and discussion on control is based on this assumption.

Irrespective of the actual incidence, the Department of Obstetrics and Gynaecology, U.C.H., Ibadan, treated eighty-seven patients with carcinoma of the cervix in 1965. When it is remembered that in a previous study of 246 patients (Lawson, Nwosu & Olafimihan, 1964) only 20% presented with clinical grades I or II—vis-à-vis 60% recorded in developed

TABLE 2. Incidence rates of carcinoma of the cervix per 100 000 of the population shown in age groups (Ibadan 1960–66)

Age group	No. of cancers	Population	Incidence
25–	2	43077	0·8
30–	5	24781	3·4
35–	16	13926	19·2
40–	15	10524	23·8
45–	19	5905	53·6
50–	24	4764	83·9
55–	11	2002	91·6
60–	14	2548	90·3
65–	6	1126	88·8
70–	4	893	74·7
75–	2	390	85·5
80–	—	469	—
85–	—	494	—
Age U.K.	4		
Total	122	269066	7·6
		Standardized rate (African population)	14·1

countries—that only ten were considered likely to survive for 5 years after surgical treatment—that radiotherapy (apart from caesium in Ibadan) is available in few centres in Africa South of the Sahara, that sophisticated medical centres are few and widely separated and may be drawing on a population of many million, it will be realized that for the great majority of women suffering from carcinoma of the cervix in Africa at the present time, there is little possibility of cure or even palliative therapy—and this may even include lack of adequate sedation.

Aetiology

Numerous factors have been considered in the aetiology of carcinoma of the cervix—early initiation into sexual life, repeated child bearing with trauma to the cervix, sexual hygiene, sociological customs regarding intercourse, polygamy, circumcisional habits in the male, chronic inflammation and hormonal influences. The possible role of schistosomiasis

is discussed below. Little has emerged from this investigation to shed new light on possible aetiological factors.

Although early marriage is considered usual in the rural Yoruba and polygamy is accepted, in the rate studies (Fig. 1) the onset of carcinoma of the cervix would not appear to occur at an earlier age in Ibadan than in the New York population, a finding which has previously been recorded in the South African Bantu (Oettle, 1964).

The condition is rare in the nulliparous—only two of the 246 patients studied by Lawson *et al.* (1964) in Ibadan were not multiparous. It is of interest to note that in South Africa the mothers' age at the birth of the first child was lower in patients with cervical cancer than in controls.

In Ibadan approximately 100% of males are circumcised in the first few weeks of life and in the 6-year study only eight penile cancers were diagnosed in 4503 malignancies—2266 of which were in males giving frequency ratios of 0·1 and 0·4% respectively—thus confirming the fact that circumcision protects against the occurrence of penile cancer. In spite of this, carcinoma of the cervix was found in a similar incidence to that recorded in Uganda where less than 10% of males are circumcised and penile cancer is one of the most frequent tumours seen (Dodge, Linsell & Davies, 1963). The incidence of carcinoma of the penis was also five times higher in the Kyadondo than in the South African Bantu whereas the incidence of carcinoma of the cervix was two to three times higher in the latter group. This study confirms that there is no relationship between the incidence of cancer of the penis and cervix—nor would the incidence of the latter appear to be related to circumcisional habits in the male in African populations South of the Sahara. It may well be that the accepted low incidence of carcinoma of the cervix in Jewish women may not be due solely to the circumcisional habits practised by that race and that other factors should be considered (Stewart *et al.*, 1966).

There is no information available regarding the hormonal status of women in Nigeria. In the Bantu, Oettlé (1964) considered there was a lowered level of hormonal activity as indicated by a later age at menarche and a lowered frequency of post-menopausal oestrus. Ellis (1950) considered that the menarche was later in Nigerian girls than in British whereas Akingba (1968) obtained a somewhat similar age in both groups—the age of the Nigerians perhaps tending to be slightly higher. These findings, however, related to literate school children and further information on the age at menarche of girls living in rural areas is required. There is no information on the incidence of post-menopausal oestrus. The condition does occur but the age structure of the population and the sociological habits of older women may well be responsible for the impression that it is not common in Ibadan.

Chronic pelvic inflammatory disease is not uncommon in Ibadan but there are no accurate figures on which to base its frequency. It will be interesting, in the future, to compare the findings on cervical smears with those recorded in East Africa and note if circumcision lowers the incidence of infection in Ibadan vis-à-vis East Africa.

Urinary schistosomiasis due to *Schistosoma haematobium* infection is common in Ibadan. In a recent necropsy study, digests of the urinary bladder revealed that over 20% of subjects were infected. Ova of *S. haematobium* have been noted in association with carcinoma of the cervix (Afifi, 1948; Berry, 1966; Charlewood, Shippell & Penton, 1949) and with cellular atypia in cervical smears (Berry, 1966; Boulle & Notelwitz, 1964). In Ibadan cervical schistosomiasis was noted in six of 19 862 surgical biopsies (Edington, 1967) and the pathology has been reviewed by Williams (1967). In spite of the high incidence of schistosomiasis in

Ibadan the infection has not as yet been seen in association with carcinoma of the cervix confirming the conclusions of previous authors that the finding of ova in association with carcinoma of cervix is fortuitous and that the infection plays little if any part in the aetiology of cervical cancer.

Lastly, as has been noted in certain other tumours in Africa, it is the impression that the great majority of cancers are of a high grade of malignancy (Broder's grades III and IV) with few in groups I and II.

Control

In Nigeria it is estimated that there is one doctor to each 50 000 of the population. Overall control of cancer of the cervix is, therefore, obviously impossible. The screening in 1 year of the 111 000 women in the age group 25–60 years in the Ibadan population alone, using Trussell's figures as a model, would require eleven technicians, 26 hr of gynaecological operating time and 310 hr of histopathological examinations per week*, once again an impossible task with the medical resources available. Nevertheless, it has been shown that carcinoma of the cervix is common and that only 4% of patients who present for surgical treatment are likely to survive for 5 years and that, for many, palliative therapy may not even be possible. In the 25 million females in Nigeria, at the very minimum 3000 are condemned to a miserable protracted and painful death each year. It is therefore essential that 'localized' control measures should be instituted wherever possible. Such a programme is at present planned in Ibadan by the Department of Obstetrics and Gynaecology in cooperation with the Department of Pathology. It is hoped to screen 400 women per week and if the results are similar to those reported in East Africa somewhere in the region of 300 patients should be treated suffering from carcinoma *in situ*, microinvasive or invasive cancer in 1 year. The approximate cost of such a project should not be more than 15 000 dollars—an insignificant sum when the amount of future suffering alleviated is considered.

MALIGNANT DISEASE OF THE TROPHOBLAST

Disease of the trophoblast has recently been classified (Park, 1967) as:

A. Hydatidiform mole, (a) non-invasive (b) invasive.
B. Chorion carcinoma.
C. Morphological diagnosis uncertain.

Refined diagnostic techniques, however, have rendered the histopathological diagnosis of the invasive mole and chorion cancer of much less importance than formerly and many cases are now notified to the Registry following percutaneous pelvic angiography and urinary gonadotropin estimations (Hendrickse, Cockshott & James, 1967). The ratio frequencies of trophoblastic neoplasia in the Ibadan and non-Ibadan populations (1960–66) were 6·3 and 6·1% respectively with an overall ratio of 6·1%. The age specific rates are shown in Table 3.

To illustrate the problem, the Department of Obstetrics and Gynaecology during the years 1960–65 saw 104 cases of proven chorion cancer of which eighty received treatment. The remaining twenty-four died before treatment could be commenced.

Trophoblastic neoplasia is common in West Africa, East Africa, in the Bantu in the

* These figures are based on a possible 3·5% incidence of positive smears, forty-five smears per day being examined by a technician, 20–30 min being taken to perform a cone biopsy—each of which requires twelve paraffin embedded blocks of tissue and a minimum of 120 sections examined.

Transvaal (Oettle, 1964), Madagascar (Dodin, Randrianarivo & Brygoo, 1963), Iraq, Southern India, Hong Kong Chinese, Indonesia, Philippines, Taiwan, Korea, Java, Papua and New Guinea (U.I.C.C. Monograph, 1967). It is not common in Europe, North America, Hawaii, nor in the American born Chinese. Little is known regarding its aetiology but its presence in high incidence is associated with lowered economic standards, undernourishment and a high birth rate. Consanguinity, the possibility of a defective gene in the chromosome due to a low protein diet (Acosta-Sison, 1967) and folic acid deficiency are further factors which have been suggested. Hydatidiform mole has been noted to be more common in women suffering from tuberculosis and chronic disease has been considered by some to predispose to trophoblastic neoplasia. In Asia the condition is more common in older multiparous women in contrast to the oligoparity and youth of patients in the Western world (Chan, 1967).

The trophoblast is unique in that it contains elements derived from the patient and her

TABLE 3. Age specific rate incidence of trophoblastic neoplasia per 100 000 of the female population per year

Age group	Population	No. seen in 6 years	Rate incidence
15–19	18520	3	2·7
20–24	50433	7	2·3
25–29	43077	15	5·8
30–34	24781	8	5·4
35–39	13926	8	9·6
40–44	10524	3	4·8
Age unknown		1	
Total	269066	45	2·7

husband. The reasons why homograft sensitization does not occur in normal pregnancy are obscure but the most likely explanation is thought at present to be that normal trophoblastic cells fail to elaborate or express transplantation antigens in an immunologically competent manner (Billingham, 1967). Chorioncancer is also therefore a homograft—and there is some evidence that it is not always completely devoid of isoantigenic activity as spontaneous regression, a manifestation of host resistance, may occur. It has also been considered that isoimmunization and chemotherapy may act synergistically to check the growth of tumours. In this connection it is of interest to note that chemotherapy very rarely causes complete tumour regression in chorioncancer in the male—an autograft—whereas chorioncancer in the female is a homograft and subject to rejection suggesting that the theory of synergistic action may be correct. It has also been shown that the patient is more tolerant to her husband's antigens by an impaired capacity to reject a skin graft from her consort (Robinson *et al.*, 1963; Mathe *et al.*, 1964) and that the absence of a mononuclear and lymphocytic response to the trophoblast may indicate also immune tolerance (Iliya, Williamson & Azar, 1967). Lymphopenia has also been noted—and it has been suggested that the absolute lymphocyte count might be a useful method of assessing the effectiveness of chemotherapy—a rise denoting a favourable response (Nelson, 1967). An increased infil-

tration of lymphocytes and plasma cells is said to occur in the tumour in patients responding to chemotherapy. From the foregoing it is obvious that there is an alteration in the immunological reactivity of patients suffering from trophoblastic neoplasia. Whether this is a primary defect or due to the effect of the hormonal action of trophoblastic tissue on the endocrine glands is not known. It is, however, known that in pregnancy similar alterations occur. Lymphopenia is usual (Nelson, 1967), the effects of malaria in stable areas, infectious hepatitis and amoebic dysentery are much more severe (Edington & Gilles, 1969) and pneumococcal meningitis (Lucas, 1964) is seen in higher incidence in pregnant when compared with non-pregnant women perhaps suggesting that it is the generalized hormonal disturbance which is responsible for the altered immunological state. It is also, however, tempting to speculate that the high incidence of chorioncancer in some of the areas described may be due to the receptive host whose immunological status has been altered by a multiplicity of infections and infestations. The relative lack of autoimmune disease, in tropical Africa, as it is known in the Western world is noteworthy. Systemic lupus erythematosus, thyrotoxicosis, pernicious anaemia and rheumatoid arthritis are very rarely encountered in Africa. On the other hand, we have such conditions as malarial nephrosis and the idiopathic tropical splenomegaly syndrome in which immunological factors may play a part—with malaria a most likely aetiologic agent. It has also been suggested that in areas of stable malaria the hypertrophy and blockade or crowding out of the reticulo-endothelial system which occurs with erythrophagocytosis of red cell debris, parasites and pigment may significantly lower the immunological response to other infections and also that this hypertrophy may predispose to malignant change, thus accounting in part for the high incidence of tumours of lymphoreticular tissue (including the Burkitt tumour) seen in some areas of stable malaria. It is therefore possible that the factors of multiple infestations and infections —especially malaria in West Africa—may lower the 'homograft sensitization' reaction and thus predispose to a higher incidence of trophoblastic neoplasia. It is unfortunate that we have no figures of the incidence of habitual abortion in the tropics which may be due to a higher degree of sensitivity to the husband's transplantation antigens. If the theory enumerated above is feasible, the incidence should be negligible in these areas in the poorer classes.

With regard to control this is obviously related to improvement in socioeconomic conditions. As an interim measure it might be worthwhile to prescribe prophylactic chemotherapy to all cases of benign hydatidiform mole and this is indeed being practised in many centres including the Department of Obstetrics and Gynaecology in the University of Ibadan. In tropical areas this is especially valuable as follow up of patients is frequently impossible and prophylactic chemotherapy may prevent 5–10% of these patients developing trophoblastic neoplasia.

CARCINOMA OF THE BODY OF THE UTERUS

The ratio frequency of endometrial carcinoma in Ibadan was 1% and the ratio to carcinoma of the cervix 1:19·4, findings which are usual in tropical Africa with the exception of the Sudan (Lynch, Verzin & El Hassan, 1963) and in contrast to the body–cervix ratio of 1:2 found in temperate climates (Editorial, 1966). Oettle (1964) has correlated the lowered incidence of cancer of the body of the uterus with a lowered incidence of breast and ovarian cancer in the Bantu and with a lowered level of hormonal activity. However, in Ibadan the age structure of the population must be remembered, with few women in the older age

groups, and further investigations are required on attitudes to post-menopausal bleeding before it can be finally accepted that carcinoma of the body is, in fact, infrequent. It is also of interest to note that metropathia haemorrhagica and endometriosis are not common in our experience, although the occurrence of the former appears to be increasing. Early marriage, frequent pregnancies and a high incidence of pelvic inflammatory disease may be factors accounting for the infrequency of the latter.

ACKNOWLEDGMENTS

The author is indebted to Professor J. B. Lawson and Professor J. P. de V. Hendrickse for their cooperation. The British Empire Cancer Campaign has generously supported financially the Cancer Registry since its inception in 1960. Mrs M. Hendrickse, of the Cancer Registry, has been an invaluable source of information and the Medical Illustration Unit has given technical assistance.

A synopsis of this paper was presented to the American Cancer Society, New Orleans, March 1969.

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