BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 15 1961

PREMALIGNANT CONDITIONS OF THE VULVA, WITH PARTICULAR REFERENCE TO CHRONIC EPITHELIAL DYSTROPHIES*

BY

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[WITH SPECIAL PLATE]

Many authorities object to any condition being called premalignant, holding that cancer is a primary pathological change. Though what follows may be taken to lend a measure of support to this view, the title of this communication is a convenient cover for a consideration of those lesions, factors, and circumstances which are alleged to determine or favour the development of cancer of the vulva. The discussion is, moreover, limited to squamous-cell carcinoma, without regard to the rarer forms of malignancy such as sarcoma, melanoma, and adenocarcinoma, which together comprise less than 10% of all malignant growths of the vulva.

Factors in the Aetiology of Squamous-cell Cancer of the Vulva

Local Irritation

The development of cancer at any site can be determined by certain types of chronic tissue injury or "irritation." In the case of epithelioma of the vulva the only reasonably well established example of this is contact with carcinogenic mineral oils. Thus in 1932 Gerrard showed that women operatives in the cotton and woollen mills of Lancashire and Yorkshire, directly exposed to oil-impregnated waste materials of their trade, were twice as liable to suffer from cancer of the vulva as were women of similar ages engaged in other occupations. Repeated exposure to x rays and radium is an acceptable theoretical cause of malignant disease of the vulva, but has not, in practice, been shown to operate. It is, nevertheless, one of several good reasons for abandoning the use of radiation therapy for intractable pruritus vulvae. Direct trauma, at one time suggested by Taussig (1917, 1940), is, however, not acceptable because cancer of the vulva occurs as frequently in virgins and nulliparous women as it does in those exposed to coitus and childbirth.

Infections, Condylomata, and Granulomata

The fact that vulval cancer commonly begins in the region of the clitoris is sometimes attributed to

irritation from collections of smegma at that site, but this is no more than conjecture. The same is true of irritation caused by chronic purulent discharges. Such discharges sometimes cause condylomata acuminata, which in the past were regarded as precancerous (Taussig, 1931, 1940). Though Stening and Elliott (1959) reported that cancer in four of their cases was superimposed on "papillomatous warts," most modern findings are opposed to the concept that condylomata can become malignant (McAdams and Kistner, 1958). Older reports to the contrary were probably based either on confusion between the histological appearances of condylomata and of cancer, or on the assumption that a papillomatous pattern of squamous carcinoma implies that an innocent papilloma has become malignant. Similarly, there is no convincing evidence to support an older impression that syphilitic and tuberculous lesions of the vulva can determine the development of cancer (Lunin, 1949; Stening and Elliott, 1959; McAdams and Kistner, 1958). Chronic inflammatory disease, especially if accompanied by hypertrophic tissue reactions, can simulate cancer both macroscopically and microscopically; this fact also makes it difficult to decide whether granuloma inguinale and lymphogranuloma can lead to epithelioma of the vulva.

Lunin (1949) reported that 60% of negroes suffering from vulval carcinoma had previously had granulomatous venereal disease, and Stewart (1959), besides finding support in the literature for the idea that granulomata can become malignant, reported six cases in which epithelioma of the vulva occurred in women suffering from either ulcerative or proliferative granulomatous lesions. Nevertheless McAdams and Kistner (1958), in their prospective study of seven women with vulval granuloma, did not encounter one case of cancer, so the matter remains unsettled.

Age

Squamous-cell cancer of the vulva, like skin cancer at any site, is a disease of old age. Involutionary changes associated with ageing in some way encourage mutations which can lead to malignant behaviour of the epithelial cells.

*Based on the Emily Blake Memorial Lecture delivered at Newcastle upon Tyne on April 12, 1961, under the auspices of the North of England Council of the British Empire Cancer Campaign.

Inherent Predisposition to Cancer

Differences in racial proclivities to cancer of the vulva are disputed (Rubin and Novak, 1956; Corscaden, 1956; Taussig, 1931), and, even if they could be demonstrated, would be open to several interpretations, because environmental as well as genetic factors might be concerned. Nevertheless, several writers point out that women with cancer of the vulva often have malignant disease at other sites, which appears either before or after the vulval condition and is unrelated to it. Thus Taussig (1940) noted that 10 out of 155 of his patients (6.4%) had malignant disease elsewhere. In the series reported by Green *et al.* (1958) coincidental malignant disease was present in 13% and there was a family history of cancer in 21%. Among the small series of 25 women suffering from cancer of the vulva treated by one of us (T. N. A. J.), four had malignant disease elsewhere. All such observations, however, are uncontrolled, and it might be possible to show that women of similar age who do not suffer from cancer of the vulva give similar histories.

Vulval Cancer as Part of a "Field Change"

Even though vulval cancer has not yet been shown to have a significant relationship to malignant disease elsewhere in the body, there is much to suggest that it is often merely one manifestation of a widespread field change in the epithelium of the vulva and even of the vagina. This explains why cancer of the vulva not infrequently presents as multiple separate primary lesions, a phenomenon noted by Berkeley and Bonney (1910) and confirmed by many subsequent observers. The not uncommon coexistence of multiple epithelial neoplastic changes is illustrated by the following two cases.

Case 1.—A. R., aged 67 years, complained of post-menopausal bleeding for two months and soreness of the vulva for four years. The skin around the clitoris and on one labium minus showed hyperkeratosis, but quite separate white patches were also seen on several areas of the vagina and on the cervix. Histological examination showed that all these lesions, from the cervix to the vulva, represented separate areas of intra-epidermal cancer with normal epithelium intervening. At one place in the vagina the cancer showed early invasion. Fifteen months after treatment by total hysterectomy, colpectomy, and simple vulvectomy, this patient presented with another lesion on the vulva which proved to be an early invasive cancer. Radical vulvectomy was then performed. Nine months later she was well and the skin covering the area where the vulva had been looked normal. Nevertheless, skin scrapings showed "cells with large nuclei which suggest dyskaryosis." She died three years after the original treatment from intrapelvic recurrence of the vaginal growth. At that time the "vulval" skin still looked macroscopically healthy.

Case 2.—R. L., aged 58 years, complained of an ulcer on the left labium minus which had been present for a few months. Ten years previously she had been treated successfully for carcinoma of the cervix by radiotherapy. Seven years after this she developed an epithelioma of the anus, which was treated by wide excision and block dissection of the inguinal nodes. The vulval lesion, which appeared three years later, was a new and separate intra-epidermal cancer with possible early invasion of the underlying stroma at one point. This patient died during the induction of anaesthesia before any surgery was undertaken. Necropsy showed no evidence of cancer in the cervix, vagina, or anal and rectal canals. Only the vulval tumour was present.

A diffuse epithelial instability not only accounts for a multifocal origin of cancer of the vulva, but may well explain certain "recurrences" of cancer after radical vulvectomy. It is all too often assumed that the "recurrence" represents an incomplete excision of the original growth. Sometimes, however, it is truly a new growth, unrelated to the original growth except in so far as it is another manifestation of an underlying field change. This was recognized by Taussig (1940), four of whose patients developed fresh tumours of the vulva several years after radical vulvectomy for cancer. The following is another example.

Case 3.—A. T., aged 68 years, complained of itching and soreness of the vulva for four years and one year respectively. She had a papillomatous lesion on one labium majus with evidence of hyperkeratosis elsewhere. Radical vulvectomy was performed and cancer was found only in the papilloma; the epithelium from all other areas was not malignant. Two years later another vulval cancer appeared and was excised widely. The tissues then showed widespread intra-epidermal cancer with invasion beginning at one point. Within another eight months the skin immediately anterior to the anus, previously healthy, showed cancer *in situ*.

Leucoplakia and Leucoplakic Vulvitis

A diffuse change in the vulval skin which is most often accepted as being premalignant, or at least as indicating that the woman has an increased risk of developing cancer, is leucoplakia. Unfortunately there is no agreement among either clinicians or pathologists as to what constitutes leucoplakia, and as to its relationship to alleged other diseases such as kraurosis, primary atrophy, leucoplakic vulvitis, and lichen sclerosus vel atrophicus. It is therefore necessary to examine the evidence which justifies the use of these terms to indicate separate disease entities before considering what truly sequential relationship they bear to frank carcinoma.

The word "leucoplakia" is derived from *leucos*—white, and *placos*—a flat plate. It was first used in medicine to denote a skin condition which is characterized by a naked-eye appearance of "white plaques," and it was applied originally to the tongue and mouth. Indeed, its early use was restricted to such an appearance occurring on mucous surfaces or mucocutaneous junctions (Hunt, 1954). Because of this restriction Berkeley and Bonney (1909), and later Hunt (1940, 1954), preferred the term "leucoplakic vulvitis" when the white plaques occurred outside a mucocutaneous junction. But neither "leucoplakia" nor "leucoplakic vulvitis" was ever originally intended to denote anything more than a clinical picture of white plaques, the plaques representing an increased deposition of keratin on the skin surface. Beneath this keratin various histological changes in the epidermis and dermis were and are described, with the possibility of at least two directly opposing pictures—namely, hypertrophy and atrophy (Special Plate, Figs. 1, 2, 5, 6). In the absence of any clear microscopical criteria the cautious pathologist has therefore long refused to accept leucoplakia as a histological diagnosis. In practice he is wise if he says no more than that the microscopical appearances of vulval skin submitted for examination are not incompatible with the clinician's diagnosis of leucoplakia.

The clinician, on the other hand, while once content to diagnose leucoplakia or leucoplakic vulvitis according to what he saw at the bedside, is, for reasons which

will become apparent, now reluctant to assume responsibility. The tendency therefore is for the gynaecologist to say that leucoplakia is a histological diagnosis and for the histologist to say that it is a clinical diagnosis. Historically and etymologically the latter is right. Nevertheless, some clinicians and pathologists (Wallace and Whimster, 1951; Wallace, 1955; McAdams and Kistner, 1958) now restrict the diagnosis of leucoplakia to those vulvas which, irrespective of their naked-eye appearances, show on section such a degree of disorderly epithelial activity ("atypism") as to make it approximate to malignant change (Special Plate, Figs. 3 and 4). Wallace and Whimster (1951) went so far as to refer to "the state of premalignant hyperplasia known as leucoplakia," at the same time admitting that they established their criteria for the histological diagnosis of leucoplakia by studying sections of 20 cases of squamous-cell carcinoma of the vulva and noting the appearances of the adjacent epithelium. This retrospective approach not only makes it easy to show that leucoplakia is related to cancer, but also makes it a comparatively rare histological disease in which the vulval skin does not always look white and thickened to the naked eye. Furthermore, it creates confusion between leucoplakia and intra-epidermal cancer, as was noted by McAdams and Kistner (1958).

This new concept of leucoplakia is not only out of keeping with the name and its origin; it is entirely different from that of Berkeley and Bonney (1909) and of Taussig (1931). While describing certain variable histological features such as thickening or thinning of the epithelium, lengthening or shortening of the rete pegs, and hyaline change beneath the epidermis, these authors, and their contemporaries, paid no particular attention to abnormal cellular activity as manifested by pleomorphism, hyperchromatic nuclei, frequent mitoses, and loss of stratification. Moreover, they regarded the macroscopic appearances as of first importance. Thus, Taussig (1931) said leucoplakia "is characterized by the formation of whitish plaques of thickened epidermis, with sclerosis of the subjacent connective tissue and absence of elastic fibres producing a parchment-like consistence of the affected skin." And it is leucoplakia as defined by these older writers which most gynaecologists believe to be premalignant—a belief which they consider justifies the almost routine performance of vulvectomy for any chronic skin lesion showing naked-eye signs of hyperkeratosis. Any doubts they may now have about these matters are due to the confusion which has arisen over other terms such as kraurosis, primary atrophy, and lichen sclerosis vel atrophicus. These are supposed to be separate clinical and pathological states despite the fact that they produce skin changes which can and do pass for leucoplakia. Nevertheless, views on these are equally variable and uncertain.

Kraurosis Vulvae

Disagreement about kraurosis extends even to the meaning of the word. It derives from *krauros*, meaning "brittle," yet Taussig (1922) and Novak and Novak (1952) said it means "shrinkage," while Hunt (1940, 1954) reached the conclusion that it means "white and dry." The last interpretation is incompatible with "kraurosis rouge," one of several forms of kraurosis described by Jayle (1906); the second explains the traditional British view that kraurosis is a condition affecting only the introitus, causing contracture and

therefore dyspareunia rather than pruritus. Kraurosis differs, it is said, from leucoplakia in that its epithelial changes are characterized by atrophy and in that cancer never supervenes. These ideas follow the teaching of Berkeley and Bonney (1909) and Bonney (1938), but have never been accepted outside Great Britain. The American concept was formulated by Taussig (1922, 1931) and envisages contracture of the introitus merely as a possible complication of leucoplakia, a result of excessive degenerative changes in the epidermis and dermis. This relating of kraurosis to the atrophic phase of leucoplakia is attractive if only because it divorces kraurosis from senile atrophy (which is physiological), and permits an explanation of those cases occurring in youth and while ovarian function is present. It also conforms to a large extent with ideas on kraurosis which have been held by workers on the Continent of Europe throughout this century (Jayle, 1906; Darier, 1928).

Taussig (1922, 1931) regarded kraurosis as complicating 10% to 20% of cases of leucoplakia, and in 1917 attributed as many vulval cancers to pre-existing kraurosis as to leucoplakia. Rubin and Novak (1956) reversed Taussig's thesis and said that kraurosis can progress to leucoplakia and hence to cancer. This fits in more with the concept of dermatologists such as Wallace and Whimster (1951) and Wallace (1955), who consider that kraurosis vulvae, or primary atrophy as they prefer to call it, changes to leucoplakia within ten years in 50% of cases, and that, with or without this intermediate change, the development of cancer is a real possibility. Nevertheless, a background of traditional British opinion is still evident in Wallace's (1955) definition of primary atrophy as "a sclerosing progressive atrophy of the mucocutaneous integument of the vulva, with a characteristic histology." When it comes to describing this characteristic histology, however, difficulty arises, for the appearances overlap with those of atrophic leucoplakia and of lichen sclerosis.

Lichen Sclerosis vel Atrophicus

Lichen sclerosis, as a cause of a whitish change in vulval skin and of pruritus, was introduced to the gynaecologists by the dermatologists comparatively recently, and some are in danger of being persuaded that, no matter what view may be taken in regard to kraurosis (primary atrophy), there is a clear clinical and pathological difference between leucoplakia and lichen sclerosis. What is the evidence for this? Hunt (1940, 1954) says that lichen sclerosis is a vulval form of lichen planus and that it is identical with leucoplakic vulvitis, or at least with the atrophic form of this disease. Wallace and Whimster (1951) and Wallace (1955), however, are equally certain that lichen sclerosis is "an atrophic form of scleroderma unrelated to lichen planus and occurring in various parts of the body, frequently in the perianal area and the vulva." From this sort of statement has evolved the idea that leucoplakia is a change limited to the vulva, and that when a white skin change is seen to affect the perianal areas the explanation is lichen sclerosis.

Apart from this alleged anatomical difference, it may be difficult, if not impossible, to distinguish lichen sclerosis from leucoplakia on naked-eye examination. Yet histological differences are claimed, the main one being that the epithelium is atrophic rather than hypertrophic. Otherwise the stated characteristics are

hyperkeratosis, disappearance of elastic tissue, hyalinization of the collagen layer, and subepithelial infiltration with leucocytes. What is the difference between this and the so-called atrophic form of leucoplakic vulvitis? We agree with Hunt; there is none. What are the differences between this and primary atrophy or kraurosis? The only ones claimed by Wallace (1955) are that in primary atrophy there is less deposition of keratin and less destruction of collagen, but these are mere quantitative distinctions, and they disappear in advanced cases (Special Plate, Figs. 2 and 5). Hunt (1940, 1954) considered that kraurosis is no more than a late stage of lichen sclerosus, and Stening and Elliott (1959) inclined to a similar view. Wallace (1955), on the other hand, concluded that lichen sclerosus can change to leucoplakia, and, in his experience, in 25% of cases the latter begins as lichen.

Those who consider leucoplakia strongly precancerous admit that malignant change is rarely seen in the perianal skin. This, it is argued, is because the perianal changes are due to lichen sclerosus. And there are some dermatologists who consider that one of the essential differences between lichen sclerosus and leucoplakia is that the former never becomes malignant. This, however, is not the view of Wallace and Whimster (1951) and Wallace (1955), who considered that lichen sclerosus carries a real risk of malignancy, possibly because of an intermediate leucoplakic change. Stening and Elliott (1959) also commented that a case diagnosed as lichen sclerosus sometimes shows "atypical" epithelial activity.

The above considerations can be summarized by saying that, according to various authorities:

Lichen sclerosus is or is not the same as leucoplakic vulvitis.

Lichen sclerosus is or is not related to lichen planus.

Lichen sclerosus is or is not related to scleroderma.

Lichen sclerosus can or cannot change to leucoplakia.

Lichen sclerosus is or is not premalignant.

Lichen sclerosus can or cannot change to kraurosis (primary atrophy).

Leucoplakia is or is not a clinical diagnosis.

Leucoplakia is or is not a histological diagnosis.

Leucoplakia presents two or more different histological pictures.

Leucoplakia is or is not a histological state of atypical epithelial hyperplasia bordering on malignancy.

Leucoplakia can or cannot supervene on lichen sclerosus.

Leucoplakia can or cannot supervene on kraurosis.

Kraurosis (or primary atrophy) is or is not a separate disease.

Kraurosis is or is not the end-result of leucoplakia or of an atrophic form of leucoplakia.

Kraurosis is or is not the end-result of lichen sclerosus.

Kraurosis does or does not have a characteristic histological appearance.

Kraurosis is or is not premalignant.

Thus critical appraisal of the literature as a whole and, indeed, of individual articles on these conditions leads to the conclusion that, unless it be accepted that leucoplakia is a purely histological finding of disorderly epithelial activity bordering on malignancy—a concept quite foreign to traditional ideas—there are no essential clinical or histological differences between kraurosis (primary atrophy), leucoplakia, and lichen sclerosus vel atrophicus. Any alleged clinical distinctions are no

more than individual impressions and opinions; any supposed histological differences are no more than variations in epithelial responses to some unknown factor. Indeed, microscopical pictures which would be accepted individually as representing each of these conditions can often all be found in the same vulva. To give them each a special name does not make them into separate diseases. Indeed, there is a real danger that the effects of a disease are being mistaken for the disease itself, and ignorance is being concealed by superficially imposing labels with classical roots. This view is all the more justified by the fact that the various protagonists of leucoplakia, leucoplakic vulvitis, lichen sclerosus, primary atrophy, and kraurosis find it impossible to state the specific cause for any of what they regard as different diseases.

If progress is to be made in this admittedly difficult field the time has come for it to be freely recognized that the vulval and perianal regions are subject to chronic skin changes, the particular characteristics of which are probably conditioned by environment rather than by causes. The fact that the vulva reacts to various toxic and adverse agents differently from the skin elsewhere is almost certainly explained in part, if not in whole, by its circumstances. Thus, its peculiar tendency to show hyperkeratosis is probably due to heat, moisture, and lack of aeration. A similar reaction is seen in the skin affections occurring between the toes, sites which offer the same environmental conditions.

The evidence suggests that not only can the same aetiological factor cause different types of epithelial reaction in the vulva, but that different aetiological factors can be the foundation of similar vulval changes (Jeffcoate, 1955, 1957) (Special Plate, Figs. 1, 2, 5, 6). It therefore seems more important to discover the underlying causes for the epithelial changes than it is to produce labels which purport to describe the different macroscopic or microscopic features of these skin reactions, and to denote separate diseases. Meanwhile, and irrespective of their appearances, all these intractable skin changes for which a specific cause is not clear are best given clinically an all-embracing and non-committal title such as "chronic epithelial dystrophy." The pathologist equally should be untrammelled by the need to append precise dermatological nomenclature to his report. His factual description of the various histological findings should, nevertheless, include an assessment of the activity and orderliness of the squamous epithelium, for it is these which will guide treatment.

Risk of Cancer Supervening on Chronic Epithelial Dystrophy

The traditional view of the seriousness of macroscopically diagnosed leucoplakia (or leucoplakic vulvitis) as a forerunner to cancer stems mainly, in Great Britain from the writings of Berkeley and Bonney (1909) and Bonney (1908, 1938), and in the New World from those of Taussig (1917, 1922, 1930, 1931, 1940). The former writers did not attempt to assess the statistical chances of such a development, whereas Taussig (1930) concluded that 50% of women diagnosed clinically as suffering from leucoplakia are destined to develop cancer within the subsequent ten years. Indeed, at other times (Taussig, 1922, 1931) he went so far as to say

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FIG. 1.—“Hypertrophic leucoplakia,” showing hyperkeratosis and acanthosis of the epithelium. The dermis has a hyaline appearance. ($\times 75$.) This section is from the vulva of a woman suffering from chronic moniliasis and previously treated unsuccessfully by simple vulvectomy.

FIG. 2.—“Atrophic leucoplakia.” A moderate degree of hyperkeratosis is associated with a thin epithelium devoid of rete pegs. A subjacent hyaline zone in the dermis is conspicuous. ($\times 75$.) The patient in this case suffered from fungus infection of the feet and was considered to have a trichophytid reaction on the vulva.

FIG. 3.—Disorderly epithelial activity sometimes labelled histological leucoplakia. The keratin layer is thin, but there is considerable irregularity and prolongation of the rete pegs into the dermis. ($\times 75$.)

FIG. 4.—High-power view of Fig. 3. ($\times 288$.) (See Case 6 in text.) This section was initially reported as showing a benign leucoplakic appearance, but the epithelium shows irregular cell activity and frequent mitoses, a picture approaching cancer *in situ*. The patient developed invasive cancer 10 years after excision of the lesion illustrated here.

FIG. 5.—Lichen sclerosus vel atrophicus. Slight keratinization is associated with a thin and inactive epithelium. Though diagnosed histologically as lichen sclerosus, the appearances correspond equally well to descriptions of atrophic leucoplakia. ($\times 70$.) This specimen came from a patient whose vulval dystrophy was subsequently proved to be caused by diabetes mellitus.

FIG. 6.—“Hypertrophic leucoplakia,” showing hyperkeratosis, long rete pegs, and hyalinization of the subepithelial zone. ($\times 70$.) This vulval skin was obtained from a patient suffering from neurodermatitis intermittently for 20 years. There were lesions on the arms, legs, and neck as well as the vulva.

that leucoplakia inevitably turns to epithelioma provided the sufferer lives long enough. Conversely, and on the same evidence, he stated that at least one-half of all cases of squamous-cell cancer are preceded by leucoplakia. But these views, so widely accepted, were based on indirect or prejudiced evidence. The main supporting argument was that in cases of established cancer it was possible to demonstrate in adjacent tissues histological signs of leucoplakia. This is not surprising, since at the time in question Taussig recognized two quite opposite histological pictures in leucoplakia, one showing underactive and the other overactive epithelium, while Berkeley and Bonney described no fewer than four different microscopical appearances. More recent writers, such as Way (1951), Langley *et al.* (1951), Corscaden (1956), Bibby (1957), Green *et al.* (1958), Stening and Elliott (1959), and Rewell (1960), also base their assessments of the frequency of coincidental leucoplakic changes in the vulva of women suffering from cancer on differing and often multiple histological criteria, so the reported incidence of the association varies from 12% to 80% of cases. The estimate that cancer develops in 50% of cases of leucoplakia was reached on the basis that, of specimens of vulval skin submitted to histological examination, there are equal numbers of cancers and leucoplakias (Taussig, 1930; Langley *et al.*, 1951; Novak and Novak, 1952). This takes no cognizance of the many cases of leucoplakia not subjected to biopsy.

When leucoplakia was found in association with established cancer it was, and is, assumed that it preceded the growth, and to bolster this idea it is pointed out that women with cancer often give a long history of pruritus vulvae. Yet even Taussig (1940) reported that only 42 out of 155 women (approximately 30%) with vulval carcinoma ever complained of pruritus, and that of unspecified duration. Indeed, all observers except Stening and Elliott (1959) record that pruritus is not present in more than 40% of cases, and this is confirmed by our experience. Only eight out of a consecutive series of 25 women treated for vulval carcinoma by one of us (T. N. A. J.) had ever had pruritus, the duration being less than one year in two cases.

The final argument in support of the idea that leucoplakia antedates malignant disease is based on age incidences, the difference at the time of treatment averaging 10 to 15 years (Taussig, 1930; Langley *et al.*, 1951).

Despite these indirect and retrospective evidences that clinical leucoplakia is a premalignant state, most gynaecologists admit that they have rarely, if ever, seen malignant change occur in a patient under observation. Even Taussig (1940) reported that during his lifetime he had seen only three women develop cancer of the vulva while under medical care. In two of these the original lesion had been studied histologically, but in only one is it mentioned that the microscopical appearances were those of "leucoplakia." In the third case biopsy was not undertaken, so the condition could well have been cancerous from the onset.

Unfortunately, few prospective or follow-up investigations are reported. Hunt (1940), however, said she had studied 96 cases of lichen sclerosis (the same as leucoplakic vulvitis to her) over a prolonged but unspecified period, and cancer developed in only four. She did not mention whether the presence of cancer was excluded

by biopsy when these patients were first seen, and this is important. Langley *et al.* (1951) studied women who had been treated by simple or partial vulvectomy for "leucoplakia," and in all cases histological examination was carried out. Of these cases 122 were followed for more than five years, and 72 (59%) had a recurrence of leucoplakia or pruritus, or both. Yet, of them all, only one developed cancer of the vulva, and that 12 years after the original vulvectomy. By that time the patient had had four operations for recurrent leucoplakia. Böttger and Dittmann (1957) followed 82 women suffering from "chronic pruritus" and 78 suffering from "kraurosis" (Continental definition) for varying periods up to eight years. Among the chronic pruritus group there were no cases of cancer, but in the kraurosis group seven women developed malignant disease. These writers pointed out, however, that a 9% incidence of skin cancer is the same as might be expected for any chronic dermatosis occurring in any part of the body amongst old women. A similar conclusion was reached by McAdams and Kistner (1958) in their valuable study of 397 women subjected to simple vulvectomy or biopsy for various diseases of the vulva. Altogether 201 women with chronic dermatoses (with or without sclerosis) were followed, 136 of them for more than three years. None developed cancer, nor did any of those who were classified separately as suffering from lichen sclerosis, granuloma, and condylomata. Cancer occurred only among the 32 women classified as suffering from leucoplakia, the criterion for this diagnosis being a histological finding of disorderly overactivity of the epithelium. These women were in fact suffering at the outset from skin changes to be regarded as near-malignant, eight of them from border-line cancer. Twenty-seven were followed for periods varying from three to 25 years, and only three developed cancer. Among this particular group the incidence of cancer was therefore 10%, the same figure as for any senile dermatosis in any site.

Our experience is similar. During 25 years one of us (T. N. A. J.) investigated and treated 117 women suffering from chronic epithelial dystrophy of obscure aetiology. This represents less than 5% of patients complaining of pruritus, for all cases in which an obvious cause such as trichomoniasis, moniliasis, and known diabetes was present are excluded. To be included pruritus had to be of long duration, intractable to simple remedies, and associated with obvious vulval skin changes. An attempt was made to follow up all these women, but this failed in 14 cases, leaving 103 in which the after-history is known. Ten of these women had died, but the condition of the vulva at the time of death is recorded. The periods of time during which these women were observed are as follows:

Less than 1 year	..	..	..	7 cases	} 22
1-3 years	..	..	..	15 "	
3-5 "	..	..	..	15 "	} 81
5-15 "	..	..	..	54 "	
15-25 "	..	..	..	12 "	
Total cases					103

Twenty of the patients had a vulval lesion which was essentially red or purple in colour, with or without ulceration; in the remainder the skin showed hyperkeratotic white patches of varying size and distribution with or without intervening red areas. All were investigated, and the over-all conclusions as to the cause of the dystrophies are to be described in detail elsewhere.

Histological examination of the skin was carried out in 65 cases, and revealed intra-epidermal cancer in four and early invasive cancer in one. Abnormal and disturbing epithelial basal-cell activity was present in another two. The five cases in which cancer was clearly present at the outset are set aside, and the findings in regard to the subsequent development of malignant disease relate to the remaining 98 women. Twenty-seven of these were treated by simple or partial vulvectomy (three of the operations being performed in clinics other than our own), and 13 had a recurrence of the vulval dystrophy while under observation. The remaining 71 patients, including nine who had already had an unsuccessful vulvectomy operation before consulting us, were treated conservatively.

Only three of the 98 women (3%) have so far developed cancer, and the details of their cases are as follows:

Case 4.—P. S., aged 54 years, complained of soreness of the vulva for one week. The perianal skin was white and thickened, the vulva looked atrophic with red areas of excoriation. Biopsy was not carried out; local applications were prescribed empirically and all symptoms subsided quickly. She reported more than two years later, having had a return of soreness during the previous eight months. The whole vulva was then red and there was a malignant ulcer on one labium majus. Radical vulvectomy was performed, but the patient died from spinal metastases one year later.

Case 5.—A. D., aged 39 years, had had pruritus vulvae for several years. The skin of the vulva, perineum, and perianal regions was the colour of raw beef with areas of superficial ulceration. Biopsy was not performed, and the skin reaction was thought to be an allergic one. Symptoms appeared to improve with medical treatment, and the patient defaulted from the clinic, only to return seven months later with a malignant ulcer on one labium majus. By that time the red reaction had disappeared; hyperkeratotic white areas were present on the labia majora, labia minora, and around the clitoris. Radical vulvectomy was carried out, and the patient is alive and well seven years later.

This case is of importance in that it illustrates that leucoplakic appearances which are commonly seen alongside cancer may well represent a simultaneous and not a preceding change. When first seen this patient showed no sign of hyperkeratosis of the vulva; this only appeared later, at the same time as the overt cancer.

Case 6.—R. O., aged 35 years, complained of pruritus vulvae for 1½ years, and was found to have two localized thick white patches of skin, one around the clitoris and the other on the fourchette. Both were excised, and sections showed what was then described as "leucoplakia." Ten years later the patient reported to another hospital, saying that she had had discharging warts for four years. This condition proved to be a papillomatous squamous-cell cancer arising in the region of the clitoris. Radical vulvectomy was carried out, and the patient is alive and well four years afterwards—that is, 14 years after the original partial vulvectomy.

This history suggests low-grade malignancy, but what is more interesting is that review of the sections prepared from the skin originally excised revealed disorderly overactivity of the epithelium of a degree approaching that of carcinoma *in situ* (Special Plate, Figs. 3 and 4).

Thus, of the three women who developed invasive cancer, two did not have an original biopsy, and one when first seen had such epithelial activity as, in retrospect, to warrant a diagnosis of borderline

malignancy. The occurrence of cancer in the last is easily understood; the other patients could well have had similar warning epithelial changes when first seen. They may even have had intra-epidermal carcinoma, which often gives the vulva a red appearance. For example, two of the four patients excluded from follow-up because they had cancer *in situ* had initially the typical red lesions of "Bowen's disease" (Jeffcoate *et al.*, 1944).

The conclusion is that none of our patients who we are certain had no histological changes suggestive of malignancy at the outset developed carcinoma of the vulva during many years of observation. This tallies with the findings of McAdams and Kistner (1958), who also make the point that atypical cellular activity which some workers are now labelling "leucoplakia" may already be cancer *in situ*. The subsequent development of invasive cancer is therefore not necessarily ever a complication of chronic epithelial dystrophy. Indeed, it would appear that many, if not all, of those women who develop cancer of the vulva after a long history of vulval dystrophy have had cancer or something approaching cancer from the onset of symptoms. Those whose dystrophy shows other histological features do not have a special tendency to develop cancer.

This means that clinical leucoplakia is not a pre-malignant state, and that the only vulval dystrophy which is one which, on histological examination, shows disorderly epithelial activity. This can lie beneath a hyperkeratotic surface or beneath one which is practically devoid of keratin (Special Plate, Fig. 3). Indeed, it is probably more likely when the skin is not becoming keratinized, since this property is, in general, a sign of good cellular differentiation. Naked-eye examination therefore gives no indication whether a particular dystrophy carries a threat of cancer.

Management of Cases of Epithelial Dystrophy

It follows from the above that two procedures are essential to the management of the woman suffering from a chronic epithelial dystrophy of the vulva. The first is to search diligently for an underlying cause such as dietetic errors; achlorhydria; deficiencies of iron, riboflavin, folic acid, and vitamin B₁₂; allergy to clothing, cosmetics, toilet preparations, and other items; skin diseases not peculiar to the vulva; hyperglycaemia; glycosuria; and particularly fungus infections of the hands and feet, which can probably cause trichophytid lesions of the vulva and perianal skin (Jeffcoate, 1949, 1955, 1957) (Special Plate, Figs. 1, 2, 5, 6). The second is to carry out biopsy of the vulval skin, and this irrespective of what aetiological factor may be found on investigation. Even diabetes can cause an epithelial dystrophy (additional to diabetic vulvitis) which can be followed by cancer (Green *et al.*, 1958; Stening and Elliott, 1959). Omission to carry out biopsy in all cases almost certainly accounts for the fact that we were unaware that two of our patients who subsequently developed cancer were at risk.

McAdams and Kistner (1958) and Stening and Elliott (1959) emphasized that any senile keratotic lesion of the vulva warrants biopsy, but we would go further and say the same for any chronic dystrophy, irrespective of its naked-eye appearance and no matter whether it looks red, purple, white, grey, or yellow. Moreover, biopsy should be carried out even if the patient is premenopausal.

There are, however, two problems associated with biopsy and its interpretation.

(1) Carcinoma of the vulva is said to arise just as frequently in atrophic as in hypertrophic epithelium (Langley *et al.*, 1951; Wallace, 1955). Taussig (1930) said that 40% of vulval cancers begin in atrophic leucoplakic vulvitis. Such statements, however, are now subject to real doubt. The follow-up results of Langley *et al.* (1951) gave no support to the idea, while McAdams and Kistner (1958) clearly showed that cancer did not develop in any vulva which had not originally showed atypical epithelial over-activity. Our experience tallies.

(2) The epithelial appearance may vary from one part of the vulva to another, and the biopsy specimen does not necessarily reflect what may be happening elsewhere. The presence of hyperkeratosis, or of any other special naked-eye appearance, is an unreliable guide to the surgeon in determining which area of the dystrophic vulva is most likely to show abnormal cellular activity. Widely spaced multiple biopsies are therefore always necessary, and, even if the findings are negative, safety is added by keeping the patient under observation at three-monthly intervals, with possibly repeat biopsy if the dystrophy persists.

In an attempt to preclude the possibility of missing the significant field during biopsy, we tentatively examined vulval scrapings obtained by a technique similar to that of Ayre's for the cervix. This method, however, is unsatisfactory, because it is unusual for the smears to contain anything more than surface keratin or keratinized squames; the underlying and more important basal epithelial cells do not appear. It may be argued that the difficulty is avoided by carrying out simple vulvectomy in all cases of chronic epithelial dystrophy. If the skin change is strictly localized there is certainly something to be said for its complete excision as the best method of biopsy. But comparatively few dystrophies show enough localization to permit this; even vulvectomy is not enough to eradicate a skin lesion which is spreading to the groins, to the perineum, and around and behind the anus. Moreover, the pathologist, when presented with the whole vulva, has the same difficulty as the clinician in deciding which areas to choose for histological examination.

Unless the lesion is strictly circumscribed, partial or simple vulvectomy has little to commend it. According to the findings of McAdams and Kistner (1958), as well as those reported here, intra-epidermal or early invasive cancer will be found in 2% to 5% of cases of chronic epithelial dystrophy. For these the operation may be inadequate. Of the remainder, only 4% to 8% will show histological evidence of such epithelial unrest as to threaten cancer, the threat being real in probably not more than one out of ten of this small special group. Vulvectomy is therefore only justified on the grounds of preventing cancer in a very small proportion of cases, and these can be chosen by preliminary biopsy. Nevertheless, even without a cancer threat, it is often said that vulvectomy is justified because its results are good and because no other treatment is effective (Rubin and Novak, 1956; Corscaden, 1956). The latter statement is not correct according to our experience (which is to be reported elsewhere), and the former is no more than a general impression unsupported by published post-operative studies.

Apart from the fact that vulvectomy is mutilating and is frequently followed by dyspareunia, it does not cure the dystrophy or its symptom of pruritus in approxi-

mately 50% of cases. Thus, in the series reported by Langley *et al.* (1951) the recurrence rate among patients who had "leucoplakia" treated by partial or total vulvectomy was 59%. The figures of McAdams and Kistner (1958) are in keeping. For those women observed for three or more years after surgery the recurrence rates were:

For chronic dermatoses	52 out of 118 (44%)
" lichen sclerosus	7 " " 11 (63%)
" leucoplakia (atypical epithelium—precancerous)	7 " " 17 (41%)
Total	66 " " 146 (45%)

It is sometimes said that such high recurrence rates mean inadequate surgery. In fact, as mentioned above, unless the surgeon is prepared to excise skin out to the groins and from around the anus, it is often impossible to remove all the affected area. In our series excision was avoided unless the lesion was so limited and demarcated that it could be removed with ease. Even so our results are not good. Nine of the 103 women whose study is complete had previously had vulvectomy carried out unsuccessfully in other clinics. Among the remainder, simple vulvectomy was carried out 15 times and partial vulvectomy 12 times. Of these 27 women treated surgically, 13 suffered a recurrence of the dystrophy and one developed cancer.

Summary and Conclusions

Except for the repeated application of carcinogens such as mineral oils, and possibly for chronic granulomatous venereal disease, a local cause for squamous-cell cancer of the vulva is not known. Like skin cancer in general, involutionary changes associated with ageing are probably important predisposing factors.

Invasive cancer often begins by way of a field change which may be widespread and in which disorderly epithelial activity is the characteristic histological change. This activity is sometimes so pronounced as to justify the term "cancer *in situ*," but in lesser degrees should not be labelled "leucoplakia," for it bears no constant relationship to hyperkeratinization, which is implicit in this name.

There is as yet no evidence to justify the view that leucoplakia, leucoplakic vulvitis, kraurosis (primary atrophy), and lichen sclerosus vel atrophicus are separate disease entities. Judged by either macroscopical or microscopical criteria, these represent no more than a variety of skin reactions to adverse factors which, although obscure, are more likely to be "general" than "local." The type of reaction is dependent on the environment of the vulva and not on the underlying cause. It is therefore suggested that all these names should be abandoned, since they hinder rather than help the elucidation of their causes. In their place, and pending further knowledge, the non-committal inclusive term of chronic epithelial dystrophy is proposed as one convenient for clinical practice.

Clinically, carcinoma *in situ* can simulate a chronic epithelial dystrophy, and can be excluded only by biopsy. Histological examination of all dystrophies reveals abnormal and disorderly epithelial activity in only 4% to 8% of cases. When it does there is possibly a 10% chance of the subsequent development of cancer, but vulvectomy is nevertheless justified as a prophylactic measure.

In the remaining majority of cases of chronic epithelial dystrophy there is no special risk of malignant

change and vulvectomy is not justified as a cancer preventive. And as an empirical treatment it does not give satisfactory results even when the skin change appears to be strictly limited and demarcated. Unless the cause is determined and eradicated, epithelial dystrophy recurs in approximately 50% of cases treated by partial or total vulvectomy.

For the searching of records and the follow-up of patients we are indebted mainly to Dr. Winifred Francis; but also to Dr. Mary Mayeur and Dr. R. E. Rewell for details of individual cases. Cases 1 and 3 were under the care of Mr. E. Parry-Jones, to whom we are grateful for permission to report them.

ADDENDUM

Since this paper was completed one more of the 98 women under observation has developed cancer of the vulva, and the circumstances confirm the above conclusions. Histological examination of biopsy specimens of the chronically affected vulval skin was carried out in 1956, and showed epithelial activity of a degree which one of us (A.S.W.) considered disturbing. The lesion was so widespread and ill demarcated clinically as to be unsuitable for excision, so it was treated conservatively with some improvement. In view of the histological findings, however, the patient was observed regularly, and when symptoms relapsed in 1960 further biopsy specimens were examined without any more alarming epithelial changes being found. In April, 1961 (after five years' observation), however, the patient reported that she had had pain in one area of the vulva for one week. This area then had a red appearance, and on section showed cancer *in situ* with possibly early invasion of malignant cells at one point.

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SYNDROME OF MITRAL INCOMPETENCE, MYOCARDITIS, AND PULMONARY HYPERTENSION IN NIGERIA

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[WITH SPECIAL PLATE]

Rheumatic mitral-valve disease has been studied intensively during the past 25 years. Mitral stenosis is rare in Nigerians, but one of us (Abrahams, 1959) described a peculiar form of mitral-valve disease which is common in West Africa but unusual elsewhere. In this paper is reported a more detailed study of the syndrome (presenting as mitral incompetence and pulmonary hypertension), which may be caused by an unusual form of rheumatic carditis.

Material

The study covered 50 patients with signs of mitral incompetence and pulmonary hypertension observed over a relatively short period; most of them were examined by both authors, and many were admitted to hospital for treatment and more prolonged observation. Electrocardiograms were recorded and a radiological examination was made in all cases. Right heart catheterization was carried out successfully in 15 cases. Necropsy was performed in 13 cases.

All the patients came from the western region of Nigeria. Most of the tribes of the south were represented, but Yorubas, who are the majority people of the western region, predominated. All were young by Western standards, but not in their own community, where the expectation of life is short. At the last official census in 1952 the population of Ibadan Province was over 1½ million, and less than 8% were over the age of 50. The diet of these people consists mainly of carbohydrate and is deficient in protein, but none of the patients was obviously malnourished at the time of examination.

Clinical Features

Women were affected at least twice as frequently as men, and over three-quarters of the series were under 30 years of age. It was not easy to obtain an accurate history, because these people have little sense of time and find it difficult to describe symptoms. However, the majority complained of substernal pain; in some cases this was clearly cardiac pain, but generally it was impossible to distinguish pain from the sense of tightness which accompanied effort dyspnoea. Nocturnal dyspnoea was uncommon, and most patients could lie flat without discomfort. Cough was a constant complaint, but haemoptysis was very rare.

Swelling of the legs and abdomen was the presenting symptom in half the cases, and in some had already

*In receipt of a grant from the Nuffield Foundation for the purpose of this study.