TO MY PARENTS,
WIFE, KESHNIE AND
SON, POOVERSAN MOODLEY

AN AETIOLOGICAL STUDY OF WHITE VULVAL SKIN LESIONS AMONGST PATIENTS ATTENDING THE GYNAECOLOGICAL CLINIC AT R. K. KHAN HOSPITAL, DURBAN

BY

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DECLARATION

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CONTENTS

Dedication	i
Title	ii
Declaration	iii
Acknowledgements	iv
Abstract	v
Contents	vi
Table of contents	vii
Chapter 1: Introduction and Literature Review	1
Chapter 2: Management of white vulval skin lesions	39
Chapter 3: The Study: Aim, methods and results	55
Chapter 4: Discussion, conclusions, recommendations, list of tables, figures and photographs	61
References	87

ABSTRACT

BACKGROUND

White vulval skin lesions may be due to various conditions, including benign and non-benign causes. The dilemma faced by the clinician with such a patient is the aetiology of the lesion, as well as the approach to management.

AIM

To establish the aetiology of white vulval skin lesions in patients attending the gynaecology clinic and to evaluate the role of Collin's test and vulvoscopy.

SETTING

R. K. Khan Hospital, which is a secondary level hospital in Durban, KwaZulu Natal.

METHOD

Sixty-two patients with white vulval skin lesions whom consented to the study were recruited. The investigations consisted of Pap smear, colposcopy of the vulva [Vulvoscopy], perineum and where appropriate, vaginoscopy and colposcopy; Collin's test and biopsy of all abnormal areas detected by these tests.

RESULTS

Pruritus vulvae was the commonest presenting symptom [70%]. No vulvoscopic abnormalities were detected in 97% of patients, whilst 3% had acetowhite areas indicative of Human papilloma virus infection. Collin's test was positive in 40% of patients, although, histologically these areas were benign. All patients in the study had benign lesions on histology.

CONCLUSION

All patients in this study had benign causes of white vulval skin lesions. However, this cannot lead us to conclude that there is no role for doing Vulvoscopy and Collin's test, as premalignant and malignant lesions should be detected by these tests had they been present.

CONTENTS

Dedication	i
Title	ii
Declaration	iii
Acknowledgements	iv
Abstract	v
Contents	vi
Table of contents	vii
Chapter 1: Introduction and Literature Review	1
Chapter 2: Management of white vulval skin lesions	39
Chapter 3: The Study: Aim, methods and results	55
Chapter 4: Discussion, conclusions, recommendations, list of tables, figures and photographs	61
References	87

CONTENTS

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

1. Introduction 1

2. Historical Perspectives and Terminology of White Vulval Skin Lesions 3
   2.1 Previous Terminology 3
   2.2 Later Correlations 5
   2.3 Current Terminology/ Classification 8
   2.4 Criticisms of the current terminology/ classification 11

3. Classification of white vulval skin lesions 12
   3.1 Depigmentation disorders 13
   3.2 Hyperkeratosis 13

4. Vulval Dermatoses 14
   4.1 Clinical features of vulval dermatoses/ non- neoplastic epithelial vulval Disorders 14
      4.1.1 Lichen sclerosus 14
      4.1.2 Squamous cell hyperplasia 17
      4.1.3 Other dermatoses
         4.1.3.1 Lichen simplex chronicus 18
         4.1.3.2 Lichen planus 19

4.2 Histopathological features of vulval dermatoses 20
4.2.1 lichen sclerosus 20
4.2.2 Squamous cell hyperplasia 21
4.2.3 Lichen simplex chronicus 21
4.3 Aetiology of vulval dermatoses 22
4.3.1 Link with autoimmune diseases 23
4.3.2 Hormone dependency 25
4.3.3 Infective cause 27
4.3.4 Miscellaneous causes 27
4.4 Relationship between vulval dermatoses and vulval malignancy 29

5. Vulval Intraepithelial Neoplasia [VIN] 31
5.1 Epidemiology of vulval intraepithelial neoplasia 31
5.2 Vulval intraepithelial neoplasia as a multicentric disease 32
5.3 Nomenclature of vulval intraepithelial neoplasia 33
5.4 Clinical features of vulval intraepithelial neoplasia 33
5.5 Histolopathological features of vulval intraepithelial neoplasia 34
5.6 Colposcopic Features of vulval intraepithelial neoplasia 34
5.7 Prognosis of vulval intraepithelial neoplastic lesions 35

6. Paget's disease of the vulva 36
6.1 Clinical features of Paget's disease 36
6.2 Histological features of Paget's disease 37

7. Invasive carcinoma of the vulva 37
7.1 Clinical features of invasive carcinoma of the vulva 38
7.2 Histological features of invasive carcinoma of the vulva 38

CHAPTER TWO: MANAGEMENT OF WHITE VULVAL SKIN LESIONS

1. Management of white vulval skin lesions 39

1.1 Investigations 39

1.1.1 Role of Colposcopy/ Vulvoscopy of the vulva 39

1.1.1.1 Background 39

1.1. 1.2 Normal vulvoscopic findings 40

1.1.1.3 Limitations of vulvoscopy 41

11.1.4 Technique of vulvoscopy 42

1.1.2 Collin's Test 42

1.1.2.1 Background 42

1.1.2.2 Limitations of Collin's test 43

1.1.2.3 Technique of Collin's test 43

1.1.3 Vulval biopsy 44

2. Therapeutic Strategies: White vulval skin lesions 45

2.1 Vulval dermatoses 45

2.1.1 Lichen sclerosus 46

2.1.2 Squamous cell hyperplasia 50

2.1.3 Lichen planus 51

2.1.4 Lichen simplex chronicus 51

2.2 Vulval intraepithelial neoplasia 51

2.3 Paget's disease 53

2.4 Squamous cell carcinoma of the vulva 54

CHAPTER THREE: THE STUDY – AN AETIOLOGICAL STUDY OF WHITE VULVAL SKIN LESIONS AMONGST PATIENTS ATTENDING THE GYNAECOLOGICAL CLINIC AT R.K. KHAN HOSPITAL

1. Introduction and aim of the study 55

2. Patients and methods 57

3. Results 58
3.1 Clinical features 58
3.2 Investigations 59
3.3 Histological features 59

CHAPTER FOUR

1. Discussion 61

2. Conclusions and recommendations 67

3. Table I: Presenting complaints 69

4. Table II: Results of Collin's Test 70

5. Table III: Histological diagnosis of all white vulval skin lesions 71

6. Photographs and Figures:

6.1 Clinical features of lichen sclerosus 72

6.2 Clinical features of squamous cell hyperplasia 73

6.3 Clinical features of Lichen simplex chronicus 74

6.4 Clinical features of Lichen planus 75

6.5 Histopathological features of lichen sclerosus 76

6.6 Histopathological features of squamous cell hyperplasia 77

6.7 Histopathological features of lichen simplex chronicus 78

6.8 Clinical features of vulval intraepithelial neoplasia 79

6.9 Histopathological features of vulval intraepithelial neoplasia 80

6.10 Clinical features of Paget's disease of the vulva 81

6.11 Histopathological features of Paget's disease of the vulva 82

6.12 Clinical features of invasive squamous cell carcinoma of the vulva 83

6.13 Histopathological features of invasive squamous cell carcinoma of the vulva 84

6.14 The Colposcope 85

6.15 Keyes cutaneous punch biopsy instrument 86

7. References 87

1. INTRODUCTION

One of the commonest symptoms of vulval diseases is pruritus vulvae. [1] It has also been shown to be one of the commonest symptoms for which women attend a gynaecological clinic.[2,3,4,5] Another important symptom is that of vulval pain [Vulvodynia]. Vulvodynia is defined as chronic vulval discomfort, characterized by the patient's complaint of burning, and sometimes stinging, irritation and rawness. [6] There are various clinical entities, which constitute the syndrome of vulvodynia [7] viz. vulval dermatoses, cyclic vulvitis, vulvovestibulitis syndrome, essential or dysaesthetic vulvodynia; vulval papillomatosis and miscellaneous causes such as neuroma of the vulva. [8]

There are many causes of pruritus vulvae. Examples include infections such as candidiasis, diabetes mellitus, hepatic or biliary disease, haematological conditions like polycythemia, systemic dermatoses, amongst others. Although some authors [9] differentiate between pruritus and vulvodynia, the sensations of itching and pain respectively, are conducted by the unmyelinated type C nerve fibres. The stimuli for both these sensations however, are quite different. It is therefore important to examine these patients thoroughly to look for precipitating factors and to establish the cause. The patient with "Burning Vulva Syndrome" [10] seldom has gross abnormal physical findings. Dermatological manifestations of vulval disease

may be confusing, the cause may be ambiguous and the course of treatment usually long and frustrating. If the patient does not complain of a specific vulval symptom, the vulva is often overlooked during a routine gynaecological examination and is often simply "the means to go through" in order to perform the routine digital examination or pap smear.

A systematic approach to establish the aetiology of the patients' symptomatology is necessary. Various authors [9,11,12,13,14] have advocated an approach, which includes a thorough physical examination, pap smear, colposcopy of the vulva, vagina, cervix and perineum, Collin's test and biopsy of all abnormal areas detected by these tests. The role and need to do these tests have been questioned, since there are both false negatives and false positives associated with colposcopy [15] and Collin's test [16]. If a macroscopic lesion is present, the difficulty then, is to decide on which areas to biopsy in order to establish diagnosis.

Lesions found macroscopically and at colposcopy are classified according to the classification of Friedrich et al [17] [1983], in accordance with their appearance, white lesions, red lesions, dark lesions, ulcers, small tumours or large tumours. Many patients present with white vulval skin lesions, the cause of which varies from benign to malignant. Thus, in order to establish a correct diagnosis, a biopsy is necessary from the representative area. The

issue therefore is to decide on which area is the most representative. The limitations of the above mentioned investigations are noted and the emphasis of the study are the causes as well as evaluation of these investigations in-patients with white vulval skin lesions.

2. HISTORICAL PERSPECTIVES AND TERMINOLOGY OF WHITE VULVAL SKIN LESIONS

2.1 PREVIOUS TERMINOLOGY

The earliest description of a white vulval skin lesion was recorded by Weir [18] et al [1875]. He noted that these lesions were persistent, pruritic and benign. This case was presented among cases of leucoplakia of the tongue, a lesion recognized as premalignant. The issue of natural progression and especially the malignant potential of these lesions have been raised many times since, often, with an accompanying plea for a change in terminology.

Schwimmer[19] et al [1877] used the term "leucoplakia", which implied a potentially malignant change in mucosal and mucocutaneous tissue. 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 was applied

originally to the tongue and mouth. This term was not 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 described, with the possibility of there being two directly opposing features – namely, hypertrophy and atrophy.

Breisky [20] et al [1885] introduced the term "Kraurosis" which means brittle. Yet, various authors later had different interpretations of this term. Taussig [21] et al [1922] regarded the term Kraurosis as meaning "shrinkage", while Hunt [22] et al [1940] regarded this term as meaning "white and dry".The British and American opinion on this term was also divided. The British view followed the teachings of Berkeley and Bonney [23] et al [1909] as a condition affecting only the introitus, causing contracture and therefore dyspareunia, rather than pruritus. This concept was never accepted outside Great Britain. Taussig regarded contracture of the introitus merely as a result of excessive degenerative changes in the epidermis and dermis. The term Kraurosis is now recognized as lichen sclerosus.

Hallopeau [25] et al [1889] described a condition of unknown aetiology in which there were small white patches of skin associated with atrophy of the vulval and perianal skin. This lesion was termed lichen sclerosus and has

survived all the changes in the literature over the past 100 years, in spite of the fact that there is neither lichen nor sclerosus present! "Lichen" implies thickening, yet the skin in this condition is thin and "Sclerosus" implies metabolic inactivity, yet several classic studies have proven that the tissue is indeed metabolically active, normal skin.[17,26] Lichen sclerosus was also called lichen sclerosus et atrophicus. The terms "et atrophicus" is no longer used since it has been shown that the epithelium is metabolically active and not atrophic.

Taussig [21] et al [1922] introduced the term Leukoplakic vulvitis, a description of which was later recognized as mixed dystrophy [Lichen sclerosus with associated hyperplasia]. Taussig [21]et al [1922] further distinguished leukoplakic vulvitis from kraurosis not only on the basis of appearance and histology, but also on that of prognosis, stating that in his experience simple kraurosis had no malignant potential, while 50% of leukoplakic vulvitis progressed to malignancy. [21,27,28]

2.2 LATER CORRELATIONS

Wallace et al [29][1951] and Wallace [30] [1955] in a series of accounts summarized by Wallace [31] [1971], attempted to overcome the confusion surrounding leukoplakia, kraurosis and leukoplakic vulvitis and their relation

to lichen sclerosus. They proposed that those cases clearly showing typical lichen sclerosus, clinically and histologically, should be noted as such. The terms Kraurosis and leukoplakic vulvitis should be dropped and where Kraurosis was seen without clear evidence of lichen sclerosus, this should be called " Primary Atrophy." Primary atrophy was regarded as having some potential for malignant change. Further, whereas Berkeley and Bonney [23] et al [1909] had found no hyalinization histologically, but much inflammation, the histology of primary atrophy was described by Wallace and Whimster [29] [1951]et al as an atrophic epidermis, reduced elastic tissue, hyalinised collagen and some inflammatory cells. They retained the term Leukoplakia as a histological entity, characterized by marked dermal hyalinization, sometimes a dermal infiltrate, a hyperkeratotic epidermis with lengthened, irregular forked rete pegs with or without cellular atypia.

Jeffcoate [32] et al [1961] tried to simplify the situation, beginning with an analysis of all putative causes of vulval malignancy. They reviewed the terms Leukoplakia and leukoplakic vulvitis and noted that in many situations the clinician expected the histopathologist to provide the diagnosis of leukoplakia and vice versa. They also noted that there were no clinical differences between leukoplakia, kraurosis and lichen sclerosus. They concluded that the same end point occurs due to different aetiological factors and that the vulval and perianal regions are subject to chronic skin changes, probably

conditioned by environment rather than causes. These skin changes irrespective of their appearances, for which a specific cause is unknown, are best given clinically by an all-embracing term such as "Chronic Epithelial Dystrophy."

Gardner et al [33] [1969] suggested a histopathological classification with terms like Atrophic Dystrophy [Lichen Sclerosus], Hyperplastic Dystrophy and mixed Dystrophy [lichen sclerosus with foci of epithelial hyperplasia]. The sixth world congress of the International Federation Of Obstetricians and Gynaecologists was held in 1970, at which Gardner led a round table discussion of vulval diseases. From the efforts of those present, the International Society for The Study of Vulval Diseases [ISSVD] was formed. The purpose of this society included the classification, study and sharing of ideas and facts related to vulval diseases. It's members included gynaecologists, pathologists and dermatologists.

Friedrich et al [33,34] [1976], reporting on behalf of the International Society for the Study of Vulvar Disease, recommended that lichen sclerosus et atrophicus, leukoplakia, neuro dermatitis, leukeratosis, Bowen's disease, erythroplasia of Queyrat, Carcinoma simplex, leukoplakic vulvitis, hyperplastic vulvitis and kraurosis vulvae be deleted from the vocabulary of

vulvar diseases. Recommendations were made for an appropriate classification as follows:

i. Hyperplastic Dystrophy – with / without Atypia

ii. Lichen sclerosus

iii. Mixed Dystrophy – with / without Atypia.

Mixed dystrophy referred to lichen sclerosus with foci of epithelial hyperplasia. A uniform terminology to facilitate the collection and analysis of data on these diseases was thus developed. This classification is strictly histopathological, while the only clinical correlate is to note if the lesions were diffuse or localized, thick or thin, white or red.

2.2 THE CURRENT POSITION

Judging from the accounts of Berkeley and Bonney [23] et al [1909], the terms Kraurosis and Leukoplakic vulvitis are, essentially unitary and fully compatible with the different patterns of Lichen sclerosus. The same is true of the descriptions by Taussig [21] et al [1922] of these two terms. On reviewing the clinical and histological findings of primary atrophy, it was found that many patients with primary atrophy developed unequivocal lichen sclerosus. Therefore the use of the term primary atrophy has fallen away.

It was found that the entity "leukoplakia" corresponds to an active, painful fissured lesion of lichen sclerosus and is therefore regarded as a severe phase of lichen sclerosus. This term, presently, is reserved for use for oral lesions, at the recommendation of the World Health Organization [35] and is defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease. Thus, this term has been restored to its original oral domain and is no longer used to describe lesions on the vulva.

On reviewing the term "Dystrophy" it is noted that it comes from "dys" which means bad or difficult and "trophe" which relates to the nutrition or vascularity of the tissue. Yet, there are no proven nutritional or vascular aberrations present. It was also recognized that well-defined entities like psoriasis or eczema should have been recognized separately. The most problematic situation was when the term "atypia" was used as it frequently led many gynaecologists to radical vulval surgery or radiotherapy with its attendant problems in a condition of unknown malignant potential.

At the Ninth Congress of the International Society for the study of vulval diseases in 1987 [36], changes were made in conjunction with the International Society of Gynaecological Pathologists, regarding terminology and classification. It was recommended that the terms "et atrophicus" be

dropped in patients with lichen sclerosus, as it has been shown that the epithelium is indeed metabolically active. The term Dystrophy has been replaced by the terms "Dermatoses" or "non-neoplastic epithelial vulval disorders"[NNEVD], emphasizing its non-neoplastic or benign nature. The term atypia is no longer used and where atypia is present, it is now grouped with the vulval intraepithelial neoplastic [VIN] lesions. The term hyperplastic dystrophy has been replaced by the term squamous cell hyperplasia. The term mixed dystrophy is no longer used as it has been recognized that lichen sclerosus may have a hyperplastic component without necessarily implying the presence of another disease entity.

Specific lesions or dermatoses affecting the vulva [e.g. psoriasis, lichen simplex chronicus, lichen planus, contact dermatitis, etc] would be specifically diagnosed and included under the term "other dermatoses". The current classification of the vulval dermatoses is therefore:

i. Lichen Sclerosus

ii. Squamous Cell Hyperplasia

iii. Other Dermatoses

Examples of other dermatoses include:

i. Lichen simplex chronicus

ii. Lichen planus

iii. Psoriasis

iv. Contact dermatitis

2.3 CRITICISMS OF THE CURRENT TERMINOLOGY / CLASSIFICATION

There are two aspects of the current classification/terminology that are open to criticism. [37] Firstly, as noted, the term lichen sclerosus does not appropriately describe the histological features. Yet, this term has survived all attempts to simplify the terminology. The second contentious issue is the term squamous cell hyperplasia, which was introduced to provide a descriptive term acceptable to both clinicians and pathologists. This term is not ideal, as epithelial hyperplasia may be the end result of a number of conditions. The diagnosis should be one of exclusion and should not be given as a pathological diagnosis if there is a definable dermatoses or pathological process which would explain the underlying process. There is also a possibility that clinicians and pathologists may confuse the term with

lichen simplex chronicus, which has squamous cell hyperplasia as one of its principle features.

3. CLASSIFICATION OF WHITE VULVAL SKIN LESIONS

Gross white appearance of vulval skin may be due to three general types of change:

i. Absence or loss of pigment

ii. Increased keratinisation [Hyperkeratosis]

iii. Relative avascularity

The following classification [38] of white vulval skin lesions is recommended:

i. Depigmentation disorders – Leukoderma or Vitiligo

ii. Hyperkeratosis:

A. Chronic infections

B. Benign tumours

C. Vulval Dermatoses

1. Lichen sclerosus

2. Squamous cell hyperplasia

3. Other- Lichen simplex chronicus

- Lichen planus

D. Vulval Intraepithelial neoplasia

E. Vulval Paget's disease

F. Invasive vulval carcinoma

3.1 DEPIGMENTATION DISORDERS

Depigmentation can occur if the basal layer melanocytes are lost or destroyed or because of chemical malfunction, they are unable to synthesize melanin pigment. Vitiligo or leukoderma may be due to congenital or acquired absence of pigment. These terms are often used interchangeably. The congenital variety often appears at the menarche suggesting a relationship between pituitary gonadotropes and melanin stimulating hormone. Many parts of the body may be involved, although the anogenital area seems to be more common.

In the acquired type the melanocytes disappear from localized areas of skin. Trauma, infection and radiation scarring can cause depigmentation. In leukoderma, newly formed skin may not have acquired a melanocyte population, resulting in white skin appearance. In albinism there are normal melanocytes, which are prevented from forming melanin pigment because of an enzymatic defect.

3.2 HYPERKERATOSIS

A number of conditions are associated with excessive surface keratin layers. If keratin is wet, it becomes opaque and appears white in colour. The thicker the keratin, the whiter the skin appears. For this reason, hyperkeratotic

vulval skin, which is in an area of constant moisture, appears typically white in colour.

The end result of chronic infection may be scarring and thickening of the skin with white change. Benign tumours such as papillomatous or verrucous lesions may demonstrate areas of hyperkeratosis and white change. Skin can also appear pale when superficial blood vessels are constricted, when interposing distance between them and the surface is increased, or when they are numerically decreased by a sclerotic process. All three of these mechanisms are indeed active in the white skin lesions seen in the vulval dermatoses.

4. VULVAL DERMATOSES

4.1 CLINICAL FEATURES OF VULVAL DERMATOSES/NNEVD

4.1.1 LICHEN SCLEROSUS

Lichen sclerosus typically occurs in childhood, regress following the menarche and recurs after the menopause. [12] The skin in affected areas appears white, crinkled, scaly and thin. [Photograph number 1, page 72] It usually affects the skin of the labia majora, minora, clitoris as well as perianal area with relative sparing of the area in-between. This produces the typical "figure of 8" appearance which is classical, but not pathognomonic of lichen

sclerosus.[39] In untreated patients there is obliteration of the clitoris by oedema with phimosis and atrophy and shrinkage of the labia minora and introitus. This commonly produces the symptom of dyspareunia or painful coitus. [9]

In the early stages of the disease, the labia minora may fuse with the labia majora and disappear completely as a result of atrophy. The skin may split in the midline especially between the clitoris and urethra. In the natural folds of the skin, fissures may develop. This may also occur in the posterior portion of the fourchette. The white plaques may become confluent and guttate; in which case it may resemble that of scleroderma, with which it is significantly associated. [31] Both these conditions can become bullous, especially scleroderma resulting in confusion in making a diagnosis.

Up to 20% of patients with lichen sclerosus have extragenital lesions, which present as small ivory, shiny macules or papules, that become atrophic and are usually asymptomatic. [11] Extragenital lesions may occur on any part of the trunk, upper and lower limbs. A common area is the anterior aspect of the wrists. The Koebner phenomenon often occurs. The Koebner phenomenon refers to the occurrence of lichen sclerosus at sites of trauma, when the lesion is also present elsewhere on the body. Lichen sclerosus has been noted to occur at the site of radiotherapy for carcinoma of the breasts

in two patients who had no lesions elsewhere. [40] The existence of oral lichen sclerosus is disputable and histological confirmation is rarely present.

Vesicles and bullae, sometimes haemorrhagic, may occur. Small telangiectases and purpuric lesions sometimes occur probably as a result of injury to the atrophic skin. The disorder is much less common in children than in adults. Published series show from 2%[41] to 15%[42] of cases begins before the age of 13. The earliest reported age of onset was 6 months. [43] In Wallace's series [31] [1971], 28 of 50 started between the ages of 3 and 6 years. The clinical features of childhood lichen sclerosus are the same as that in adults. [44]

The general health remains normal and often the condition is asymptomic. A vaginal discharge may precede the vulval lesions in about 20% of patients. However, the commonest presenting symptom is that of pruritus vulvae which may occur in up to 60-70% of patients. It seems that the more hyperplastic the lesion, the more severe is the pruritic symptom.

PROGNOSIS OF LICHEN SCLEROSUS

Whilst it is generally agreed that extragenital lesions of lichen sclerosus usually remit following puberty, there is uncertainty as to the anogenital

lesions. Wallace [31] et al [1971] noted that in two thirds of patients with anogenital lesions, the lesions cleared around the time of puberty. Detailed follow-up is usually not available. In Wallace's report, the regression is mainly of symptoms rather than signs. It seems therefore, that although the condition looks and feels better around the time of puberty, proof that it actually remits is lacking. The condition does not seem to remit in middle age, except in the extragenital sites. Therefore, it may very well be that lichen sclerosus does not remit at all. This is often supported by the fact that adult patients often recollect symptoms of lichen sclerosus in childhood. Adult women with lichen sclerosus may complain of dyspareunia, but pregnancy appears to be uneventful. [19]

4.1.2 Squamous Cell Hyperplasia

Squamous cell hyperplasia typically presents as thick white skin involving the labia majora, outer aspect of the labia minora, interlabial sulci and perineum. [Photograph number 2, page 73] In both lichen sclerosus and squamous cell hyperplasia there is hyperkeratosis producing the white skin appearance. In addition, in squamous cell hyperplasia, the rate of melanin production by the melanocytes cannot keep pace with the rate of growth of epithelial cells. Areas of squamous cell hyperplasia may be localized, elevated and well defined. In some patients the lesions are poorly defined. The vulva is usually

white in colour and due to the hyperplasia and hyperkeratosis, the skin is thick in texture.

In black patients the appearance may be dramatic and is often confused with vitiligo. However, in vitiligo the skin usually has a smooth surface. There may be fissures and excoriation, the result of chronic scratching. Many patients present with pruritus vulvae although some may present with soreness, burning and vulval pain [vulvodynia]. [7] Most patients are younger than 50 years of age, although it may occur in the older patients. In a small percentage of patients, the lesions may be detected at routine gynaecological examination. There are an even smaller percentage of patients whose presenting complaint is one of a white vulval skin lesion.

4.1.3 OTHER DERMATOSES

4.1.3.1 LICHEN SIMPLEX CHRONICUS

Lichen simplex chronicus presents as thick, leathery white skin, which affects the labia. It is thought to be a secondary dermatoses, following chronic rubbing or scratching of the skin. Chronic contact or irritant reactions can provoke scratching as can any infection. The provoking stimulus may resolve, but lichen simplex chronicus persists because the patient continues to irritate the involved area. The affected skin becomes

lichenified, thickened and leathery with prominence of normal skin markings. [Figure 1, page 74] Pruritus is always a major symptom and with time, it may become impossible to tell whether the patients' scratching has triggered the itch or vice versa. Lichen simplex chronicus seems to develop more easily in-patients with atopic eczema. [40] The lesions may be confined to the vulva or may be part of general dermatoses with the antecubital and popliteal fossae being the commonest extragenital sites involved. [45]

4.1.3.2 LICHEN PLANUS

Lichen planus is typically a pruritic eruption of shiny, smooth, flat-topped papules on the skin and white patches or erosions on the mucous membranes. [Figure 2, page 75] The papules are usually purplish-white in colour forming a lacy pattern. Patients first notice lesions on the lips and the gynaecologist may be the first to find asymptomatic vulval lesions. Almost two thirds of patients with lichen planus have mucous membrane involvement [39] and some have disease limited to either the genitalia or oral mucosae.

The lesions typically occur on the anterior aspect of the wrist, lumbar area of the back, medial thighs, ankles and shins. In the acute

widespread variety, lesions begin on the extremities and spread rapidly centrally to involve the trunk, sparing the face. Another type of lichen planus lesion is that described as the erosive lichen planus which may involve the vagina causing extensive desquamation of the vaginal mucosa, with resultant synechiae formation.[39] A grey pseudomembrane is usually noted. The vestibule may be erythematous and friable with an adherent exudate. There may be marked resorption of the labia minora. Atrophy may occur including obliteration of the clitoral head. Patients sometimes complain of pruritus, burning, dysparenia and the feeling of "rawness". The onset of the erosive type of lichen planus may preceed or follows vulvovaginal lesions many months later.

4.2 HISTOPATHOLOGICAL FEATURES OF THE VULVAL DERMATOSES

4.2.1 LICHEN SCLEROSUS

The histological features of lichen sclerosus are usually typical. [39] There is hyperkeratosis or thickening of the keratin layer producing the white skin lesions. The epidermis is markedly thinned with flat rete pegs. There is cytoplasmic vacuolization of basal cells and follicular plugging. Beneath the epidermis there is a characteristic zone of homogeneous, pink-staining, collagenous-appearing tissue which appears acellular. Oedema is usually noted in these areas. Immediately below this area, in the mid-dermal zone,

lies a band of chronic inflammatory cells made up mainly of plasma cells and lymphocytes. There may be areas of hyperplastic squamous epithelium present, which usually occurs secondary to chronic scratching of the vulval skin. [Photograph number 3, page 76]

4.2.2 SQUAMOUS CELL HYPERPLASIA

The histological features consist of a variable increase in thickness of the keratin layer [Hyperkeratosis] and irregular thickening of the malpigian layers [Acanthosis]. Acanthosis results in epithelial thickening associated with lengthening and distortion of the rete pegs into either clubbed or pointed structures. The granular layer is sometimes prominent. Due to the elongation of the rete pegs, the papillae become conspicuous and oedematous. A chronic inflammatory cell infiltrate consisting of plasma cells and lymphocytes is often present within the dermis. [Photograph number 4, page 77] Squamous cell hyperplasia is usually a diagnosis of exclusion when the acanthosis cannot be attributed to a specific dermatosis, or a pathological process that would explain the hyperplastic process. [46]

4.2.3 Lichen Simplex Chronicus

In well-developed cases of lichen simplex chronicus, there is hyperkeratosis, acanthosis, and elongation of the rete pegs, fibrosis of the papillary dermis

and a mild inflammatory infiltrate. [Photograph number 5,page 78] There is also an underlying dermatosis seen which results in epithelial thickening. [36]

4.2.4 LICHEN PLANUS

The histological features of lichen planus of the vulva are similar to that found elsewhere in the body. These features include hyperkeratosis, acanthosis, a dense subepithelial band – like infiltrate composed mainly of T-Lymphocytes, which extends up to the basal layer where there may be liquefaction, degeneration and the formation of colloid bodies. The rete pegs are elongated and pointed. These histological features are as a rule, definite and may be necessary if there are pale isolated papules similar to that of lichen sclerosus.

4.3 AETIOLOGY OF VULVAL DERMATOSES

The aetiology of the vulval dermatoses remains obscure although various theories have been suggested, viz.:

4.3.1 LINK WITH AUTOIMMUNE DISEASES

An association of lichen sclerosus with autoimmune diseases has been suggested. Wallace[31] et al [1971] suspected a significant association with vitiligo. Meyrick-Thomas[47] et al [1983] studied the relationship between autoimmune diseases, autoantibodies and lichen sclerosus in 25 men. They found a significantly higher frequency of autoimmune related disorders compared to a control population. There was also a higher frequency of autoantibodies than expected in a normal male population.

Ridley et al [39], later confirmed these findings in a study of more than 200 patients. A later study by Meyrick-Thomas[48] et al [1988] found autoimmune related disorders in 59.5% of patients studied. Of the 350 women studied, 21.5% had one or more autoimmune related disease, 21% had one or more first degree relatives with autoimmune related disease, 42% had an autoantibody titre greater than 1 in 20 and almost 60% had one or more autoimmune related phenomenon, i.e. a personal or a family history of an autoimmune related disease including allopecia, vitiligo, thyrotoxicosis, hypothyroidism, pernicious anaemia, diabetes mellitus, systemic lupus erythematosus and primary biliary cirrhosis. The conditions most often linked in affected women are thyroid disease and allopecia.

Goolamali[49] et al [1974] reported a link between patients with vitiligo and lichen sclerosus. In twenty-six patients with lichen sclerosus, it was found that 40% had anti-thyroid antibodies and 44% had antibodies against gastric parietal cell. It was therefore felt there could be a link between lichen sclerosus and an autoimmune process. It has been noted that there is a relationship between patients with Sjogren's syndrome and vulval dermatoses. Thus, it is postulated that there may be a relationship between autoimmunity and vulval dermatoses.

Achlorhydria has been noted to be present in some cases of vulval dermatoses of which many were probably lichen sclerosus. Jeffcoate[50] et al [1966] noted this to be the case in 23% of 269 patients with vulval dermatoses. Lavery[51] et al [1984] found achlorhydria in 10 of 18 patients with "chronic vulval dystrophy" and speculated, about a relationship between the effect of urogastrone [epidermal growth factor] on the skin and on gastric acidity and the opposing effect of somastatin. Johansson[52] et al [1986] noted immunoreactivity to a substance like vasoactive intestinal peptide in cells of the epidermis in two out of four patients with lichen sclerosus and cells of the epidermis to substance like vasoactive intestinal polypeptide.

In contrast, Harrington and Dunsmore[53] et al [1981] noted a low occurrence of autoimmune phenomena and lichen sclerosus, especially with regards the natural history. This was further supported by the failure to demonstrate an association between lichen sclerosus and HLA-B 8 or DRw3, the tissue types found to have an increased prevalence in individuals with diseases considered to have autoimmune basis.

Meyrick-Thomas[48] et al [1988] further noted no relationship between autoimmune phenomenon and the natural history of lichen sclerosus [sites of involvement, age of onset, onset in relation to menarche and menopause or the development of malignancy] of those with or without antibodies.

Harrington[54] et al [1984] found a non-statistically significant increased incidence of HLA-B40 in 50 women with lichen sclerosus. Meyrick-Thomas[55] et al [1984] also found a non-statistically significant association with HLA types in 92 women and 28 men with lichen sclerosus.

4.3.2 Hormone Dependency

It is well recognized that when lichen sclerosus occurs in pre-pubertal girls there is often resolution when puberty is reached. [11] This would suggest that

lichen sclerosus may be influenced by oestrogen, but the use of topical oestrogens have been disappointing. Cinberg[56] et al [1945] noted an improvement in vulval lichen sclerosus following the application of topical testosterone and others have investigated this further. Friedrich and Kalra[57] et al [1984] studied 30 patients with untreated lichen sclerosus and found reduced serum levels of dihydrotestosterone and androstenedione and significantly increased levels of free testosterone. When patients were treated there were significant increases in total testosterone and dihydrotestosterone levels than in a control group.

These findings provide the basis for the treatment of lichen sclerosus with testosterone cream. It is hoped that, by inundating the skin with substrate, some of it will undergo conversion, thereby exposing the tissues to the deficient hormone.

These authors suggested that there may be a block in converting testosterone to dihydrotestosterone and postulated a reduction in 5 alpha reductase activity. However, in females with documented reduction in 5 alpha reductase activity, there has not been shown to be any increase incidence of lichen sclerosus. Other authors [58] have looked at hormone receptor levels and have found that there is elevated levels of progesterone receptors. This

could explain the beneficial effects of progesterone therapy for lichen sclerosus.

4.3.3. INFECTIVE LINK

There have been suggestions that lichen sclerosus may be due to a spirochetal infection.[59] There is similarity in the skin lesions of scleroderma and Lyme disease. Lyme disease is caused by the spirochete Borrelia *burgdoferi.* There is similarity in the skin lesions of scleroderma and lichen sclerosus.[60] However, these spirochetes as well as anti-Borrelia antibodies have not been found in lichen sclerosus. This link has not been confirmed. Karram[61] et al [1988] studied the relationship between the vulval dystrophies and the presence of the human papilloma virus. There were no associations noted between the non-atypical dystrophies and the human papilloma virus.

4.3.4 MISCELLANEOUS CAUSES

There may be yet, other unknown causes, which may play a role in the vulval dermatoses. Barnes[62] et al [1985] noted an increase in collagen inhibitor enzyme and an absence of collagenase in lichen sclerosus compared with the normal vulval tissue and that from other vulval conditions. The same authors later suggested that the activity of elastase is increased.[63]

Bushbell [64] et al [1980] and Carli [65] et al [1991] suggested that the skin's immune system might play a role in the pathogenesis of lichen sclerosus. They observed an increase in activated T lymphocytes in the dermis as well as persistent increase in the number of epidermal Langerhan's cells in lichen sclerosus.

The concept of familial predisposition to the development of lichen sclerosus is well supported by reports of Wallace [31] et al [1971], Friedrich [64] et al [1984] and Barker [67] et al [1962]. Murphy [68] et al [1982] noted lichen sclerosus to be present in three sisters, one of whom had pernicious anaemia and vitiligo. Meyrick-Thomas [69] et al [1986] reported the presence of vulval lichen sclerosus in identical twins.

It is felt that although the environment of the vulva influences the various pathologic processes, the role of chronic trauma, allergy, nutritional deficiency, psychoneurosis, metabolic disturbances and other factors are unknown. There seems to be a likely relationship of chronic vulvovaginal infections like candidiasis to lichen simplex chronicus, especially in-patients with diabetes mellitus. [39]

The role of race or ethnicity is not clear, although, it appears to be commoner in Caucasian females. [19] Barclay [70] et al[1966] and Dogliotti [71] et al [1974] described lichen sclerosus in Black patients.

4.4 RELATIONSHIP BETWEEN VULVAL DERMATOSES AND VULVAL MALIGNANCY

Lichen sclerosus at extragenital sites seems to have no risk of progression to malignant change. [19] Basal cell carcinoma has been noted to occur in-patients with lichen sclerosus. [72,73] It is unclear if this association is fortuitous or not. Freidman [74] et al [1984] noted the association of malignant melanoma with lichen sclerosus on the vulva of a 14-year-old. One area of debate has been the risk of progression of the vulval dermatoses to invasive squamous cell carcinoma of the vulva.

McAdams [72] et al [1958] found lichen sclerosus to be present in 16 out of 400 cases [4%] and leukoplakia, presumably lichen sclerosus in 31 patients [12%],with vulval carcinoma. Buscema [75] et al [1980] studied 98 patients of squamous cell carcinoma and found "dystrophies" in 49 patients. Zaino [76] et al [1982] examined squamous cell carcinoma in 60 patients whom had vulvectomy. It was found that 32 patients had "Atypical Hyperplastic Dystrophy,"15 lichen sclerosus, 14 hyperplastic dystrophy and

19 carcinoma in situ. Hewitt [77] et al [1976] found lichen sclerosus to be present in 96% of 104 women with squamous cell carcinoma.

Very few prospective studies have been done with regards to the risk of progression of the vulval dermatoses to invasive squamous cell carcinoma of the vulva. [22, 50, 72] It was noted that cancer rarely develops subsequently in women under close clinical supervision for chronic vulval diseases. Jeffcoate [50] et al [1976] noted that the risk of developing invasive carcinoma of the vulva in-patients with chronic vulval dystrophy in 138 women studied, ranged from 3-5% over a period of 3-25 years. Walkden [78] et al [1993] found the incidence of progression to be close to 9%.

Buckley [79] et al [1984] found that vulval intraepithelial neoplasia and lichen sclerosus may co-exist and this could increase the number of malignancies found with lichen sclerosus. Leibowitch [80] et al [1990] noted lichen sclerosus in 61% of women with vulval carcinoma. Fifty percent of these women had associated well-differentiated vulval intraepithelial neoplasia grade III. It was further observed that the undifferentiated form of vulval intraepithelial neoplasia grade III was not associated with lichen sclerosus. In those patients with carcinoma associated with lichen sclerosus, there was no evidence of the human papillomavirus [HPV/ DNA]. However, HPV/ DNA was found in association with severe vulval intraepithelial neoplasia.

In contrast, it was found that HPV type 16/18 was present in invasive squamous cell carcinoma in patients with lichen sclerosus.

In summary, the risk of vulval squamous carcinoma developing in a patient with vulval dermatoses is in the order of 1- 5% over a prolonged period of time. The risk factors for the progression of the vulval dermatoses to invasive carcinoma include a history of lichen sclerosus in childhood, co-existence of HPV 16/18 and the erosive type of lichen planus. [39]

5. VULVAL INTRAEPITHELIAL NEOPLASIA [VIN]

5.1 EPIDEMIOLOGY OF VULVAL INTRAEPITHELIAL NEOPLASIA

During the past 20 years there has been an increase in the reported incidence of vulval intraepithelial neoplasia, especially in premenopausal, sexually active women. [81] Knight [82] et al [1973] reported 26 cases of carcinoma in situ of the vulva while Woodruff [83] et al [1943] reported on 44 cases diagnosed between 1966 and 1972. Sturgeon [84] et al [1992] noted that the incidence rate of VIN III had nearly doubled between 1973 and 1976 and 1985 to 1987. During the same period, however, the incidence rate for invasive carcinoma of the vulva remained stable. They also found that the incidence of VIN III increased from 1.1 to 2.1 cases per 100

000 women/year. The largest increase occurred in white women less than 35 years of age.

In the past the mean age of presentation of VIN was 50 years. [85] However, today the commonest age of presentation ranges between 28 – 35 years. [81,86] This could be due to the fact that there is heightened awareness of neoplasia and increased tendency to take a biopsy as well as the frequent occurrence of viral infections of the lower genital tract.

There is no particular racial predisposition, with Whites and Blacks being equally affected. Whilst there is no relationship between the NNEVD and sexually transmitted diseases, there is a strong relationship between VIN and sexually transmitted diseases. [81] The most common pathogens implicated include Human papillomavirus, Treponema pallidium, Trichomonas vaginalis, Gardnerella vaginalis etc. There is a common association with immunosuppressed states [87,88] viz. renal transplants, systemic lupus erythematosus, cytotoxic agents etc.

5.2 VIN AS A MULTICENTRIC DISEASE

Vulval intraepithelial neoplasia is commonly associated with cervical intraepithelial neoplasia in 11 – 80% [89,94] of patients as well as with intraepithelial neoplasia of other genital tissues, including the anal canal. All

these intraepithelial neoplastic lesions are well-documented precursors of invasive squamous carcinoma in these areas. It is thought that a common oncogene affects the lower female genital tract, with the vulva and cervix being the most susceptible sites. When VIN is diagnosed, the chance of finding a concurrent cervical intraepithelial neoplastic lesion ranges from 11 – 80%.

5.3 NOMENCLATURE OF VIN LESIONS

In 1984 and again in 1987, the nomenclature committee of the International Society For The Study Of Vulval Diseases [39] proposed a classification for intraepithelial neoplasia involving the vulva. They grouped the diseases of squamous cell type under a single heading. On the other hand, Paget's disease and melanoma in situ, having distinctly different histopathological appearances, histochemical characteristics and natural histories, were subclassified. The classification of VIN lesions depend on the level in the epithelium the dysplastic cells are found and is as follows;

A. Squamous: VIN – I [Dysplasia – mild]

VIN – II [Dysplasia – moderate]

VIN – III [Dysplasia – severe, carcinoma in situ]

B. Other: Paget's disease [Intraepithelial]

Melanoma in situ [Level 1]

5.4 CLINICAL FEATURES OF VULVAL INTRAEPITHELIAL NEOPLASIA

Vulval intraepithelial neoplastic lesions commonly present as white skin lesions of the vulva, because of the hyperkeratosis. The lesions may be asymptomatic and discovered at routine gynaecological examination, or present more commonly as pruritus vulvae.[90] The diagnosis is confirmed by histological examination.[Figure 3, page 79]

5.4 HISTOPATHOLOGICAL FEATURES OF VULVAL INTRAEPITHELIAL NEOPLASIA

The histological features of VIN are classified according to whether the cellular abnormalities and lack of stratification are limited to the lower third of the squamous epithelium [VIN I], middle third [VIN II] or upper third of the epithelium[VIN III].[Photograph number 6, page 80] In the basaloid form of VIN, a parakeratotic layer overlies an epithelium containing closely packed, non-stratified cells which show nuclear crowding and a high nucleocytoplasmic ratio. In the Bowenoid form of VIN, there may be hyperkeratosis, premature cellular maturation, variable retention of stratification and pleomorphism and koilocytosis. Both the basaloid and the Bowenoid types may extend into the pilosebaceous units and sweat ducts. All these changes are confined to the squamous epithelium of the vulva.

5.5 COLPOSCOPIC FEATURES OF VIN

Andreasson[90] et al [1985] and Buckley [79] et al [1984] described the colposcopic findings of VIN lesions. These include abnormal vascular patterns with punctations, mosaicism or vascular irregularities present in up to 60% of patients. The epithelial changes include the presence and degree of acetowhitening of the epithelium following the application of 3% acetic acid. The colposcopic findings may be limited by the presence of thick keratin layers or congestion following infection or scratching.

5.6 PROGNOSIS OF VIN LESIONS

The risk of VIN grades I/II developing into invasive carcinoma is not clear, although, Friedrich [91] et al [1981] regarded the risk to be low. It is generally felt that the behaviour of VIN III is not comparable to that of CIN III. Freidrich [91] et al [1981] reported only 4 of 106 patients [4%] with VIN III to have developed invasive disease. Andreasson [90] et al [1985] quoted a figure of 2% risk of progression of severe grade VIN . Most reported cases where VIN had progressed to invasive carcinoma have occurred where the patient was old or immunosuppressed. [87,88]

Friedrich [91] et al [1981] and Bernstein [92] et al [1983] found that even untreated cases of aneuploid VIN III may undergo spontaneous regression.

Data on progression rates may be biased since majority of patients with VIN have been subjected to multiple treatments or diagnostic excisional biopsies. Bergeron [93] et al [1987] noted that untreated long standing, histologically verified VIN has high progression rates in the order of 90 – 100%. Progression transit times range from 2 – 10 years. The human papillomavirus type 16 in association with VIN has been frequently noted to progress to invasive disease as compared to HPV types 6/11.

6. PAGET'S DISEASE OF THE VULVA

Extramammary Paget's disease is a slowly growing intraepithelial carcinoma containing vacuolated Paget's cells. Of significance is that Paget's disease may be associated with an underlying carcinoma of the apocrine structures of the vulva, e.g. Bartholin's gland as well as anorectal carcinoma, breast carcinoma and squamous cell carcinoma of the vulva, vagina and cervix. [94]

6.1 CLINICAL FEATURES OF PAGET'S DISEASE

Paget's disease of the vulva generally affects Caucasian women in the postmenopausal age group, with the mean age of diagnosis being 65 years. The clinical presentation may be striking, with white epithelium scattered over a bright red base.[Figure 4, page 81] As a rule, the disease begins on the hair-bearing parts of the vulva, genital folds or perianal region, but may

extend to involve the labia minora and introital structures. Less frequently, Paget's cells may spread into the mucosa of the urethra, urinary bladder, ureters and even endocervix. [95] The commonest presenting symptoms are pruritus vulvae, soreness and burning. [96]

6.2 HISTOLOGICAL FEATURES OF PAGET'S DISEASE

The histological features of Paget's disease are quite typical.[Photograph number 7, page 82] The characteristic cell is the Paget cell which are large irregular cells containing clear vacuolated cytoplasm. The nuclei are vesicular and vary in size and shape. These cells may be isolated or occur in clusters at the tips or adjacent to the rete pegs deep in the epithelium. Paget's cells can be found in the epidermis well beyond grossly visible normal surgical margins. [39] Histochemical staining confirms the diagnosis of Paget's disease and exclude melanoma or squamous cell carcinoma in situ.

7. INVASIVE CARCINOMA OF THE VULVA

Vulval carcinoma is rare, representing only 3 –5% of genital cancers. Green [97] et al [1978] found there is an increase in incidence to about 8% in recent years. Vulval cancer is mainly a disease of the aged, with the average age being the seventh decade. However, it has been documented in girls in their teens as well as in women in their 20's and 30's. No definite cause has been identified with regards the aetiology of vulval cancers. However, certain

risk factors have been identified such as a long standing history of VIN, viral agents such as human papillomavirus types 16/18, vulval condylomata and immunodefficiency states. [98, 99]

7.1 CLINICAL FEATURES OF INVASIVE CARCINOMA OF THE VULVA

Up to 75% of patients may present with a mass lesion of the vulva.[Figure 5, page 83] Between 27 – 71% of patients complain of pruritus vulvae and 6 – 41% have a discharge or present with bleeding. Some patients may also complain of pain. Whilst the macroscopic features may be exophytic or ulcerated, some patients may present with a white vulval skin lesion. [19]

7.2 HISTOLOGICAL FEATURES OF INVASIVE VULVAL CARCINOMA

There are many variants of squamous carcinoma of the vulva. Well-differentiated tumours usually have islands, anastomosing masses and infiltrating cords of squamous cells. These cells show progressive nuclear and cytoplasmic maturation and keratinization towards the center of these masses. The underlying tissue usually has plasma cells and lymphocytes in varying amounts.[Photograph number 8, page 84]

CHAPTER TWO

1. MANAGEMENT OF WHITE VULVAL SKIN LESIONS

1.1 INVESTIGATIONS

There have been various modalities of therapy proposed for the treatment of white vulval skin lesions. These include medical and surgical approaches. An area of uncertainty has been the approach to management of a patient with a white vulval skin lesion. There has been a tendency to treat these patients without any investigations. However, since the causes of a white vulval skin lesion are variable ranging from benign to malignant causes, many authors [11,12,13,14] advocate an approach which includes doing a Pap smear, colposcopy of the vulva [vulvoscopy], vagina and cervix, Collin's test [toludine blue test] and biopsy of abnormal areas to establish the cause. This would guide clinical management as well as exclude the presence of underlying premalignant or malignant conditions.

1.1.1 ROLE OF COLPOSCOPY OF THE VULVA AND ADJACENT SITES

1.1.1.1 BACKGROUND

The colposcope [Photograph number 9, page 85] was introduced to evaluate abnormal cervical cytology since it has been shown to be reliable in predicting histological alterations. [100] Several studies [101,102,103] assessing various therapeutic agents in the treatment of the vulval dermatoses have used vulvoscopy in their methods. Vulvoscopy

is also used now to evaluate vulval complaints and pathology, [104,105] for diagnostic workup in women with abnormal pap smears [106] and to remove all vulvoscopically visible VIN III lesions. [107,108] The main aim is to select abnormal sites to biopsy in order to exclude malignancy. [109] The predictive value of vulvoscopy has been regarded to be uncertain mainly because normal vulvoscopic findings had not been determined in women without vulval complaints. It was therefore difficult to distinguish normal from abnormal findings.

1.1.1.2 NORMAL VULVOSCOPIC FINDINGS

Recently Van Beurden [13] et al [1997] and Apgar [110] et al [1996] have described normal vulvoscopic findings. It has been shown that vestibular erythema, vestibular papillomatosis and acetowhite lesions [30%] are common in healthy sexually active women without vulval complaints. It is thought that vestibular papillomatosis is probably congenital in origin and could be accentuated by any inflammatory condition. These micropapillae have been found to lack HPV DNA on hybridization studies.

A "cobblestone" appearance at the inferior part of the vestibule is thought to represent sebaceous hyperplasia, which occurs secondary to age or inflammation, producing hypertrophy of these glands. Non – specific acetowhite areas have been described at the junction of the

inferior part of the vestibule with the perineum. These changes are not due to the human papillomavirus infection but are thought to occur secondary to the trauma of intercourse, yeast infections or any other inflammatory conditions of the vulva. This type of acetowhitening is usually diffuse and flat, whereas that due to HPV infection is slightly raised with satellite lesions. Acetowhite lesions without vascular abnormalities are common on the vulva. Therefore not every acetowhite area contains dysplastic cells.

1.1.1.3 LIMITATIONS OF VULVOSCOPY

There are 3 limitations to colposcopy of the vulva and perineum. These include hyperkeratosis preventing underlying vascular and epithelial abnormalities being visible, light reflection from keratin and the presence of hair – bearing skin at the site of the lesion. To overcome these problems, it has been recommended that hair be clipped at the site of the lesion and KY Jelly be applied on the skin to reduce the light reflection from the keratin. [111] KY Jelly is a non-toxic water-soluble agent, which does not interfere with other substances used during colposcopic examination.

1.1.1.4 TECHNIQUE OF VULVOSCOPY

Colposcopy is done using the technique described by Hatch [112] et al [1993]. A colposcope with multiple magnification settings is necessary to facilitate the examination. The patient is placed in the lithotomy or dorsal position. The tissue to be examined is cleaned with saline, and then 3% acetic acid is applied. After 2 – 3 minutes the skin is examined under the colposcope for epithelial and vascular abnormalities. All abnormal areas are biopsied.

1.1.2 COLLIN'S TEST [TOLUDINE BLUE TEST]

1.1.2. 1 BACKGROUND

The Collin's test was first used by Richart [113] et al [1963] and later modified by Collin's [14] [1966], for vulval conditions as a diagnostic aid to delineate suspicious skin for biopsy. Toludine blue is a nuclear stain and when applied to tissues in vivo, becomes fixed to cell nuclei. Dilute acetic acid decolourizes any dye, which is not bound to nuclear material. In normal skin, keratin has no nuclei and therefore the dye is usually washed away with acetic acid.

Whenever there is a break in continuity of the epidermis, as occurs with an ulcer, or if nucleated squames are present in the upper epithelial layers, the skin would retain the dye. This would occur if

there are premalignant or malignant cells with nuclear material present in the upper epidermis.

1.1.2.2 LIMITATIONS OF COLLIN'S TEST

Reid [111] et al [1995] and Cavanagh [16] et al [1985] considered this test to be useful although, limited by false negatives associated with hyperkeratosis and false positives due to excoriation. Thus, areas, which are ulcerated or excoriated, as is often the case in patients with pruritus vulvae, would stain positive.

Freidrich [17] et al [1983] disregarded the false positive results and felt that much of the disappointment expressed with regards this test stemmed from the lack of understanding of its basic method of action. Many clinicians regard this test as a test for cancer, when in fact it is a simple test to indicate the presence of superficial nuclei. The presence or absence of cancer can only be confirmed by biopsy and histological assessment.

1.1.2.3 TECHNIQUE OF COLLIN'S TEST

The skin to be examined is first cleaned with saline or acetic acid. Toludine blue aqueous solution [1%] is then applied to the skin with a cotton swab and allowed to dry for one minute. The entire vulva is

then rinsed gently with 1-% aqueous acetic acid solution. Abnormal epithelium, if present, will stain royal blue.

The main argument for these investigations is to obtain directed biopsies rather than doing random biopsies, [14,114] which could miss representative areas. This needs to be appreciated, as the abnormal areas can be quite large, making it difficult to select sites for biopsy. Another significant fact is that some of the lesions tend to be multicentric, therefore, colposcopy of these areas is necessary to determine the extent of the underlying disease process.

1.1.3 VULVAL BIOPSY

All abnormal areas detected by colposcopy and Collin's test need to be biopsied for diagnosis and treatment. Vulval biopsy is a minor procedure which does not require general anaesthetic and can be done as an out – patient procedure. Anaesthesia can be accomplished by the local infiltration of 1% lignocaine injected subcutaneously using a dental syringe. Biopsies can be taken using a special vulval skin biopsy instrument such as a Keyes biopsy punch [Figure 6, page 86] or cervical biopsy instrument or using a scalpel blade. The Keyes cutaneous instrument [17] is used to core out a small circular plug of skin. It is obtainable in diameters ranging from 2 – 12 millimeters. The instrument is pressed against the skin, turned clockwise and

then anti-clockwise. A core of tissue is obtained containing epidermis and dermis. Alternatively, biopsy specimens can be obtained using a scalpel with a number 11 blade. An elliptical incision is made and the tissue removed. Minor bleeding can be stopped using a silver nitrate stick or a drop of Monsel's solution. Large defects or significant bleeding is treated by inserting 3 – 0 chromic sutures. These biopsy sites usually heal within 2-3 weeks. Post biopsy discomfort is usually minimal and simple analgesia usually suffice. Specimens are sent in formalin solution to the laboratory for histopathological assessment.

2. THERAPEUTIC STRATEGIES: WHITE VULVAL SKIN LESIONS

Depending on the aetiology, there have various modalities of treatment proposed for the management of white vulval skin lesions. These modalities of treatment usually range from medical to surgical.

2.1 VULVAL DERMATOSES

Generally, a search should be made for any possible aggravating factors such as Trichomoniasis, Candidiasis and allergy to various agents. If any of these are present the patient should be treated appropriately.

2.1.1 LICHEN SCLEROSUS

Since lichen sclerosus has atrophic histological features, treatment has generally consisted of using androgenic steroids such as topical Testosterone preparations. [106] Androgenic steroids are trophic hormones and are therefore appropriate in these conditions.

2.1.1.1 CHILDHOOD LICHEN SCLEROSUS

Lichen sclerosus in childhood, which is usually asymptomatic usually, does not require any treatment, except patient reassurance and follow up. The aim of treating childhood lichen sclerosus is to relieve the pruritus. The recommended initial treatment consists of topical 1% Hydrocortisone cream, alternating with bland emolient cream. [43] If there is no response to topical 1% hydrocortisone cream, then Progesterone ointment [compounded as 100 mg of progesterone in 1 ounce of petroleum] may be effective. Topical testosterone should not be prescribed for prepubertal females because of the risk of masculinising side effects. [45] Most children who respond to topical methods remain asymptomatic, although, careful follow up is necessary to exclude the development of malignancy in later life.

2.1.1.2 ADULT LICHEN SCLEROSUS

Various steroid preparations have been used for the treatment of adult lichen sclerosus. Initially 1% topical hydrocortisone cream should be applied. In most cases this is all that may be needed for the relief of pruritic symptoms. [115] Testosterone propionate in sesame oil, 100 mg/ml is mixed in petroleum base to obtain a 2% ointment. This medication is applied 2-3 times daily for 3-6 months or until the pruritus has subsided. Therefore the frequency can be reduced over 1 to 2 years when it may be used once or twice weekly. Generally, testosterone and progesterone preparations for this purpose is not available commercially and has to be compounded by the pharmacist on request. Mahmud [116] et al [1992] reported symptomatic improvement and reduction in lesion size in 80% of patients with lichen sclerosus treated with testosterone and corticosteroids.

One of the most effective agents reported for the treatment of vulval lichen sclerosus is clobetasol propionate [0.05%] [DERMOVATE, Glaxo, UK.] Bracco [117] et al [1993] in a randomized comparative study compared the efficacy of topical testosterone, topical 2% progesterone in petroleum base, topical 0.05% Clobetasol propionate and a placebo. The symptoms, gross appearance and

histology were scored and repeated after 3 months of treatment. Only the clobetasol group improved significantly with regards relief of symptoms and improvement of objective and histopathological findings. Patients treated with clobetasol experienced no adverse effects, which can occur with 2% topical testosterone preparation. Clobetasol [0.05%] should be applied twice daily for one month, once daily for two months and then twice weekly for an additional 3 months. Equally satisfactory results were reported by Dalziel [118] et al [1991].

Bornstein [106] et al [1998] reported the results of topical testosterone [2%], clobetasol dipropionate [0.05%] versus topical testosterone propionate [2%] for the treatment of severe lichen sclerosus and confirmed a 75% resolution of symptoms with the clobetasol group. However, unlike the high success rates previously reported over the past 40 years with the use of testosterone, this study found a lower success rate of 20% in patients treated with testosterone.

Occasionally vulval pruritus is so severe that it is not relieved by topical drugs. Here, the subcutaneous injection of Triamcinolone acetonide [0.1%] 5 mg is diluted in 2 ml of saline and injected

subcutaneously. Satisfactory results have been recently reported with the use of oral retinoids for vulval lichen sclerosus. Bousema [119] et al [1994] studied the efficacy of Acitretin [20 – 30 mg/day] for 16 weeks in a randomized, double – blind, placebo controlled trial using 78 patients. They found a 64% response rate in the acitretin group compared to 25% in the placebo group. The major drawback with the use of retinoids are their teratogenic potential and side effects. Young patients need effective contraception during therapy as well as for up to 2 years following discontinuation of therapy, as it has been shown that the drug can be stored in adipose tissue for up to 2 years after discontinuation of therapy, due to its highly lipophilic nature. Major side effects reported with these drugs include skin dryness, eye irritation, allopecia, myalgia and pseudoporphyria.

Sonnendecker [6] et al [1993] and Larsen [120] et al [1993] reported on the use of intralesional injection of interferon alpha 2b, when vulval dystrophy occurs in association with human papillomavirus infection. They noted the relief of chronic vulval discomfort and limited reversal of histological changes.

The role of surgery in the treatment of vulval lichen sclerosus is limited, as it has been shown that the risk of progression to cancer is very small. Also, lesions often reappear in transposed skin over the excised areas. [11] Surgery is justified only if pre -malignant or malignant lesions are found in association with the vulval dermatoses.

2.1.2 TREATMENT OF SQUAMOUS CELL HYPERPLASIA

Hyperplastic lesions are best treated with topical corticosteroids. Various agents are recommended including 1% or 2.5% hydrocortisone cream, 0.025% Flucinolone acetonide, and 0.01% triamcinolone acetonide. There is a risk of atrophy of the tissues by using potent topical steroids. Therefore, once the pruritus has settled, the potent topical steroids should be discontinued and replaced with mild topical hydrocortisone cream.

Various adjuvant agents have been used with topical steroids for the relief of pruritus. Some of these agents include topical Crotamiton and Calamine lotion as well as oral anti- histamines such as chlorpheniramine 4 mg given at bedtime. [11] For patients with recaltricant pruritus, local injection of absolute alcohol subcutaneously has been described to relief symptoms for up to 12 months. [39, 121]

2.1.3 LICHEN PLANUS

Unfortunately, the course of vulval lichen planus is prolonged with or without treatment. Corticosteroids, systemic and topical, are recommended. Also, intravaginal Betamethasone valerate is recommended for vaginal lichen planus. If there is extensive desquamatative vulvovaginal lichen planus, a short course of oral prednisone, up to 70 mg / day for 14 days may provide relief.

2.1.4 LICHEN SIMPLEX CHRONICUS

Lichen simplex chronicus responds to topical steroids. It is recommended that initial therapy should consist of potent steroids such as flucinolone acetonide used for 6 weeks to control the inflammatory response. Thereafter, lower potency steroids like triamcinolone acetonide 0.1% should be applied daily or twice daily for up to 2 months as response occurs. Topical 1% hydrocortisone cream should be used as maintenance therapy.[39] In children mild topical steroids are recommended.

2.2 MANAGEMENT OF VULVAL INTRAEPITHELIAL NEOPLASIA

Since the early 1960's and 1970's, there has been a radical change in the management of vulval intraepithelial neoplastic lesions. The treatment has become more conservative with the recognition that spontaneous regression occurs, as well as the fact that progression to invasive disease may be less

likely in younger females. In addition, there may be functional impairment, cosmetic as well as psychosexual sequelae with more radical procedures.

Generally, treatment should be individualized according to the location, severity and extent of lesions. The presence or absence of factors increasing the risk of occult invasive carcinoma should be considered. Treatment modalities range from medical to surgical methods. Medical treatment includes topical 5% 5- Fluorouracil cream [91], photodynamic therapy using dihaematoprotoporphyrin and dinitrochlorobenzene sensitization therapy. The problems encountered with medical therapies include extensive tissue sloughing, severe discomfort, delayed healing, variable response rates and insufficient patient numbers to evaluate success.

Surgical therapy includes wide local excision, skinning vulvectomy, carbon dioxide laser therapy and cryotherapy. Skinning vulvectomy [15] is reserved for very extensive four quadrant lesions followed by the application of split thickness skin grafts. [122] Wide local excision is recommended for localised lesions provided a I centimetre clear margin of normal skin is excised. [122] Excellent therapeutic and cosmetic results may be obtained with the carbon dioxide laser treatment of hairy and non- – hairy skin to a depth of 2 millimetres and 1 millimetre, respectively. [123] Deeper vaporization would

destroy subcutaneous fat, skin appendages, resulting in delayed and painful healing, scarring, dyspareunia and allopecia.

Cryotherapy has not gained popularity mainly because it produces delayed and painful healing and failures or recurrences are common. [122, 81] Generally the recurrence rates for the surgical methods are variable, ranging from 10%, if the surgical margins are free of disease, to 50% if the surgical margins have residual disease. [124]

2.3 MANAGEMENT OF PAGET'S DISEASE

There is a high incidence of associated carcinoma of the breast and genitalia in a patient with Paget's disease of the vulva. Therefore a thorough search for these tumours should be made as the treatment of these tumours takes precedence over the treatment of vulval Paget's'disease. If no associated malignancies are found, then the recommended treatment of the lesion consists of excision of the lesion down to subcutaneous fat, in order to exclude underlying sweat gland carcinoma. Previously, excision of the lesion with wide margins was recommended. [39] However, it has been found that recurrence rates of 12% occurs irrespective of the extent of histological involvement. [91]

2.4 MANAGEMENT OF SQUAMOUS CELL CARCINOMA OF THE VULVA

It is recognized that early invasive squamous carcinoma of the vulva can present as a white vulval skin lesion. If invasive disease is diagnosed then the current surgical staging should be used. [125] Management should be individualized according to the stage of the disease and the trend is to use less radical surgery due to recurrence rates, psychosexual sequelae, complications and the fact that invasive carcinoma is now being diagnosed earlier in younger patients with smaller lesions. [126,127] The surgical management consists of two main aspects. Firstly, surgery of the vulval primary lesion itself and secondly, management of the regional lymph nodes, where applicable, as described by Helm [126] et al [1992].

CHAPTER 3: THE STUDY - AN AETIOLOGICAL STUDY OF WHITE VULVAL SKIN LESIONS AMONGST PATIENTS ATTENDING THE GYNAECOLOGICAL CLINIC AT RK KHAN HOSPITAL, DURBAN.

1. INTRODUCTION AND AIM OF THE STUDY

White skin lesions may be confined to the vulva or may involve the vulva as well as other parts of the body. These lesions may occur in all age groups but some tend to occur in childhood, regress following the menarche and recur after the menopause. The aetiology of white vulval skin lesions are classified into benign and non–benign causes. Whilst it is recognized that benign causes such as those which constitute the entity of vulval dermatoses [Lichen sclerosus, squamous cell hyperplasia and other dermatoses] commonly manifest as white vulval skin lesions, vulval intraepithelial neoplasia, Paget's disease of the vulva and early invasive squamous carcinoma of the vulva can also present as similar clinical entities.

The dilemma faced by the clinician who manages a patient with a white vulval skin lesion is the exact cause in that particular patient. There is often uncertainty as to whether one should observe the lesion, biopsy the lesion or treat without biopsing the lesion. There is also a problem of knowing which site to biopsy since these lesions tend to be uniformly white and diffuse.

In contrast, some authors recommend a structured approach consisting of doing a Pap smear, colposcopy of the vulva, vagina and cervix and adjacent sites, where appropriate, Collin's test and a biopsy of all abnormal areas detected by these tests. This may seem to be unnecessary to those who believe that many such lesions are benign, and justify treatment without workup or tissue diagnosis.

However, judging from the literature, it is evident that benign as well as premalignant and malignant conditions can present as white vulval skin lesions. It is also recognized that benign disorders such as the vulval dermatoses can present adjacent to premalignant and malignant lesions. It seems therefore that it is difficult to guess from just inspecting the lesion, as to whether the lesion is benign or not.

The modalities of treatment of these various conditions vary widely from medical to surgical methods. It would therefore be inappropriate to treat without biopsy or to biopsy the lesion randomly as there is a risk of not obtaining the representative areas that can be achieved by doing vulvoscopy or Collin's test. The aim of the study was therefore, firstly, to determine the aetiology of white vulval skin lesions amongst patients attending the gynaecological clinic at RK KHAN Hospital and secondly, to evaluate the role of vulvoscopy and Collin's test.

2. PATIENTS AND METHODS

Ethical institutional permission was obtained and all patients gave informed consent. The study was done over an 18-month period from January 1997 to June 1998. All patients with white vulval skin lesions as well as those patients with similar lesions in other parts of the body were recruited for the study. Initially an appropriate history was taken including complaints, age and parity. A thorough general examination was done to exclude similar lesions elsewhere in the body. The vulva was inspected and the distribution of the white skin lesion recorded. If there was no vulvovaginal infection, vulvoscopy was done using the method described by Hatch [112] et al [1993]

Any abnormality detected by was noted and later biopsied as described below. A Collin's test was then performed using 1% toludine blue, which was applied to the vulval skin and washed off after 1 minute with 1% acetic acid. Those areas, which retained the stain including those areas detected by vulvoscopy, were selected for biopsy. The vulva was cleansed with antiseptic solution and 1% lignocaine was injected into the skin using a dental syringe.

These areas were then excised using a scalpel and sutures inserted where necessary. All specimens were sent in formalin for histopathological assessment. This was then followed by colposcopic assessment of the vagina and cervix and

all abnormal areas were similiarly biopsied. Patients were given post operative analgesia as well as antiseptic cream [Povidine- Iodine] to apply to the biopsied areas. A follow up visit was arranged 3 weeks later at which the histology results and further management was discussed with the patients.

1. RESULTS

The findings of this descriptive study were analyzed by a qualified statistician attached to the University of Natal Medical School, and are as follows:

1.1 CLINICAL FEATURES

This study covered a period of 18 months and included 62 patients in total. The mean age of the patients was 47.2 years [range 6 – 73]. The mean parity was 2.5 [range 0 – 4]. The commonest presenting symptom was pruritus vulvae [70%] [Table]. Only 18% of patients reported the presence of a white vulval skin lesion. In a small percentage of patients [1.7%], these lesions were detected on routine gynaecological examination.

The majority of patients [94%] did not have similar lesions elsewhere in the body, whilst 5% of patients also had similar skin lesions involving the trunk, limbs and abdomen in addition to the vulval lesion. In 43% of patients, the white skin involved the vulva and perineum with relative sparing of the area in-between. This type of skin lesion was called the "Figure of 8" pattern. The

remainder of the patients had white skin lesions involving the clitoris, labia majora, labia minora, posterior fourchette and perineum, alone or in combination.

1.2 INVESTIGATIONS

The majority of patients [n=47] had a benign pap smear of the cervix, whilst 5 patients had human papillomavirus infection detected on pap smear. Two patients had mild cervical intraepithelial neoplastic lesions [low-grade squamous intraepithelial lesion] detected on smear and 2 patients had acetowhite areas of the vulva detected on vulvoscopy.

Two patients had mild to severe grade cervical intraepithelial neoplastic abnormalities detected on colposcopy. There were no abnormalities detected on colposcopy of the vagina and no premalignant or malignant abnormalities of the vulva. The Collin's test was positive in 40% of patients and the commonest area in which this test was positive, was the posterior fourchette, where it was noted that many of these patients had fissures. [Table II]

1.3 HISTOLOGICAL FEATURES

The commonest histological diagnosis was lichen sclerosus in 70% of patients, with squamous cell hyperplasia being the second commonest histological finding. [20%] Of the remaining patients, 9% had non –

specific dermatitis and 1.7% had lichen simplex chronicus. None of the patients had vulval intraepithelial neoplasia or invasive carcinoma of the vulva. [Table III]

The commonest histological diagnosis across all age groups was lichen sclerosus. Those patients who had white skin lesions involving other sites of the body also had lichen sclerosus when it was also present on the vulva. [N= 3] On comparing the pattern of white vulval skin distribution with histological diagnosis, it was found that those patients who had white skin lesions in a "Figure of 8" distribution, also had lichen sclerosus on histology. Two patients had cervical intraepithelial neoplasia [CIN] diagnosed histologically. The 2 patients who had acetowhite areas detected on vulvoscopy where found to have features of human papillomavirus infection histologically.

CHAPTER 4

1. DISCUSSION

The present study done over an 18 month period included 62 patients in total, all of whom were of the Asiatic race group. Previous studies have found that most of the vulval dermatoses tend to occur mainly in Caucasian groups, although, it has been documented in Black patients by Barclay [70] et al [1966] and Dogliotti [71] et al [1974]. Meyrick – Thomas[48] et al [1987] found lichen sclerosus to occur in 1% of Asian women in a study involving 350 patients, although, here the study population consisted mainly of White females. The reason for this racial predilection is as yet unknown. Although RK Khan Hospital is situated in an area, which drains predominantly Indians patients, many Black patients from surrounding areas attend the hospital for medical attention.

The distribution of the patients with regards age varied widely with most of this variation being accounted for by lesions detected in premenarchal girls with lichen sclerosus. Only 7 patients [11%] were under the age of 30 years. The majority of patients were above the age of 50 years and the mean age of all patients was 47.2 years. The occurrence of lichen sclerosus in prepubertal females as well as postmenopausal females is similar to that reported by Kaufman [39] et al [1994]. Majority of the patients with

squamous cell hyperplasia were under the age of 50 years, in keeping with that reported by Kaufman [39] et al [1994].

The parity of all patients studied ranged from 0 – 4 and greater, whilst the mean parity was 2.5. There is no evidence from the literature that there may be any relationship between parity and the occurrence of white vulval skin lesions.

Only 18% of patients reported the presence of a white vulval skin lesion. Here the lesion was either detected by their general practitioner or in a few cases by the patients themselves. Most patients who noted the lesions themselves did not present immediately. Reasons for this varied. Some patients were embarrassed and therefore did not seek medical opinion, whilst others thought that the lesion was harmless. This was in spite of the fact that most of these lesions were associated with troublesome pruritus vulvae. The presenting complaints varied with pruritus vulvae being the most frequent [70%]. A very small percentage [1.7%] of patients were asymptomatic. These findings are in keeping with that reported by Kaufman [39] et al [1994]. This stresses the need to carefully examine the vulva at every gynaecological examination to detect asymptomatic lesions. It has been shown that the prognosis of vulval malignancies is better the earlier the lesion is detected. [14] There were 3 patients[5%] who had white skin lesions

involving the genitalia as well as extragenital sites. These lesions were usually detected at routine examination. These findings concur with that of Kaufman[39] et al [1994] who found the incidence of lichen sclerosus in extragenital sites to be 3% in 200 women with genital lichen sclerosus.

White skin lesions can involve any site of the vulva. Whilst 43% of patients had the so called "figure of 8" type distribution of white skin lesions, where the lesion involved the vulva and perineum with relative sparing of the area in-between, the majority of the remaining patients had white skin distribution involving multiple random sites with no particular pattern. Although the "figure of 8" pattern is classical of lichen sclerosus, some patients with varied pattern of white vulval skin distribution, also had lichen sclerosus on histology. Thus, the clinical appearance of the white skin distribution correlates with that described in the literature, with the exception that no patients in the study with lichen sclerosus had phimosis or clitoral stenosis. These features emphases the point that a diagnosis cannot be made by simply inspecting the lesions macroscopically.

Vulvoscopy was done using a standard colposcope used for microscopic examination of the cervix. Generally most lesions were covered with keratin and only 2 patients had colposcopic evidence of human papilloma virus infection, which was confirmed histologically. The limitation of vulvoscopy

due to keratin has been reported by Reid [111] et al [1995]. In some patients KY jelly was applied to the skin to reduce the reflection of the light from the colposcope. However, there seemed to have been little improvement in this respect. There were no specific vulvoscopic patterns noted in patients diagnosed with vulval dermatoses.

The Collin's test was positive in 40% of patients and the posterior fourchette was the most common area to stain positive. Here it was noted that majority of patients had fissures present which could have followed on scratching or intercourse. It was noted histologically that those patients with positive staining of the posterior fourchette had lichen sclerosus present. However, this does not imply that the commonest site to find lichen sclerosus is the posterior fourchette, as lichen sclerosus was also detected at other sites. This is in keeping with the observations of Collin that areas devoid of epithelium, exposing nuclear material would stain positive with application of toludine blue. Some would interpret this findings as being "false positives". However, Collin [14] [1966] stated that this test is not a test to detect areas with malignancy, but to select sites for biopsy in order to exclude malignancy histologically. If random sites are biopsied without doing vulvoscopy or the Collin's test, significant areas could be missed where premalignant or malignant disease is present. These conditions frequently tend to be multicentric and therefore the determination of the extent of the disease is

vital to guide therapy. The histopathologists are also faced with a problem when large random specimens are sent to them for assessment, as it may be difficult to decide which part of the specimen to choose for histological assessment.

Histological findings showed that lichen sclerosus was the commonest diagnosis [70%] across all age groups, in keeping with that reported in the literature [17]. The histological features supporting the diagnosis of lichen sclerosus included: hyperkeratosis, epithelial thinning, flat or absent ret pegs, follicular plugging, a homogenous acellular area beneath the epidermis and an inflammatory cell infiltrate in some cases. Friedrich [17] [1983] also reported that lichen sclerosus was the commonest cause of white vulval skin lesions, occurring in 70% of patients.

There were 13 patients with a histological diagnosis of squamous cell hyperplasia. The features supporting this diagnosis included hyperkeratosis, acanthosis or epithelial thickening, elongation and distortion of the rete pegs and a chronic inflammatory cell infiltrate in the dermis. None of these patients had any underlying dermatosis, which could have resulted in these changes. The diagnosis of squamous cell hyperplasia was therefore made by exclusion, as recommended by Wilkinson [46] [1992].

Six patients in the study had non-specific dermatitis diagnosed histologically. Histologically, it was found there were no specific features to arrive at a specific diagnosis. The features consisted mainly of inflammatory cells as well as perivascular inflammation in some cases. Non-specific dermatitis as the histological finding in some patients with white vulval skin lesions, is not commonly reported in the literature. O' Keefe [37] et al [1995] found the incidence of non-specific dermatitis to be 6% in 114 patients studied.

There were no patients in the study with vulval intraepithelial neoplasia or vulval invasive carcinoma. Of note is that the biopsy specimens were either taken from areas found to stain with toludine blue or random sites when the Collin's test was negative. In view of the negative vulvoscopic findings as well as negative histological findings of those areas biopsied when the Collin's test was positive, the role of vulvoscopy and the Collin's test may be questioned. However, it must be remembered that the aim of these tests is to select areas to biopsy to exclude malignant or premalignant lesions histologically and not to diagnose such lesions by these tests directly.

The findings in this study confirm the fact that there are many different causes of a white vulval skin lesion. Since the treatment of the different causes of white vulval skin lesions vary from medical to surgical, with surgery

having its attendant problems, it is imperative that clinicians treat these lesions based on histological findings.

2. CONCLUSIONS AND RECOMMENDATIONS

A plethora of terms have been applied to lesions of the vulva, characterized by shrinkage, whitening or reddening. Many such terms were used interchangeably as clinical and histological descriptions. The looseness of such terminology led to a wide variety of therapeutic modalities such as surgery and radiotherapy, for conditions or unproven malignant potential. The present study shows that the majority of white vulval skin lesions are benign in nature. This has been the reason why there has been uncertainty in the past as regards the approach to these patients. There has been a tendency to treat empirically without doing any investigations.

The approach adopted in this study and which is therefore recommended should be to do a Pap smear, vulvoscopy, vaginoscopy, colposcopy, Collin's test and directed biopsies of abnormal areas detected by these tests. In spite of the limitations of these tests, we can expect premalignant areas to be detected if they are present in a patient. The value of these tests is akin to the practice of doing colposcopy and directed biopsies of the cervix if a patient has an abnormal pap smear. Here, the implications are similar if a

premalignant or malignant lesion is diagnosed in addition to the fact that prognosis is better the earlier the diagnosis is made.

IN SPITE OF THE LIMITATIONS OF THESE TESTS AND THE FACT THAT NO PATIENT IN THIS STUDY HAD PREMALIGNANT OR MALIGNANT LESIONS, MY RECOMMENDATION TO DO THESE TESTS CONCURS WITH THAT OF LEADING VULVOLOGISTS.[17,19,91]

TABLE I : PRESENTING COMPLAINTS

Pruritus vulvae	43	[70%]
White vulval skin	11	[18%]
Vaginal discharge	21	[36%]
Post menopausal bleeding	1	[1.7%]
Hot flushes	2	[3.4%]
Generalized white skin of body	1	[1.7%]
Asymptomatic	1	[1.7%]

TABLE II : RESULTS OF COLLIN'S TEST

Negative	35	[60%]
Positive	23	[40%]

No. of Positive Areas	Site	Diagnosis
2	Lower labia majora	Lichen sclerosus
13	Posterior Fourchette	Lichen sclerosus
3	Posterior Fourchette	Squamous cell hyperplasia
2	Right/left labia majora	Lichen sclerosus
1	Clitoris	Squamous cell hyperplasia
2	Posterior Fourchette	Non-specific dermatitis

TABLE III : HISTOLOGICAL DIAGNOSIS OF ALL WHITE VULVAL SKIN LESIONS [n = 62]

Lichen Sclerosus	43	[70%]
Squamous Cell Hyperplasia	13	[20%]
Non-specific Dermatitis	5	[9%]
Lichen Simplex Chronicus	1	[1.7%]
Vulval Intraepithelial Neoplasia	0	
Vulval Carcinoma	0	

PHOTOGRAPH NUMBER 1

CLINICAL FEATURES OF LICHEN SCLEROSUS

Photograph shows white vulval skin in a background of normal skin.

Note the peri- introital and peri-anal involvement.

PHOTOGRAPH NUMBER 2

CLINICAL FEATURES OF SQUAMOUS CELL HYPERPLASIA

Photograph shows white vulval skin lesion involving multiple areas of the vulva with no particular pattern.

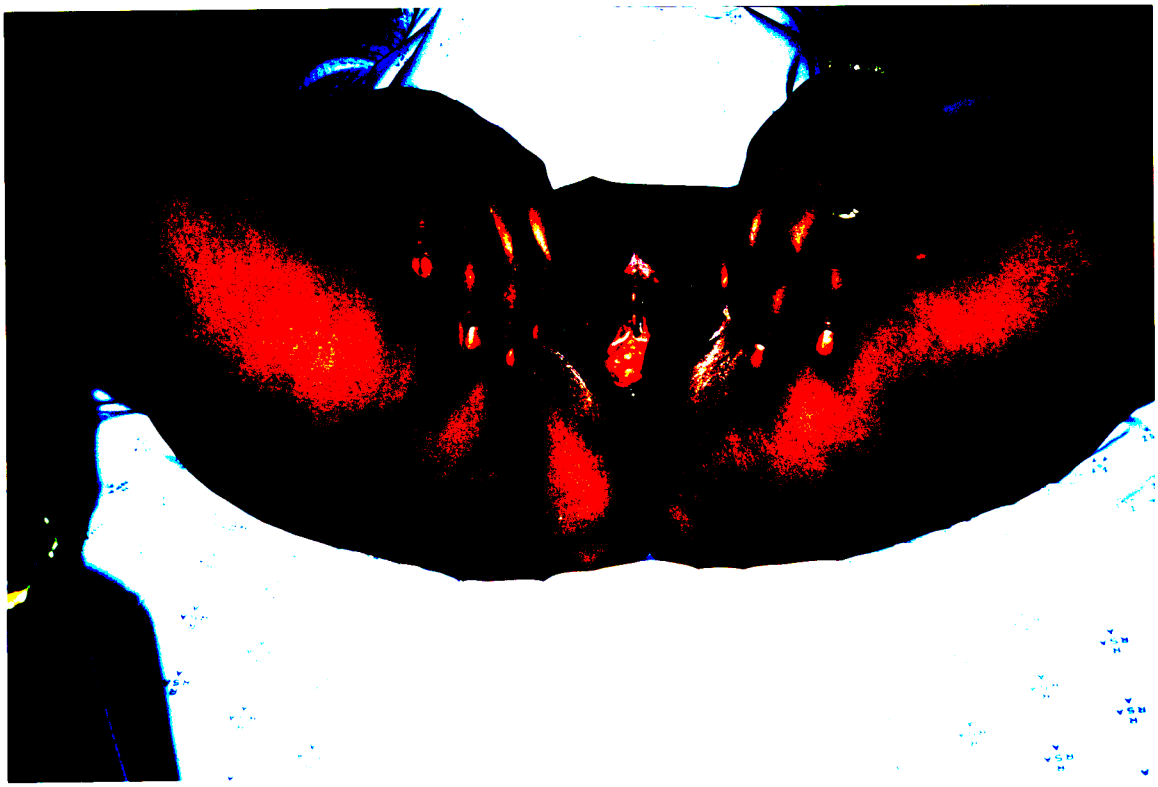


FIGURE 1

CLINICAL FEATURES OF LICHEN SIMPLEX CHRONICUS

Figure shows white leathery appearing vulval skin

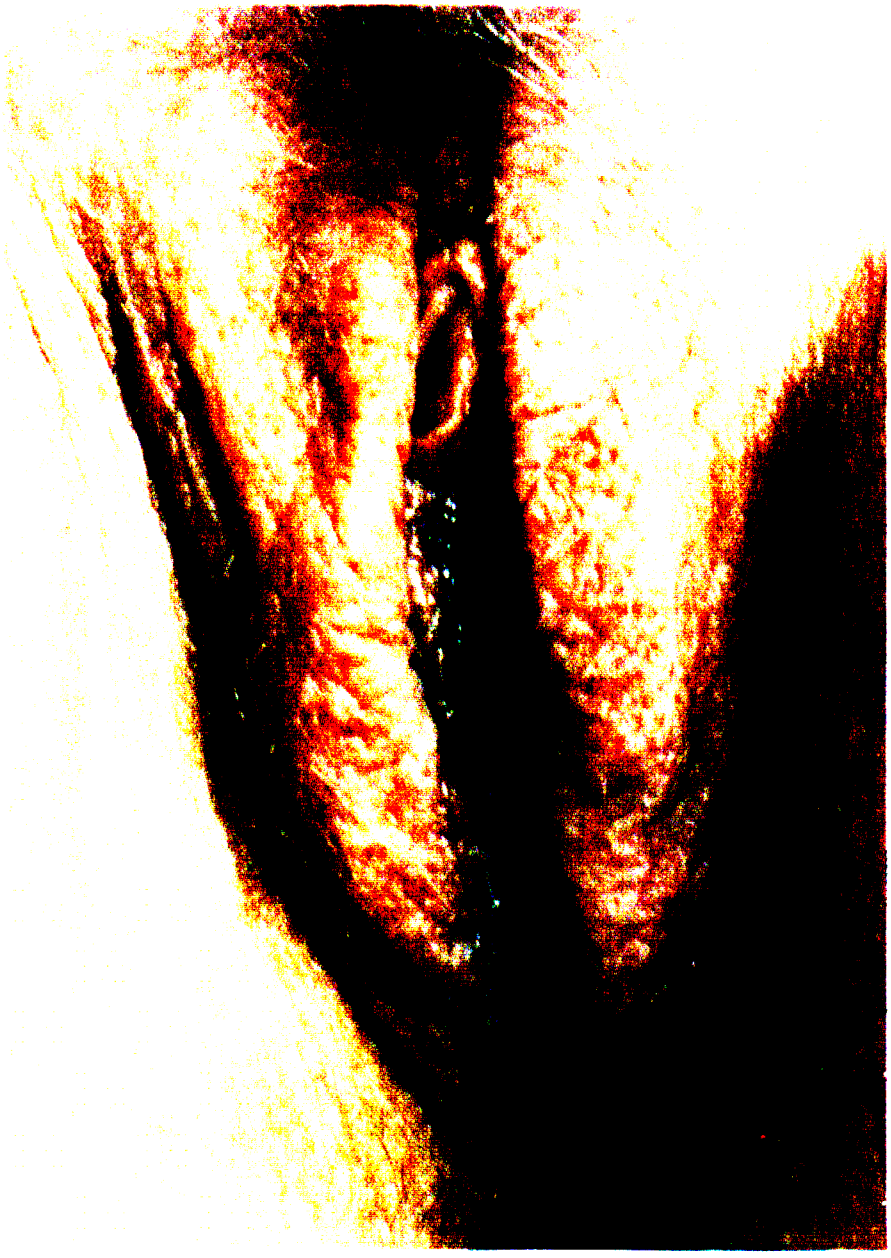
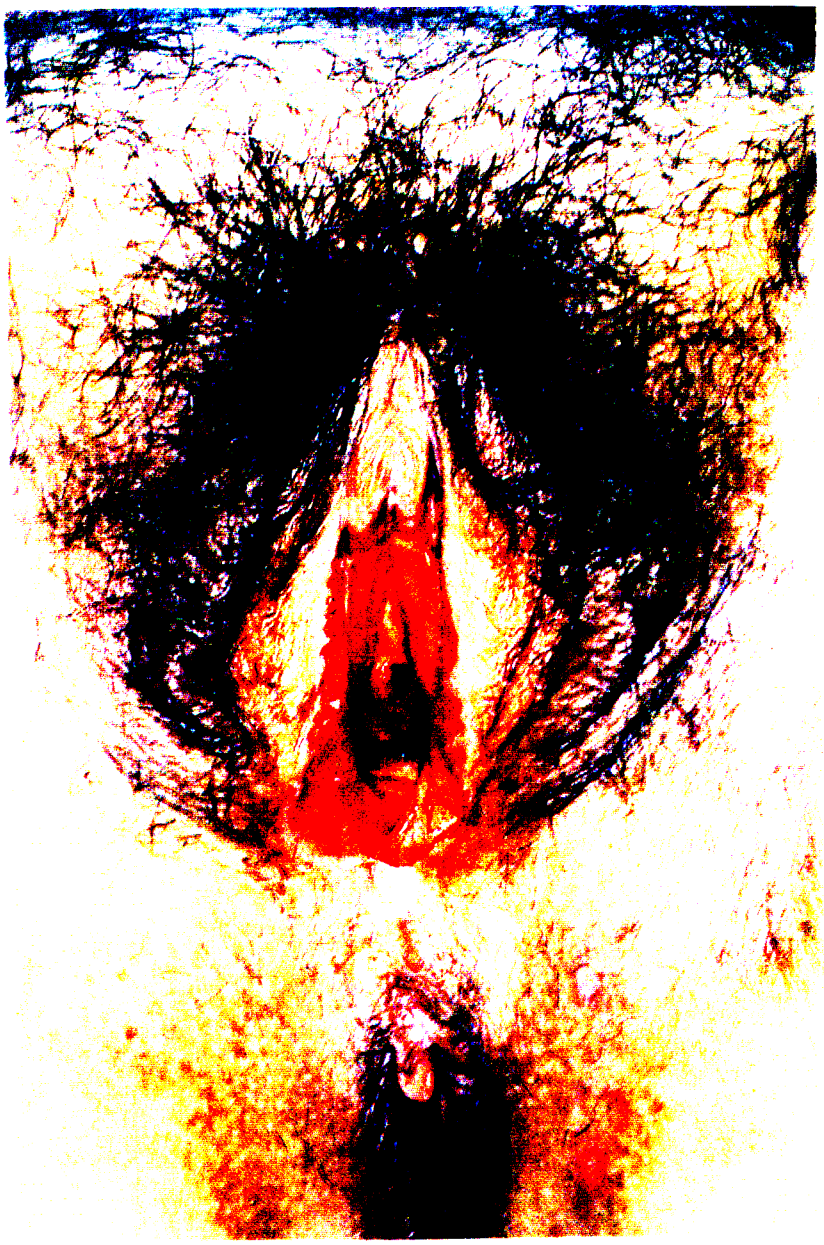


FIGURE 2

CLINICAL FEATURES OF LICHEN PLANUS

This figure shows the erosive type of lichen planus as can be seen in the region of the introitus where there is desquamation of the skin. The skin surrounding this region appears white in colour. There is also a purplish-white skin lesion noted in the surrounding areas which is typical of lichen planus.

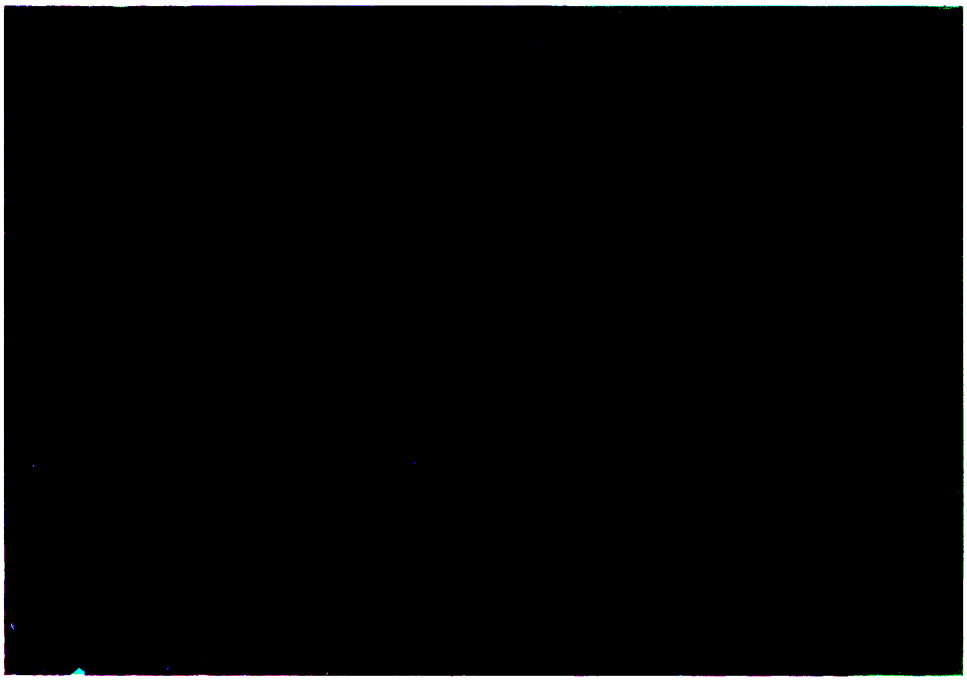


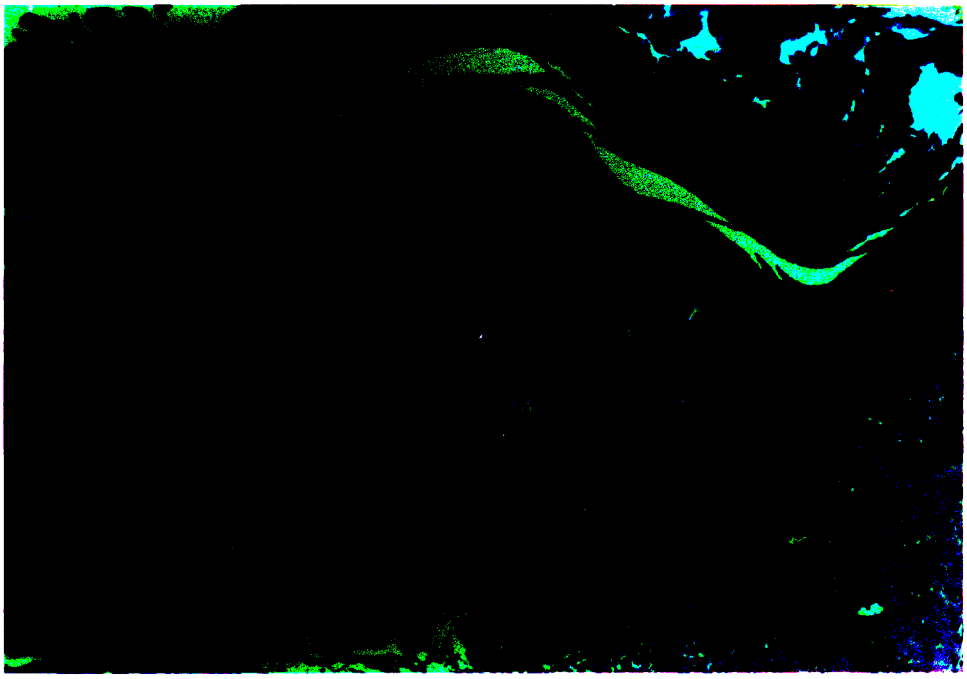
PHOTOGRAPH NUMBER 3

HISTOPATHOLOGICAL FEATURES OF LICHEN SCLEROSUS

PHOTOGRAPH NUMBER 4

HISTOPATHOLOGICAL FEATURES OF SQUAMOUS CELL HYPERPLASIA





PHOTOGRAPH NUMBER 5

HISTOPATHOLOGICAL FEATURES OF LICHEN SIMPLEX CHRONICUS

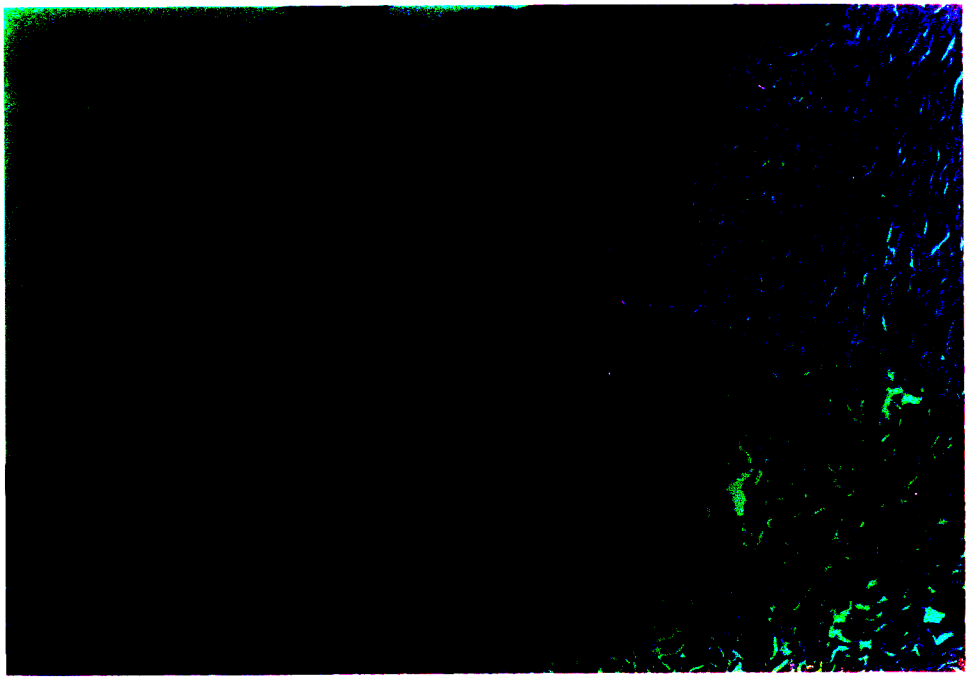


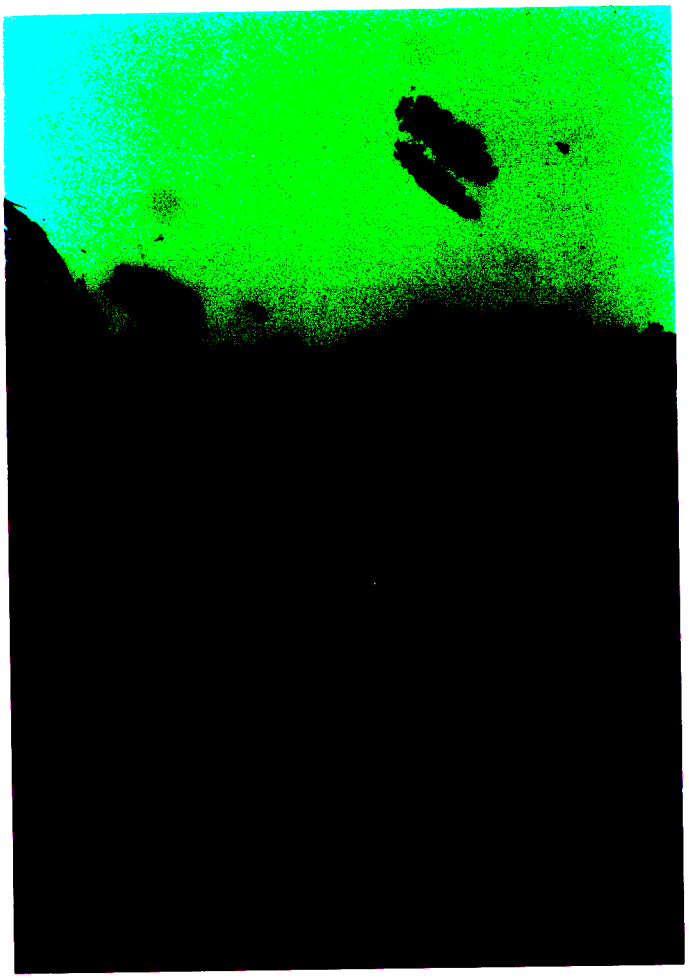
FIGURE 3

CLINICAL FEATURES OF VULVAL INTRAEPITHELIAL NEOPLASIA

The figure shows white vulval skin lesion with areas of plaque formation in a patient with vulval intraepithelial neoplasia.

PHOTOGRAPH NUMBER 6

HISTOPATHOLOGICAL FEATURES OF VULVAL INTRAEPITHELIAL NEOPLASIA



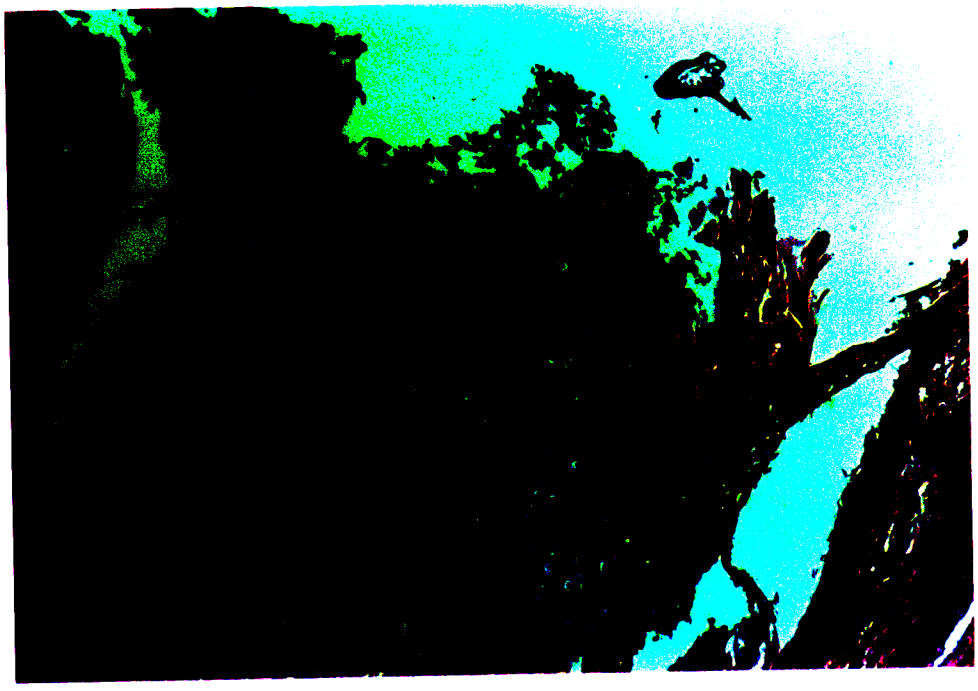
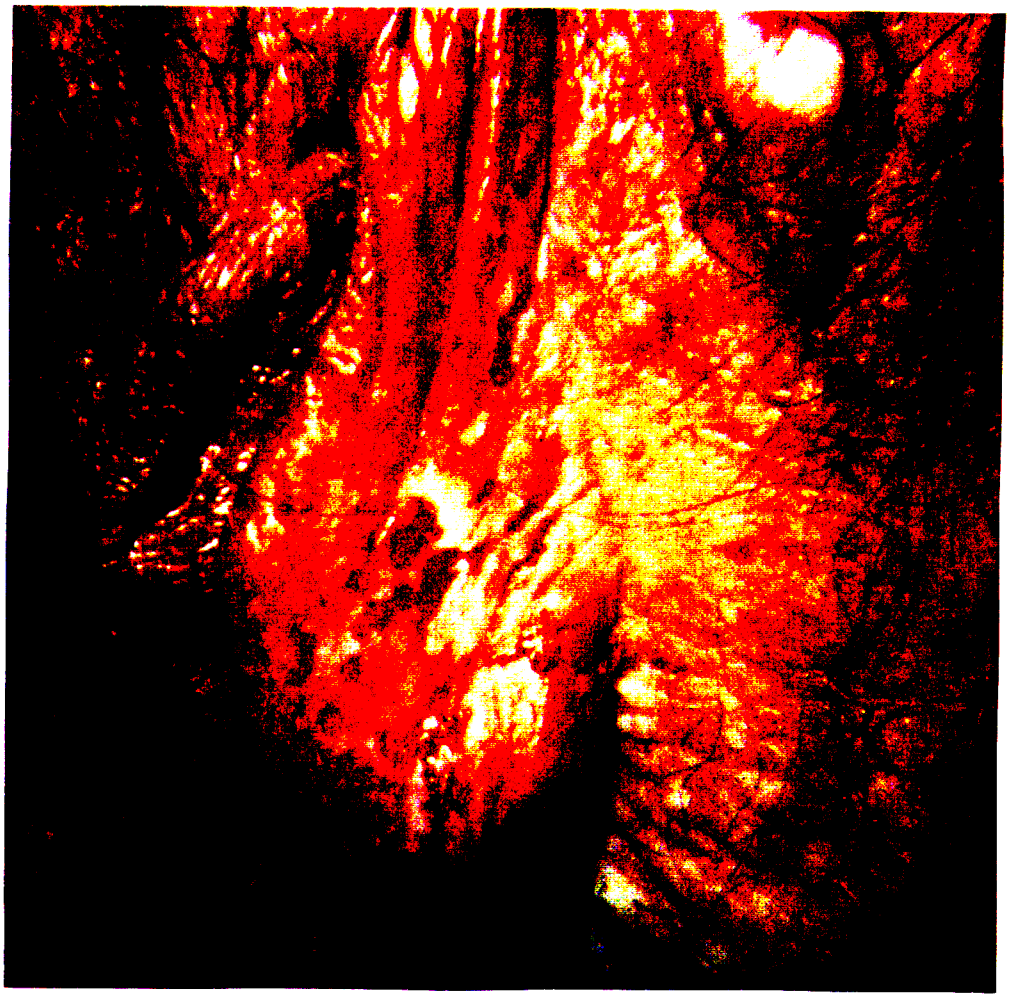


FIGURE 4

CLINICAL FEATURES OF PAGET'S DISEASE OF THE VULVA

The figure shows white vulval skin lesion scattered over a bright red base, typical of Paget's disease of the vulva.



PHOTOGRAPH NUMBER 7

HISTOPATHOLOGICAL FEATURES OF PAGET'S DISEASE OF THE VULVA

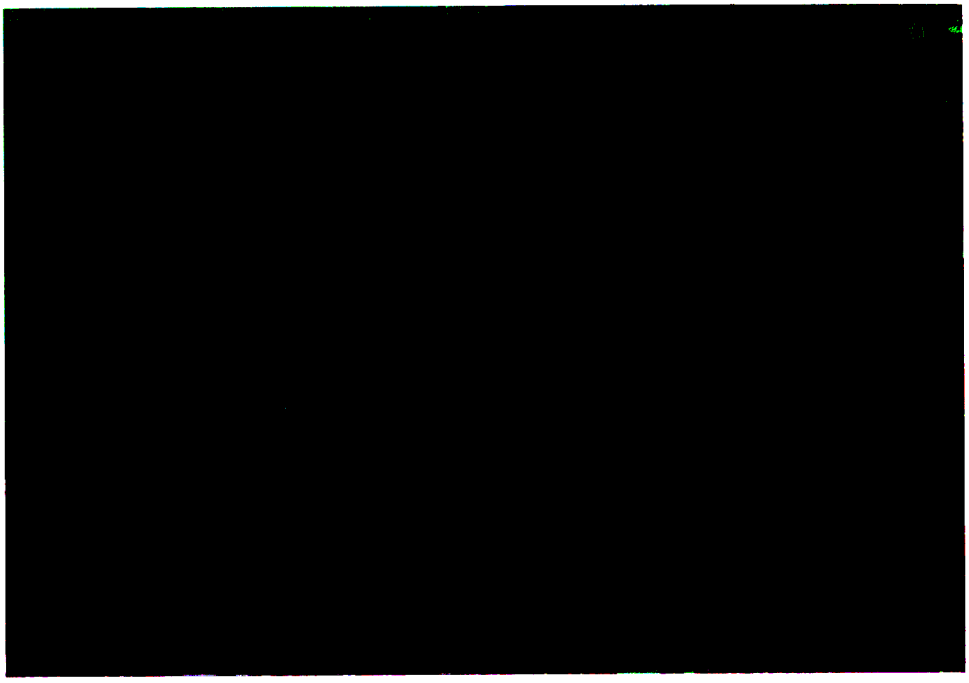
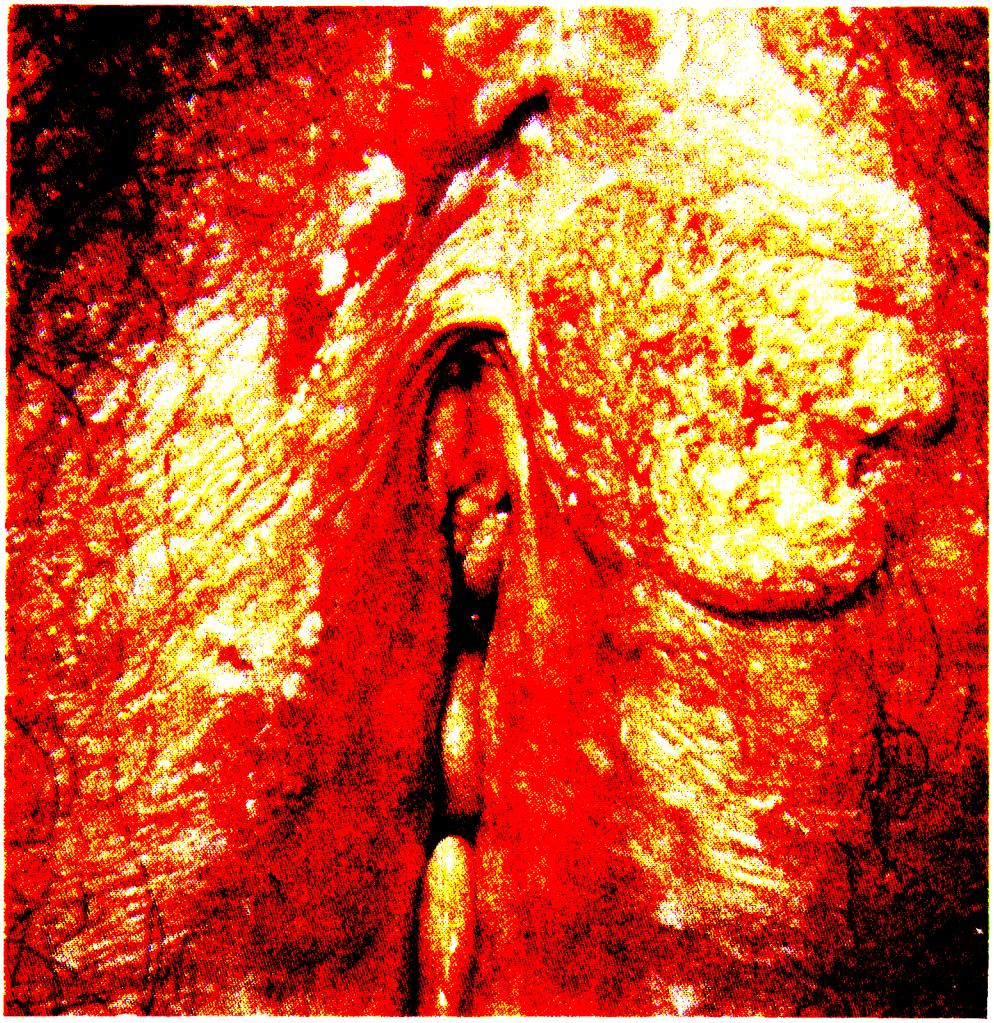


FIGURE 5

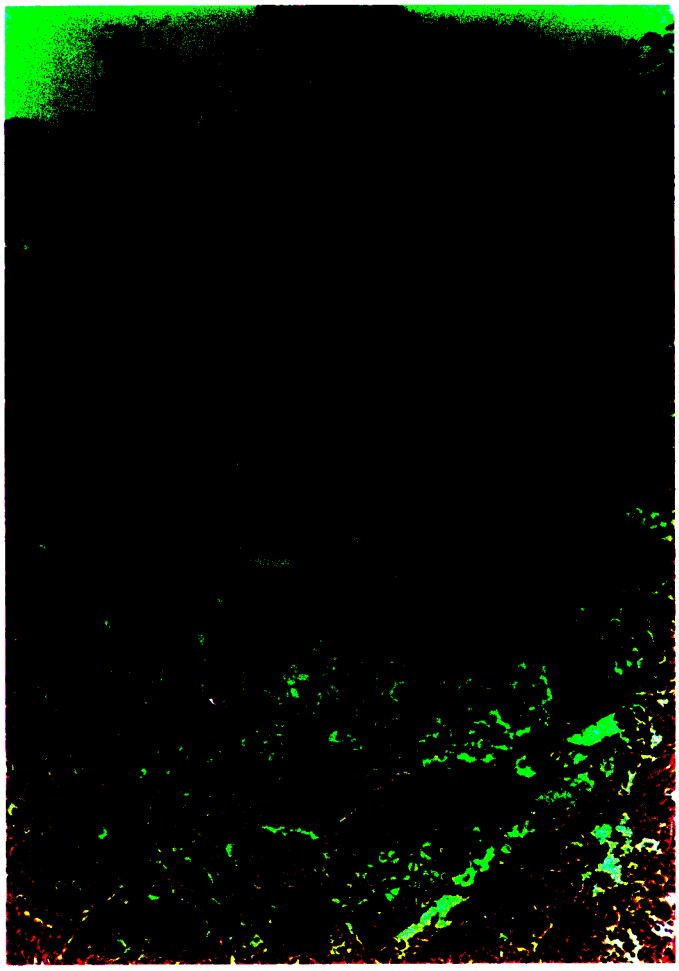
CLINICAL FEATURES OF INVASIVE SQUAMOUS CELL CARCINOMA OF THE VULVA

White vulval skin with areas of nodularity. This lesion cannot be clinically differentiated from the other causes of white vulval skin lesions.



PHOTOGRAPH NUMBER 8

HISTOPATHOLOGICAL FEATURES OF INVASIVE SQUAMOUS CELL CARCINOMA OF THE VULVA



PHOTOGRAPH NUMBER 9

THE COLPOSCOPE

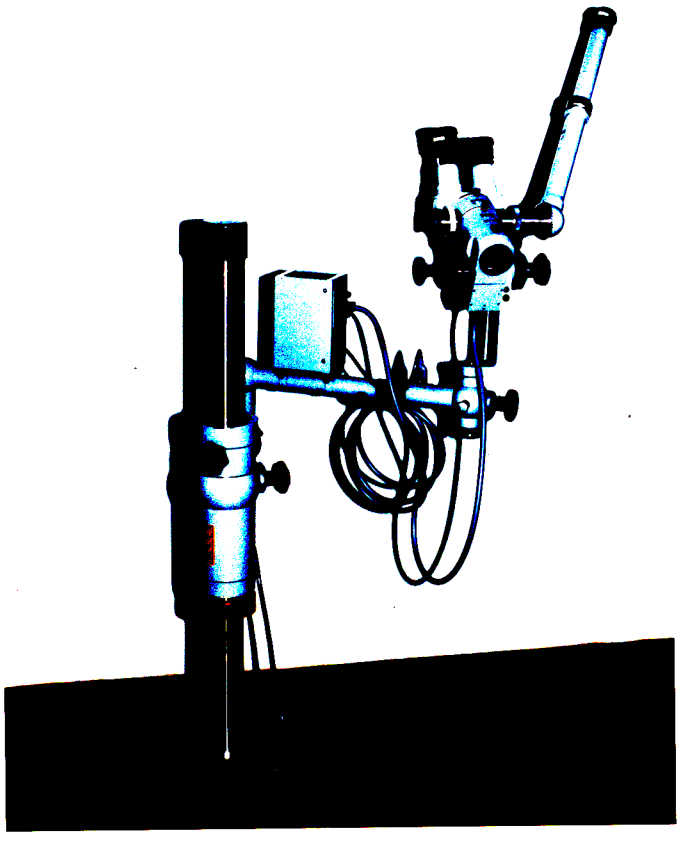
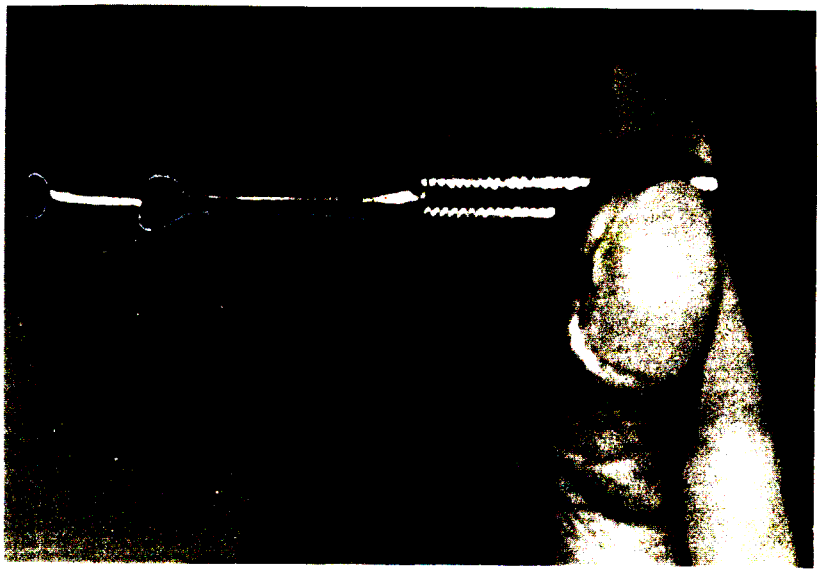
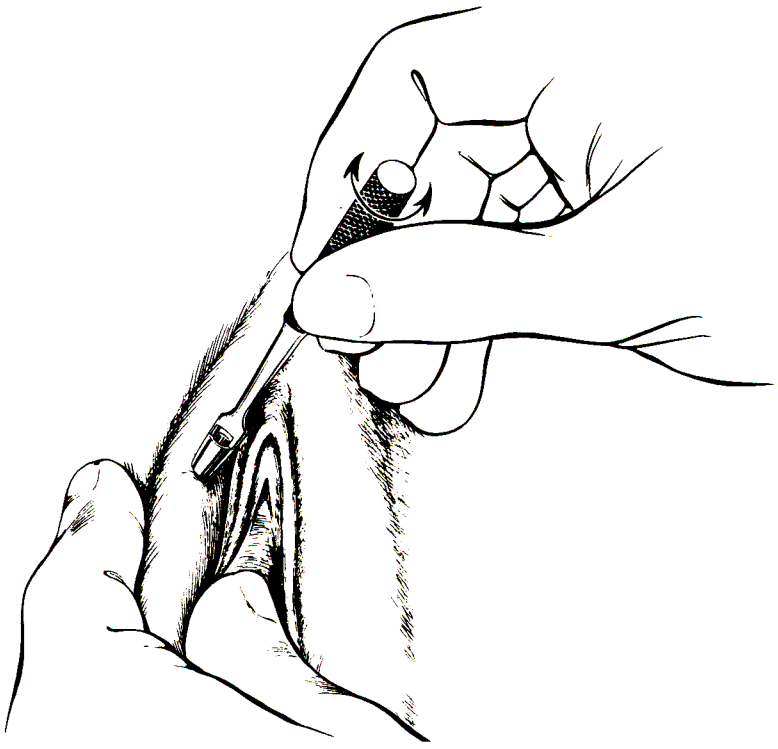


FIGURE 6

KEYES CUTANEOUS PUNCH BIOPSY INSTRUMENT





REFERENCES

1. Bornstein J, Pascal B, Sova J. et al. The Vulvar Clinic. Harefua. 1990; 119: 413.

2. Kaufman RH. The many causes of pruritus vulvae. Consultant. November. 1975: 182.

3. McFarlane CN. Pruritus Vulvae. Br Med J. 1973; 2: 553.

4. Strunin R. Pruritus Vulvae. Br Med J. 1973; 3: 106.

5. Ward GD, Sutherst JR. Pruritus Vulvae. Br Med J. 1973; 2: 243.

6. Sonnendecker EWW, Sonnendecker HE, Wright CA, Simon GB. Recalcitrant Vulvodynia. A Clinicopathological Study. S Afr Med J. 1993; 83: 730 – 733.

7. McKay M. Vulvodynia. A Multifactorial Clinical Problem. Arch Dermatol. 1989; 125: 256 – 262.

8. Sonnendecker EWW, Cohen RJ, Dreyer L, Sher RC, Findlay GH. Neuroma Of The Vulva. J Rep Med. 1993; 38: 33 – 36.

9. Bornstein J, Pascal B, Abramovic H. The Common Problem Of Vulva Pruritus. Obstets Gynecol Surv . 1993; 48: 111 – 118.

10. Williams DN, Knight AH, King H, Harris DM. The microbial flora of the vagina and it's relationship to bacteruria in diabetic and non – diabetic women. Br J Urol. 1975; 47: 453 – 457.

11. Gleeson NC. The Management Of Vulval Dystrophy. In: Bonnar J. Editor. Rec Advan Obstet Gynaecol. Edinburgh: Churchill Livingstone, 1995; 19: 191 – 200.

12. McClean AB. Vulval Dystrophy – The passing of a term. Obstet Gynecol. 1991; 1: 97 – 102.

13 Van Beurden M, Van der Vange N, De Croen AJM et al. Normal findings in vulvar examination and vulvoscpoy. Br J Obstet Gynaecol. March. 1997; 104: 320 – 324.

14. Collins CG, Hansen LH, Theriot E. A Clinical stain for use in selecting biopsy sites in patients with vulvar disease. Obstet and Gynecol Aug 1966; 28; 2: 158-163.

15. Chafe W, Ferguson K, Wilkinson EJ. Vulvar intraepithelial neoplasia[VIN]: Principles of surgical therapy. Colpo Gynecol Laser Surgery. 1988; 4: 125.

16. Cavanagh D, Ruffolo EH, Marsden DE. Cancer of the vulva. In: Cavanagh D [Editor] Gynecologic Cancer – A clinocopathological approach. Appleton – Century – Crofts, Connecticut. 1985: 1-40.

17. Friedrich EG. Diagnosis and therapy. Friedrich, editor. Vulvar Diseases2.WB Saunders, Philadelphia, 1983: 35-59.

18. Weir RJ. Ichthyosis of the tongue and vulva. NY Med J. 1875; 21: 240.

19. Ridley CM. General dermatological conditions and dermatoses of the vulva. In: Ridley CM, editor – The Vulva. Churchill Livingstone, Edingsburgh. 1988: 138-211.

20. Breisky D. Uber Kraurosis Vulvae. Zeitshrift fur Heilkunde. 1885; 6: 69 -80.

21. Tausig FJ. Chronic leukoplakic vulvitis followed by cancer. Surg Clin North Am 1922; 2: 155a.

22. Hunt E. Diseases affecting the vulva. 1st Ed. Kimpton, London. 1940.

23. Berkeley C, Bonney V. Leucoplakic vulvitis and its relation to Kraurosis vulvae and carcinoma vulvae. Proc. Royal Society Medicine 1909; 3 [2]: 29-51.

24. Bonney V. Leukoplakic vulvitis and the conditions liable to be confused with it. Proceedings of the Royal Society of Medicine. 1938; 38: 1057-1060.

25. Hallopeau H. Lichen plan sclereux: Ann Dermatol Syphilligr: 10; 447: 1889.

26. Kaufman RH, Friedrich EG, Gardner HL. Benign Diseases of the Vulva and Vagina, ed. 3. Year Book Medical Publisher Inc. Chicago, 1989.

27. Taussig FJ. Cancer of the vulva. Am J Obstet Gynecol. 1940; 40: 764.

28. Taussig FJ. Contributions to the pathology of vulvar diseases. Am J Obstet Gynecol. 1923; 6: 407.

29. Wallace HJ, Whimster IW. Vulval atrophy and leucoplakia. Br J Dermatol. 1951; 63: 241-257.

30. Wallace HJ. Vuval atrophy and leukoplakia. In: Bowes K [editor]. Modern trends in Obstetrics and Gynaecology, 2nd ser., Butterworth, London; 1955: 386-394.

31. Wallace HJ. Lichen sclerosus et atrophicus. Trans St John's Hospital Dermatol Soc London 1971; 57: 9-30.

32. Jeffcoate TNA, Woodcock AS. Premalignant Conditions of the Vulva, with particular reference to Chronic Epithelial Dystrophies. British Medical Journal 1961 July 15: 127-134.

33. Gardner HL, Kaufman RH. Benign Diseases of the vulva and vagina 1969: Mosby CV [Ed]. St. Louis, Missoon.

34. Friedrich EG. New nomenclature for vulvar disease: Report of the Committee on Terminology. Obstet Gynecol 1976; 47: 122-124.

35. Kramer IRH. Oral Leukoplakia – Journal of the Royal Society of Medicine. 1980; 73: 75-767.

36. Ridley CM, Frankman O, Jones ISC et al. New nomenclature for vulvar disease. Am J Obstet Gynecol 1989; 160: 769.

37. O' Keefe RJ, Scurry JP, Dennerstein G, Sfameni S, Brenan J. Audit of 114 non-neoplastic vulvar biopsies. Br J Obstet Gynaecol Oct 1995; 102: 780-786.

38. Woodruff JD. Diseases of the vulva. In: Jones HW, Jones GS, editors. Novak's textbook of Gynecology. Williams and Wilkins, Baltimore, London 1981: 229-261.

39. Kaufman RH, Brown D. Current Concepts in Vulvar Disease. Curr Probl Obstet and Gynecol Fertil. Jan/Feb 1994; 17 [1]: 1-40.

40. Yates VM, King CM, Dave VK. Lichen sclerosus et atrophicus following radiation therapy. Arch Dermatol. 1985; 121: 1044-1047.

41. Montgomery H, Hill WR. Lichen sclerosus et Atrophicus; Arch Dermatol Syphilol 1940; 42: 755-79.

42. Chernosky ME, Derbes VJ, Burks JW. Lichen sclerosus et atrophicus in children. Arch Dermatol 1957; 75: 647-52.

43. Ridley CM. Lichen sclerosus et atrophicus. Arch Dermatol . 1987; 123: 457-60.

44. Clark JA, Muller SA. Lichen sclerosus et atrophicus in children. Arch Dermatol. 1957; 75: 647-652.

45. McKay M. Vulvar dermatoses. Clinical Obstetrics and Gynaecology Sept. 1991; Vol 34: 614-629.

46. Wilkinson E. Normal histology and nomenclature of the vulva, and malignant neoplasms including VIN. Dermatol Clin. 1992; 10: 283-296.

47. Meyrick-Thomas RH, Ridley CM, Black MM. The association of lichen sclerosus et atrophicus in autoimmune related diseases in males. Br J Dermatol. 1983; 109: 661-664.

48. Meyrick-Thomas RH, Ridley CM, Mcgibbon DH, Black MM. Lichen sclerosus and autoimmunity – a study of 350 women. Br J Dermatol 1988; 118: 41-46.

49. Goolamali SK, Barnes EW, Irvine WJ, Shuster S. Organ-specific antibodies in patients with lichen sclerosus. Br Med J. 1974, ii: 78-79.

50. Jeffcoate TNA. Chronic vulval dystrophies. Am J Obstet Gynecol 1966; 95: 61-71.

51. Lavery HA. Vulval Dystrophies: new approaches. In: Fox H [ed] Clinics in Obstetrics and Gynaecology, 1984; 61: 155-169.

52. Johansson O, Nordlind K. Immunoreactivity to material like vasoactive intestinal polypeptide in epidermal cells of lichen sclerosus et atrophicus. Am J Dermatopath. 1986; 8: 105-108.

53. Harrington CI, Dunsmore IR. An investigation into the incidence of autoimmune disorders in patients with lichen sclerosus et atrophicus. Br J Dermatol 1981; 104: 563-6.

54. Harrington CI, Gelsthorpe K. The association between lichen sclerosus et atrophicus and HLA-B40. Br J Dermatol. 1981; 104: 561-562.

55. Meyrick-Thomas RH, Ridley CM, Sherwood F, Black MM. The lack of association of lichen sclerosus et atrophicus with HLA-A and B tissue antigens. Clin Exper Dermatol. 1984; 9: 290-292.

56. Cinberg BL. Postmenopausal pruritus vulvae. Am J Obstet Gynecol 1945; 49: 647-657.

57. Friedrich EG, Kalra PS. Serum levels of sex hormones in vulvar lichen

sclerosus, and the effect of topical testosterone. N Eng J Med 1984; 310: 488-491.

58. Onnis A, Nardelli GB, Lamina V et al. Hormonal receptors in vulvar tissues Eur J Gynaecol Oncol 1985; 6 [2]: 125-128.

59. Cantwell AR. Histologic observations of pleomorphic, variably acid-fast bacteria in scleroderma, morphoea and lichen sclerosus et atrophicus. Int J Dermatol. 1984; 23: 45-52.

60. Aberer E, Stanek G. Histological evidence for spirochetal origin omorphoea and lichen sclerosus et atrophicus. Am J Dermatopath 1987; 9: 375-379.

61. Karram M, Tabor B, Smotkin D, Wettstein F, Bhatia N, Micha J. Detection of human papilloma virus deoxyribonucleic acid from vulvar dystrophies and vulvar intraepithelial neoplastic lesions. Am J Obstet Gynecol. 1988; 159 [1]: 22-23.

62. Barnes CJ, Douglas CP. Preliminary findings on levels of collagenase and its tissue inhibitor in some vulval dystrophies. J Obstet Gynaecol. 1985; 6: 55-56.

63. Douglas CP, Barnes CJ. Proteolytic enzyme activity measured on extracellular matrix in vulval dystrophies. J Obstets Gynaecol. 1986; 6 : 193 – 195.

64. Bushbell LL, Friedrich EG Jr, Jordan RE. An appraisal of routine direct immunofluoresence in vulvar disorders. Acta Dermatol Venereol. 1980; 61: 157 – 160.

65. Carli P, Sonni L, de Marco L, et al. Immunohistochemical evidence of skin immune system involvement in vulvar lichen sclerosus. Proceedings of the International Society For The Study Of Vulvovaginal Disease, Oxoford, England, September, 1991.

66. Friedrich EG, MacLaren NK. Genetic aspects of lichen sclerosus. Am J Obstet Gynecol. 1984;150: 161 – 166.

67. Barker LP, Gross P. Lichen sclerosus et atrophicus of the female genitalia. Arch Dermatol. 1962; 85: 362 – 371.

68. Murphy FR, Lipa M, Haberman HF. Familial vulvar dystrophy of lichen sclerosus type. Arch Dermatol. 1982; 118: 329 – 331.

69. Meyrich – Thomas RH, Kennedy CT. The development of lichen sclerosus et atrophicus in monozygotic twin girls. Br J Dermatol. 1986; 114: 377 – 379.

70. Barclay DL, Macey HB, Reed RJ. Lichen sclerosus et atrophicus of the vulva in children: A review and report of 5 cases. Obstets Gynecol. 1966; 27: 837-642.

71. Dogliotti M, Bentley-Phillips CB, Schmann A. Lichen sclerosus et atrophicus in the Bantu. Br J Dermatol. 1974; 91: 81-85.

72. McAdams AJ, Kistner RW. The relationship of chronic vulvar disease, leukoplakia and carcinoma in situ to carcinoma of the vulva. Cancer. 1958; 11: 740-757.

73. Meyrick-Thomas RH, McGibbon DH, Munro DD. Basal cell carcinoma of the vulva in association with vulval lichen sclerosus et atrophicus. Journal of the Royal Society of Medicine Supplement II. 1985; 78: 16-18.

74. Friedman RJ, Kopf AWJ, Jones WB. Malignant melanoma in association with

lichen sclerosus on the vulva of a 14 year old. Am J Dermatopath 1984; 6 [1]: 253-256.

75. Buscema J, Stern J, Woodruff JD. The significance of histologic alterations adjacent to invasive vulvar carcinoma. Am J Obstet Gynecol 1980; 137: 902-909.

76. Zaino RJ, Husseinzadeh N, Nahhas W, Mortel R. Epithelial alterations in proximity to invasive squamous carcinoma of the vulva. Int J Gynaecol Path 1982; 1: 173-184.

77. Hewitt J, Pelisse M. Correlation between cancer and lichen sclerosus of the vulva: Preliminary report. In: Friedrich EG, Gregori CA, Lynch PJ [editors]. Proceedings of the International Conference of the ISSVD. 1976.

78. Walkden V, Chia Y, Wojnarowska F. Squamous carcinoma of the vulva: association with lichen sclerosus. Proceedings of the British Society for the Study of Vulval Diseases inaugural meeting, Sheffield. 1993.

79. Buckley CH, Butler EB, Fox H. Vulvar intraepithelial neoplasia and microinvasive carcinoma of the vulva. J Clin Path. 1984; 37: 1201-1211.

80. Liebowitch M, Neill S, Pelisse M et al. The epithelial changes associated with squamous cell carcinoma of the vulva. Br J Obstets Gynaecol. 1990; 97: 1135-1139.

81. Friedrich EG, Wilkinson EJ, Fu YS. Carcinoma in situ of the vulva – A continuing challenge. Am J Obstet Gynecol 1980; 136: 830.

82. Knight R, Van D. Bowens disease of the vulva. Am J Obstet Gynecol 1973; 115: 677.

83. Woodruff JD. The contemporary challenge of carcinoma in situ of the vulva. Am J Obstet Gynecol 1943; 46: 514.

84. Sturgeon SR, Brinton LA, Deveasas S, Kurman RJ. In situ and invasive vulva cancer incidence [1973-1987]. Am J Obstet Gynecol 1992; 166: 1482-5.

85. Beecham CT. Pagets disease of the vulva – recurrence in skin grafts. Obstet Gynecol 1976; 47: 55.

86. Compion MJ, Franklin EW, Burrel MO, Crozier MA. Vulvar neoplasia in

relation to other genital tract neoplasias. Colpo Gynecol Laser Surgery 1988; 4: 111.

87. Buscema J, Woodruff JD. Progressive histobiologic alterations in the development of vulvar cancer. Report of five cases. Am J Obstet Gynecol. 1980; 138: 146-150.

88. Buscema J, Woodruff JD, Prinley TH, Genadry R. Carcinoma in situ of the vulva. Obstets Gynecol 1980; 55: 225-230.

89. Choo YC, Morley GW. Multiple primary neoplasms of the anogenital region. Obstet Gynecol. 1980; 56: 365.

90. Andreasson B, Bock JE. Intraepithelial neoplasia in the vulvar region. Gynecol Oncol 1985; 21: 300-305.

91. Friedrich EG. Intraepithelial neoplasia of the vulva. In: Coppleson M [editor]. Gynecologic Oncology: Fundamental Principles and Clinical Practice. Churchill, New York, 1981: 303-319.

92. Bernstein SG, Kovacs BR, Townsend DE, Morrow CP. Vulvar carcinoma in situ. Obstets Gynecol. 1983; 61: 304-307.

93. Bergeron C, Naghashfar Z, Canaan C, Shah KV, Fu Y, Ferenczy A. Human papillomas type 16 in intraepithelial neoplasia. [Bowenoid papulosis] and coexistent invasive carcinoma of the vulva. Int J Gynecol Pathol. 1987; 6: 1.

94. Bornstein J, Kaufman RH. Multicentric intraepithelial neoplasia involving the vulva. Cancer 1988; 62: 1601.

95. Costello TJ, Wang HH, Schnitt SJ et al. Paget's disease with extensive involvement of the female genital tract initially detected by cervical cytosmear. Arch pathol Lab Med 1988; 112: 941.

96. Boehm F, Morris JM. Paget's disease and apocrine gland carcinoma of the vulva. Obstet Gynecol 1971; 38: 185.

97. Green TH. Carcinoma of the vulva: reassessment. Obstet Gynecol. 1978; 52: 462-468.

98. Penn I. Cancers of the anogenital region in renal transplant recipients. Analysis of 65 cases. Cancer 1986; 58: 611-616.

99. Lindeque BG, Nel AE, Du Toit JP. Immune deficiency and invasive carcinoma of the vulva in a young woman: a case report. Gynecol Oncol. 1987; 26: 112-118.

100. Coppleson M, Pixlen EC. Colposcopy of cervix. In: Coppleson M, editor. Gynecologic Oncology. Churchill Livingstone, Edinburgh. 1992: 297-323.

101. Leuchter RS, Townsend DE, Hacker NF, Pretorius RG, Lagasse LD, Wade ME. Treatment of vulvar carcinoma in situ with C02 laser. Gynecol Oncol. 1984; 19: 314-322.

102. Cattaneo A, Bracco GL. Malstun G et al. Lichen sclerosus and squamous hyperplasia of the vulva. A clinical study of medical treatment. J Reprod Med. 1991; 36 [4]: 301-305.

103. Ayhan A, Tuncer ZS, Kaya H. Vulvar dystrophy: an evaluation of 285 cases. Eur J Gynaec. Oncol. 1997; 18: 139-140.

104. Reid R, Greenberg MD, Daoud Y, Hussain M, Selvaggi S, Wilkinson E.

Colposcopic findings in women with vulvar pain syndromes. A preliminary report. J Reprod Med. 1988; 33: 523-532.

105. Byrne MA, Walker MM, Leonard J, Pryce D, Taylor-Robinson D. Recognizing covert disease in women with chronic vulval symptoms attending an STD clinic: value of detailed examination including colposcopy. Genitourin Med. 1989; 65: 46-49.

106. Bornstein J, Heifetz S, Kellner Y, Stolar Z, Abramovci H. Clobetasol dipropionate 0.05% versus testosterone propionate 2% topical application for severe vulvar lichen sclerosus: Am J Obstet Gynecol. 1998; 178: 80-84.

107. Bornstein J, Kaufman RH. Combination of surgical excision and carbon dioxide laser vaporization for multifocal vulvar intraepithelial neoplasia. Am J Obstet Gynecol. 1988; 158: 459-464.

108. Cagler H, Tarner S, Hreschyshyn MM. Vulvar intraepithelial neoplasia. Obstet Gynecol 1982; 60: 346.

109. Edwards CL, Tortolevo-Lung G, Linares AC et al. Vulvar Intraepithelial

neoplasia and vulvar cancer. Obstets Gynecol Clin North America. 1996; 23 [2]: 295.

110. Apgar BS, Cox JT. Differentiating normal and abnormal findings of the vulva. Am Fam Physician. 1996; 53 [4]: 1171-1180.

111. Reid WMN, MaClean AB. Vulval pain. Contemp Rev Obstet Gynaecol. 1995; 7: 44-51.

112. Hatch K. Colposcopy of vaginal and vulvar Human Papilloma virus and adjacent sites. In: Wright VC, editor. Obstet and Gynecol Clinics of North America. Philadelphia: Saunders WB, March 1993: 203-344.

113. Richart RM. A clinical staining test for the in vivo delineation of dysplasia and carcinoma in situ. Am J Obstet Gynecol. 1963; 86 [6]: 703-712.

114. Broen EM, Ostergard DR. Toludine blue and colposcopy for screening and delineating vulvar neoplasia. Obstet Gynaecol 1971; 36: 775-778.

115. Van Gelderen CJ. Vaginal discharge and pruritus vulvae. Cont Med Edu J. 1994; 12 [8]: 997-1006.

116. Mahmud M, Murakam T, Gyotoku Y, Nakazima H, Ishimuru T, Yamabe T.

Vulvar dystrophy: A clinical follow-up. Asia Oceania Journal of Obstetrics & Gynaecology. 1992; 18: 231-238.

117. Bracco GL, Carli P, Souni L et al. Clinical and histological effects of topical treatments of vulval lichen sclerosus: A critical evaluation. J Reprod Med. 1993; 38: 37-42.

118. Dalziel KL, Wojuarowska F. Long term control of vulval lichen sclerosus after treatment with a potent-topical steroid cream. Br J Dermatol. 1991; 124: 461-464.

119. Bousema MT, Romppanen V, Geiger JM et al. Acitretin in the treatment of severe lichen sclerosus et atrophicus of the vulva: a double-blind, placebo-controlled study. J Am Acad Dermatol. 1994; 30: 225-231.

120. Larsen J, Peters K, Petersen CS et al. Interferon alpha 2D treatment of symptomatic chronic vulvodynia associated with Koilocytosis. Acta Dermatol Venereol. 1993; 73: 385-387.

121. Woodruff JD, Thompson B. Local injection in the treatment of vulvar pruritus. Obstet Gynecol. 1972; 40: 18-22.

122. Forney JP, Morrow CP, Townsend DE, DiSaia PJ. Management of carcinoma in situ of the vulva. Am J Obstet Gynecol. 1977; 127: 801.

123. Ferenczy A. Laser treatment of patients with condylomata and squamous carcinoma precursors of the lower female genital tract. CA-A Cancer Journal for Clinicians. 1987; 37: 334.

124. Benedet JL, Murphy KJ. Squamous carcinoma in situ of the vulva. Gynecol Oncol. 1982; 14: 213.

125. Creasman WT. New Gynecologic Cancer Staging. Gynecologic Oncology. 1995; 58: 157-158.

126. Helm CW, Shingleton HM. The management of squamous cell carcinoma of the vulva. Curr Obstet Gynaecol. 1992; 2: 31-37.

127. Monaghan JM. The management of carcinoma of the vulva. In: Sheperd JH, Monaghan JM, editors. Clinical Gynaecological Oncology. Blackwell Scientific Publications, 1990: 140-167.