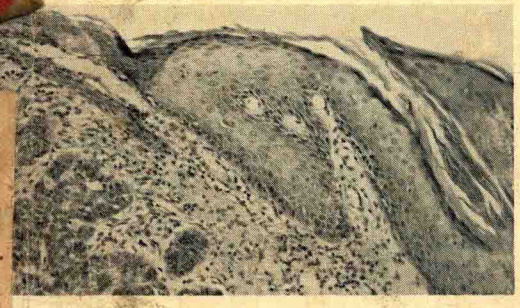
Edited by

E. J. Ambrose & F. J. C. Roe

THE BIOLOGY OF CANCER



Van Nostrand

The Biology of Cancer

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E. J. AMBROSE and F. J. C. ROE

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THE BIOLOGY OF CANCER

PREFACE

This book has evolved from a course of lectures for science and medical graduates. Each chapter, written by an authority on his subject, is based upon a lecture given during the first of these courses in the spring of 1964. The course is to be repeated every two or three years at the Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital, London.

Although the chapters have been written by different authors, the editors have striven to achieve a sense of continuity in order to present a co-ordinated picture of recent work in this important field.

The question of the form of the first lecture and, therefore, of the first chapter in the present volume, received special attention. It was decided not to commence the book conventionally with a detailed study of the structure and function of the smallest living unit of life and cancer, the cell, but instead to begin it by considering the whole organism which is affected by cancer. In the event, the first chapter has been written on a broad basis, whilst those which follow treat parts of the subject with greater precision.

Rapid progress in experimental and molecular biology is having much impact on, and giving rise to, new growing points in the field of cancer research. It is the purpose of this book to highlight these growing points and to view them in perspective.

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Chapter 1

CANCER AS A DISEASE OF THE WHOLE ORGANISM

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Introduction

Definitions of phenomena of which knowledge is limited tend either to prejudge issues, or to be too broad to be useful. In the case of cancer, all the more widely acceptable definitions fall into the latter category, with the result that what today would be called 'images', rather than definitions, tend to provide the framework for both endeavour and emotion in relation to cancer. The purpose of this introductory chapter is, firstly, to destroy what is false in some of these images and then to fuse what is left of them into a theory capable of supporting the content of subsequent contributions to the volume.

The layman's view of cancer

A reasonably well-informed layman might regard cancer as follows: 'It starts as a growing lump, which spreads by infiltrating surrounding tissues and by being carried to distant sites by the blood and the lymph. It is painful and causes considerable loss of weight.' It is not generally realized that cancer, because of its structure and origin, is not intrinsically painful. To be capable of registering pain a tissue must contain functional nerves with specialized pain-sensitive endings. Cancerous tissues contain no nerves or pain endings. On the other hand cancer may cause pain, secondarily, by invading or pressing on surrounding tissues which are supplied with nerves, by causing distension of the gut or bladder behind an obstruction, or by leading to pressure on nerves themselves. Thus, characteristically, the earliest stages of cancer are unaccompanied by pain, and pain is often not the first symptom and, indeed, may not occur at any time during the disease. Similarly, loss of weight does not necessarily accompany cancer and is frequently a late, rather than early, symptom of the disease. More cancers present without a visible lump than with one, and the first symptoms and signs of the disease are often good imitations of more innocent

disorders. Haemorrhage, a persistent cough, an attack which simulates influenza, indigestion, jaundice, abnormal behaviour, and a wide variety of other signs and symptoms may all be the first manifestations of cancer.

On the other hand, a growing lump may well not be a malignant cancer.

TABLE 1.1

Age specific death rates per 1000 living per year, for males and females aged 60–65, for cancer of different sites

Cause of death (cancer site)	*Cohort born around 1871* ♂	♀	*Cohort born around 1901* ♂	♀
Stomach	1·35	0·85	1·27	0·54
Intestines and rectum	1·31	0·91	0·89	0·71
Liver and gall bladder	0·30	0·29	0·16	0·13
Tongue, oral cavity and pharynx	0·51	0·05	0·14	0·06
Larynx	0·23	0·04	0·12	0·02
Oesophagus	0·46	0·11	0·19	0·09
Skin	0·08	0·04	0·05	0·03
Breast	0·01	0·99	0·01	0·87
Uterus	—	0·64	—	0·49
Testes	0·01	—	0·01	—
Prostate	0·28	—	0·25	—
Lungs	0·36	0·12	**2·48**	**0·29**
Bladder	0·18	0·06	**0·27**	**0·06**
Kidneys and adrenals	0·07	0·05	**0·11**	**0·05**
Leukaemia	0·04	0·04	**0·13**	**0·10**
Ovaries	—	0·21	—	0·29
All neoplasms	6·15	5·10	**6·98**	4·37
All causes	28·78	21·07	28·54	15·02

After R. A. M. CASE (1956)[6]. Bold figures indicate sites at which the incidence of cancer had increased in cohorts.

Benign, non-invasive growths, abscesses, cysts, and a variety of inflammatory conditions may present as growing swellings. Sometimes the difference is obvious to the general practitioner who is first consulted, but sometimes only careful and complicated investigations or surgical removal and examination of the lesion under the pathologist's microscope are adequate for the distinction to be made.

Cancer as seen by the general practitioner

A general practitioner with 3500 patients on his books may, on average, expect to sign 40 death certificates each year, and cancer will appear as the primary cause of death on 8 of them. He will also refer a number of cases to

TABLE 1.2

Cancer as seen by the general practitioner

		Per 1000 different patients consulting		*Per 1000 consultations*	
		♂	♀	♂	♀
Cancer of	Breast	0·0	1·5	0·1	15·4
	Lung	1·0	0·1	16·5	1·2
	Prostate	0·7	—	7·8	—
	Uterus	—	0·6	—	6·6
	Skin	0·6	0·6	2·2	2·7
	Colon and rectum	0·8	0·8	7·3	9·7
	Stomach and oesophagus	0·7	0·5	9·1	5·2
	Bladder and Kidney	0·2	0·1	2·7	1·0
	Central Nervous System	0·1	0·0	1·1	0·5
Leukaemia, Hodgkin's disease and reticuloses		0·2	0·1	2·9	1·5
ALL NEOPLASMS: Benign as well as malignant		8·7	12·5	67·7	80·4
Disease of Respiratory System		258	270	938	829
Disease of Nervous System		116	124	314	345
Disease of Digestive System		110	104	345	303
Disease of Skin		107	104	287	269
Accidents		116	90	294	201
Senility		83	105	203	273

After LOGAN and CUSHION (1958)[8].

hospital because of suspected cancerous or precancerous lesions. Some of these will be found not to have cancer, others will be successfully treated for it. Table 1.1 shows the relative frequencies of deaths from cancers of different sites in men and women. Table 1.2, for comparison, shows the

estimated occurrence of cancer in different organs as seen by the general practitioner. The biggest differences between the two tables occur in relation to the more easily cured types of cancer, e.g. cancer of the skin.

Cancer from the point of view of the hospital consultant

Cancer, or suspected cancer, is the reason for admission of approximately 20 per cent. of all patients to general and teaching hospitals (see Table 1.3).

TABLE 1.3

Diagnosis on admission to hospital as percentage of total admissions (excluding normal labour)

Benign neoplasms	5·1
Malignant neoplasms	3·2
Total neoplasms	8·3
Tonsils and adenoids and other E.N.T. conditions	7·3
Gynaecological conditions including complications of pregnancy	6·6
Appendicitis	5·9
Fractures and other injuries including burns	4·6
Hernia	4·2
Bronchitis, influenza and pneumonia	3·6
All other conditions	59·5
	100·0

After LOGAN and CUSHION (1958)[8].

Individual specialists differ considerably in the extent to which they are preoccupied with cancer. Those who do encounter it tend to regard it as a series of problems in diagnosis and treatment. The first problem is to make the distinction between cancerous and non-cancerous conditions; the second to ascertain the type and extent of the cancer, if present; and the third to decide the most appropriate form of treatment. In these problems the clinician obtains help from the pathologist, whose view of cancer we consider next. Both the clinician and pathologist view their findings in the light of previous experience of cancers of the same type in other patients. The usual mode of spread of cancer arising in different sites dictates which special examinations and investigations should be undertaken. For instance, in cases of cancer of the upper limb or breast, the axillary lymph

glands will be examined for enlargement, because it is known that such cancers tend to spread to them (Fig. 1.1). Similarly, a chest X-ray is taken, almost as a matter of routine, in cases of cancer of many different organs, because of the tendency for secondary deposits of cancer to find their way to the lungs (Fig. 1.2).

FIG. 1.1 Squamous-cell carcinoma of skin of left wrist with metastatic spread to axillary lymph nodes.

When the evidence is assembled the clinician decides the most suitable therapy. Characteristically, the surgeon directs his skill to removing the cancer as completely as possible. The radiotherapist focuses his beam of lethal radiation as accurately as possible, so as to kill all the cancerous tissues whilst inflicting as little damage as possible on surrounding normal

tissues; and the cancer chemotherapist seeks to exploit favourably differences in response between normal and cancerous tissues to hormones and certain special toxic agents. These specialists are all the time edging their way forward towards more and more radical procedures, using new techniques such as hypothermia and the grafting of inert or living materials

FIG. 1.2 Multiple shadows in the lung fields of a patient with primary cancer arising in one kidney. The shadows are caused by metastatic deposits of cancer.

to replace tissues removed or destroyed. The possibility that organs may be successfully transferred from one individual to another is the bright horizon before these cancer therapists, whose image of cancer is that of a situation requiring action.

The hospital pathologist's view of cancer

The hospital pathologist's view of cancer is geared to that of the clinicians with whom he is associated. His main problems are: 'Is it cancer?' 'If so, how far has it spread?' and 'How is it likely to behave in the future?' If the

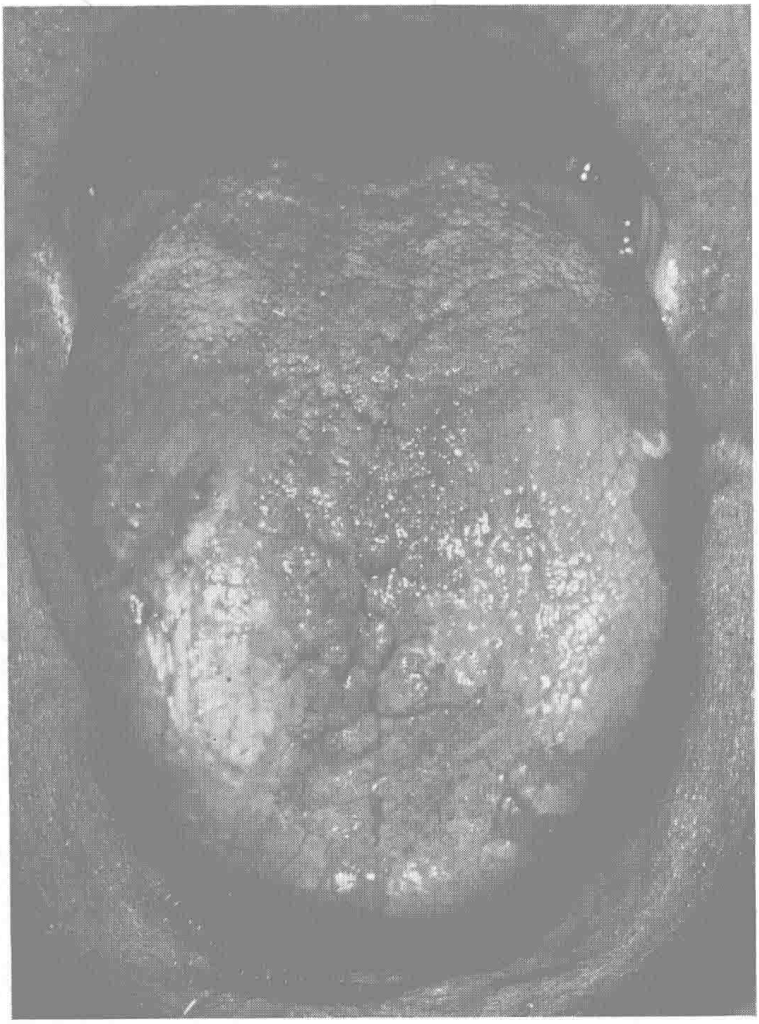

FIG. 1.3 Thickened opaque white areas of 'leukoplakia' on the tongue. It is highly likely that this lesion will progress to invasive cancer.

pathologist provides answers to these three questions he has carried out his duties to the patient. The standard textbook of cancer pathology is rather like a book of common law; a history of judgements based on experience gained from previous cases and in similar situations. WILLIS's *Pathology*

of Tumours[1] is the assemblance of clinical notes, and notes of careful dissections of biopsy and post-mortem specimens, matched with the histological features of cancers as seen under the microscope. Given similar information about any subsequent case, its future course can be predicted. As in the case of common law, new experience is constantly modifying judgements, and hitherto unrecognized situations are continually being uncovered. Every so often the actual subsequent behaviour of a cancer is

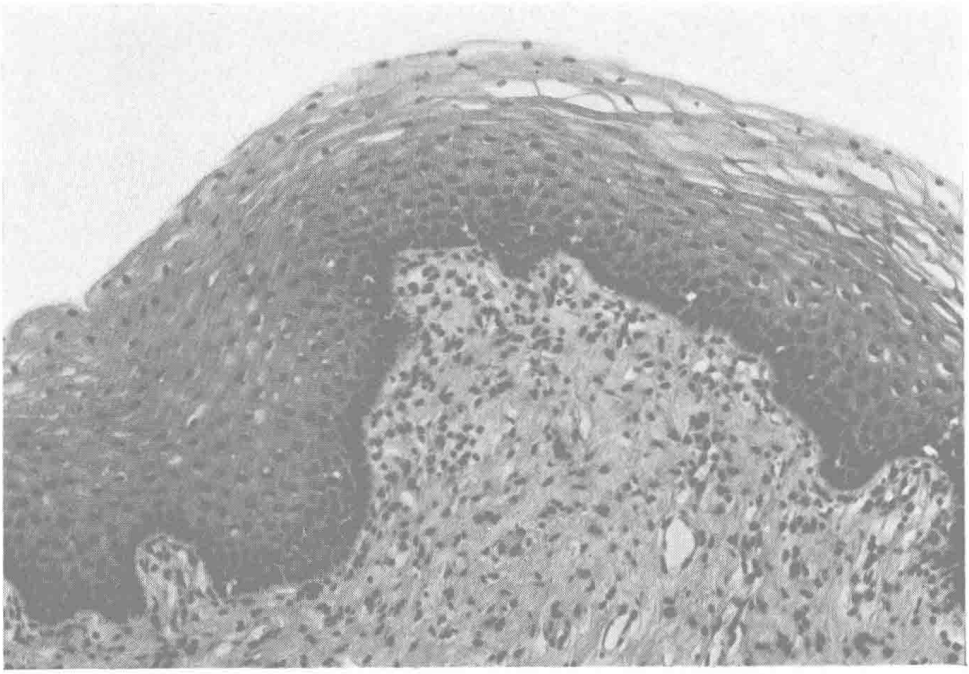

FIG. 1.4 Normal squamous epithelium from the uterine cervix. (H & E ×200.)

quite different from the predicted one; a patient expected to die within a few months from a rapidly growing cancer lives for years and dies from some other cause; and very occasionally a malignant tumour stops growing and disappears without treatment.

Advance would have been slow if this had been the only method of progress. Fortunately, however, many a pathologist has done more than simply serve the needs of the patient, the clinician and the therapist. He has recognized the fact that the biopsy or autopsy specimen is but an incomplete cross-section of an ever-changing situation; and he has set about studying the natural history of the disease. A practical outcome of this endeavour is the recognition of certain so-called 'pre-malignant states'. The latter are in reality macroscopic appearances such as 'leukoplakia' (Fig. 1.3), or microscopic appearances such as collections of 'atypical cells' or

'intraepithelial carcinoma', which it is known from experience have a tendency to progress to cancer in due course. The best-documented example of such 'progression' is in the case of the cervix of the uterus. It has been known for a long time that, within the vicinity of some invasive cancers, there is a zone of atypical cells or intraepithelial carcinoma (Figs. 1.4–1.8), and for many reasons it seems that the former probably originated from the latter. Recently, in a region of British Columbia, the

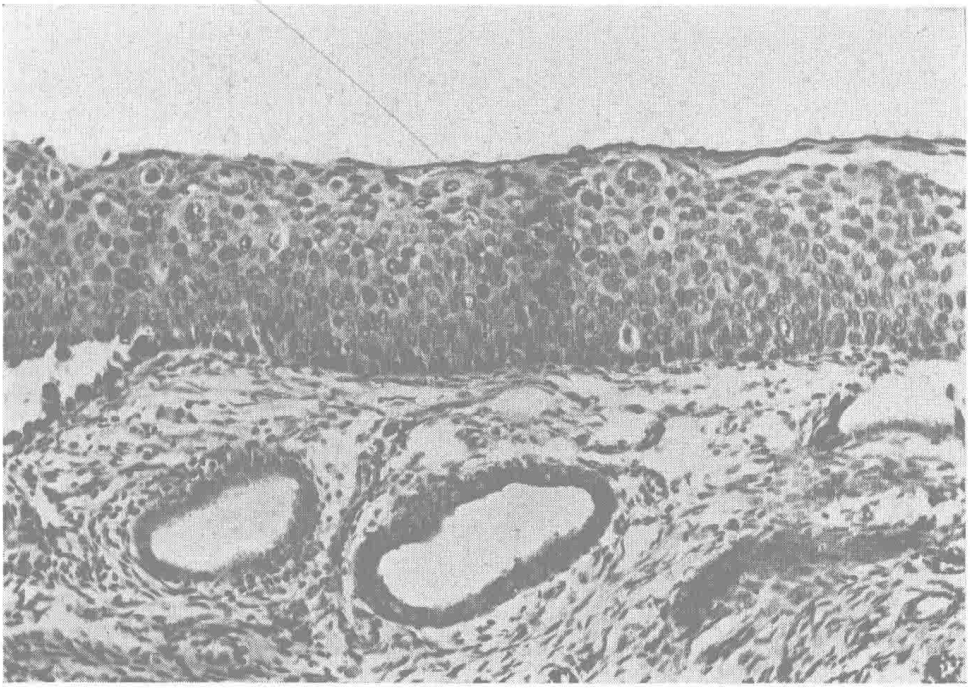

FIG. 1.5 Epithelium from the uterine cervix showing regular hyperplasia of the basal cells. The demarcation between the epithelium and underlying connective tissue is still intact. The spaces lined by columnar epithelium in the lower half of the picture are the cervical glands. (H & E ×200.)

cervices of women have been regularly examined, and any areas of intraepithelial carcinoma have been removed by minor surgery. The incidence of invasive cancer of the cervix, and the necessity for major surgery and radiotherapy to deal with it, have dropped dramatically in the same region.

Later, we must return to the question of tumour progression, but first we must look at certain other images of cancer.

The newspaper editor's image of cancer

From time to time dramatic headlines appear in some of our newspapers, which suggest that the cause of cancer has been found, and that the finding of the cure will follow automatically within a year or so. Articles of this

type use expressions such as 'major breakthrough', and demote factors previously described as causative to the level of 'trigger mechanisms'. An animal-like organism with legs is a fond favourite, though the crab seems a little out of fashion.

In his book *The Riddle of Cancer*, which for many years served as an excellent introductory book for entrants to the field of cancer research, the late Charles OBERLING[2] reviews the many claims, mainly since the end of

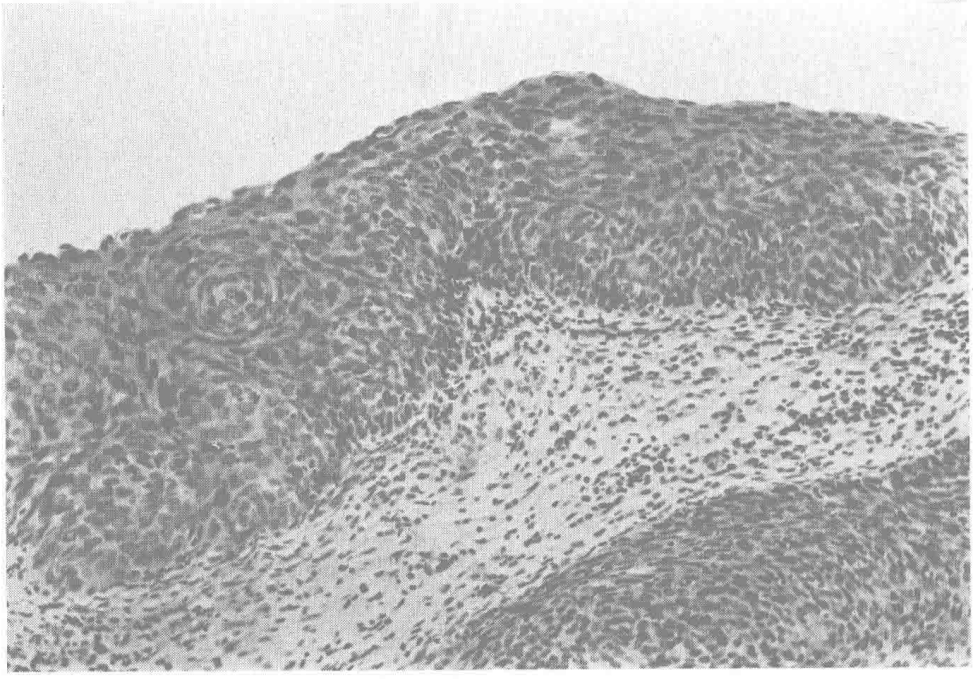

FIG. 1.6 Irregular hyperplasia of the epithelium. The cells differ widely in shape and are arranged in haphazard manner. The demarcation between epithelium and connective tissue is intact. This is regarded as an 'intraepithelial carcinoma' (i.e. non-invasive cancer, cancer confined to the epithelium, or carcinoma *in situ*). This type of lesion tends to progress to invasive cancer. (H & E ×200.)

the last century, to have found the cause of cancer. Two quotations from Woglom's translation of this book are given as illustrations:

'In 1896 Rappin inaugurated what was to become an endless series of short-lived discoveries, with a diplococcus isolated from cancer. Its inoculation produced results that were variable but all disappointing, for the lesions that it set up in the livers of rabbits were certainly infectious rather than neoplastic, yet with a tenacity that might have been better applied he pursued the study of his microbe for forty years without

contributing the slightest proof that it could initiate a malignant new growth.'

'Besides germs, innumerable other micro-organisms have been found in malignant neoplasm: yeasts of all sorts, including blastomycetes and saccharomycetes, and even protozoa like the rhizopods and spirochetes. Many investigators, finally, have described cell inclusions which they interpreted as protozoa and held responsible. Such were the coccidia of

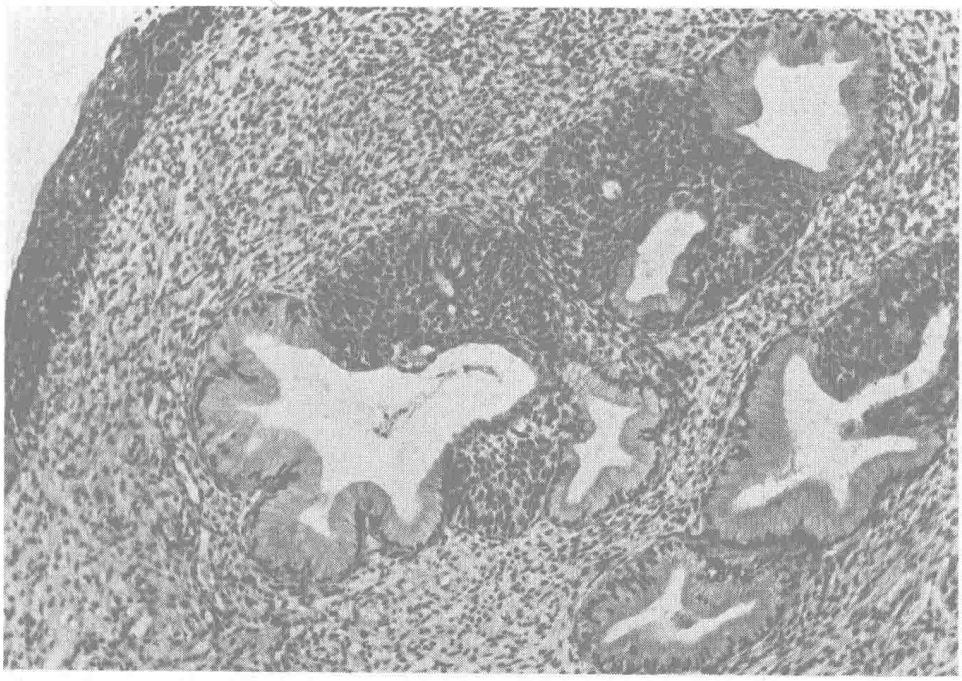

FIG. 1.7 Intraepithelial carcinoma affecting the surface epithelium of the cervix and spreading into the cervical glands. (H & E ×200.)

Darier, the roundish or sickle-shaped bodies of Sawtschenko, the *Histoporidium carcinomatosum* of Feinberg, and others by the dozen. An enormous literature on this subject has accumulated, but none of the alleged organisms has been able to survive criticism, all having been recognized eventually as artefacts due to the degeneration of nucleus or cytoplasm.'

Clearly all these claims were made in the first place on insufficient evidence, for none has withstood the test of time. However, the earlier claimants may perhaps be excused since, in the light of general knowledge available at the time, their suggestions were not basically absurd. Today similar claims are patently ridiculous, and the giving of publicity to them in the lay press can only be regarded as irresponsible.