RECENT ADVANCES IN PATHOLOGY

SEVENTH EDITION

By Various Authors

EDITED BY

C. V. HARRISON, M.D.

Professor of Morbid Anatomy, University of London, Postgraduate Medical School

With 140 Illustrations

First Edition (Hadfield & Garrod) . 1932
Second ,, ,, . 1934
Third ,, ,, . 1938
Fourth ,, ,, . 1942
Reprinted 1943
Fifth Edition (Hadfield & Garrod) . 1947
Reprinted 1948
Translated into Italian . . 1950
Sixth Edition (Ed. Hadfield) . . 1953
Seventh ,, *(Ed. Harrison)* . . 1960

Printed in Great Britain

PREFACE TO THE SEVENTH EDITION

In the last edition Professor G. Hadfield, one of the original authors, enlisted the help of a group of contributors and in this edition I have done the same. In a work of this type I think it is essential for each section to be written by someone who is actively engaged in the particular subject and I was fortunate in being able to call on colleagues who were able and willing to write about the subjects I had selected for this edition. Within the subjects chosen the individual authors have been completely free to write about whatever topics they thought fit. The guiding principle has been to select subjects in which there have recently been advances that we hope will prove to be permanent and in which the latest information is not readily available in standard text books. This has naturally meant totally rewriting the whole volume.

I have kept editorial interference to a minimum, only trying to ensure that the various chapters are understandable by ordinary non-specialist readers. In places where it has been necessary to evaluate complex or voluminous data to arrive at an opinion I have asked authors to add summaries.

I should like to take this opportunity of thanking all the contributors for their co-operation and forbearance, and to thank Professor Doniach as well for much helpful advice about the book as a whole. Finally I am grateful to the publishers and in particular to Mr. J. Rivers and Mr. J. A. Rivers for their kindly help and understanding.

C. V. HARRISON

CONTRIBUTORS

J. BALL, M.D.
Senior Lecturer in Pathology, Victoria University, Manchester.

GEORGIANA M. BONSER, M.D., F.R.C.P.
Reader in Cancer Research, University of Leeds.

MARY E. CATTO, M.B., CH.B.
Lecturer in Orthopaedic Pathology, University of Glasgow.
Lately, Institute of Orthopaedics, London.

D. B. CLAYSON, B.A., PH.D.
Department of Experimental Pathology and Cancer Research, University of Leeds.

I. DONIACH, M.D.
Professor of Morbid Anatomy, University of London, London Hospital Medical School.
Lately, Postgraduate Medical School, London.

J. GOUGH, M.D.
Professor of Pathology, Welsh National School of Medicine, Cardiff.

C. V. HARRISON, M.D.
Professor of Morbid Anatomy, University of London, Postgraduate Medical School.

R. H. HEPTINSTALL, M.D.
Visiting Professor of Pathology, Washington University School of Medicine, St. Louis, U.S.A.
Lately, St. Mary's Hospital, London.

J. W. JULL, B.SC., PH.D.
Department of Experimental Pathology and Cancer Research, University of Leeds.

BERNARD LENNOX, M.D., PH.D.
Senior Lecturer in Pathology, University of Glasgow.

R. H. MOLE, B.M., B.CH., M.R.C.P.
Medical Research Council Staff, Radiobiological Research Unit, Harwell.

CONTENTS

CONTENTS

CONTENTS

CHAPTER 1

THE HISTOPATHOLOGY OF TUMOURS: SOME TOPICS OF RECENT INTEREST

THE literature on the histopathology of human tumours can be exceedingly hard to follow. New tumours are constantly being described, together with new variants on old tumours and innumerable new interpretations. Names multiply, adding greatly to the confusion. It is exceedingly hard to assess progress. Nevertheless, in terms of those hard factual decisions that have a real bearing on prognosis and treatment, very substantial progress has in fact been made, as anyone who cares to review the reports coming from his pathology department twenty or even ten years ago can very soon verify. More than in most fields of pathology, time, both for pathologists to learn a new approach and for long follow-up of patients, is necessary in the trial of novel ideas. It could be argued against all the topics included in this chapter that they cannot really be called recent advances, for most of the ideas expressed are at least twenty years old. Proof of their practical usefulness and general acceptance of their significance is in every case, however, much more recent.

MOLLUSCUM SEBACEUM

This curious imitation of a squamous carcinoma of the skin lacks some of the characters of a true tumour, but is at least a close enough relative to justify inclusion in this chapter. The definitive description was made by McCormac and Scarff in 1936, but general recognition of its practical importance had to wait until the 1950s (Rook and Whimster, 1950; Beare, 1953; Linell and Månsson, 1957), and it is only in the last few years that experimental work (itself also a revaluation and expansion of earlier work) has thrown light on the nature of the process. These new experimental findings have considerable theoretical implications.

Molluscum sebaceum is a skin nodule which bears a remarkable resemblance to squamous carcinoma in both gross and microscopic appearance in the early stages of its growth, but which remains

localized, never invades or metastasizes, and ultimately regresses and disappears entirely. It occurs in either sex and has a bias towards the older age groups. It grows with what by skin tumour standards is explosive rapidity, a dry papule appearing in completely normal skin and enlarging to form a rounded nodule 10–20 mm. in diameter within, usually, about 6 weeks. Growth then slows and stops. The rough dry crater which has appeared on the domed summit of the nodule (ulcer-like, but never discharging fluid) enlarges; dry flakes and later larger plugs come away from it; the core of the nodule is lost in this way, and finally a thin-walled pit is left which shrinks down to leave a puckered scar. The whole process may take as long as a year, though six months is usually enough. (Some I suspect persist even longer, and give rise to one form of cutaneous horn.)

Histologically the resemblance to squamous carcinoma is remarkable. Many student classes have been taught on a "typical epithelioma of skin" which was a molluscum. This is especially the case with lesions of about 5–8 weeks old, when they are fully developed and still active. Crowded irregular masses of squamous epithelium radiate from the central crater into the underlying dermis; near the crater they are heavily keratinized, but the deeper part consists of active epithelium with many mitoses, and invasion seems to be actively in process (Fig. 1). This is not invasion, however. Deductions based on a study of the few available early lesions (Baumann and Lennox, 1954; Calman and Haber, 1955) have been confirmed by more recent experimental work. The lesions result from the proliferation of hair follicles (including the attached sebaceous glands). The hair follicles in the area thus disappear from the start while the overlying epidermis and the sweat glands are involved only secondarily. The hair follicles proliferate actively and irregularly; cell differentiation into hair matrix and sebum cells is lost. The masses of epithelium formed are much larger than the normal hair follicles, and an expanded rounded nodule is thus formed (Fig. 1), but the lesion never extends deeper than the deepest parts of the follicle could reach at the stage of maximum development (in the face outside the beard area, it is the sebaceous glands which penetrate deepest—usually just short of the deepest layer of the dermis). Soon after the lesion appears, keratinization begins in the most superficial parts of the hyperplastic hair follicles; the plugs so formed fuse and break off, forming the characteristic dry crater. As growth ceases, keratinization extends deeper and deeper, until finally the whole central area is occupied by a single horny mass, surrounded by a thin irregular

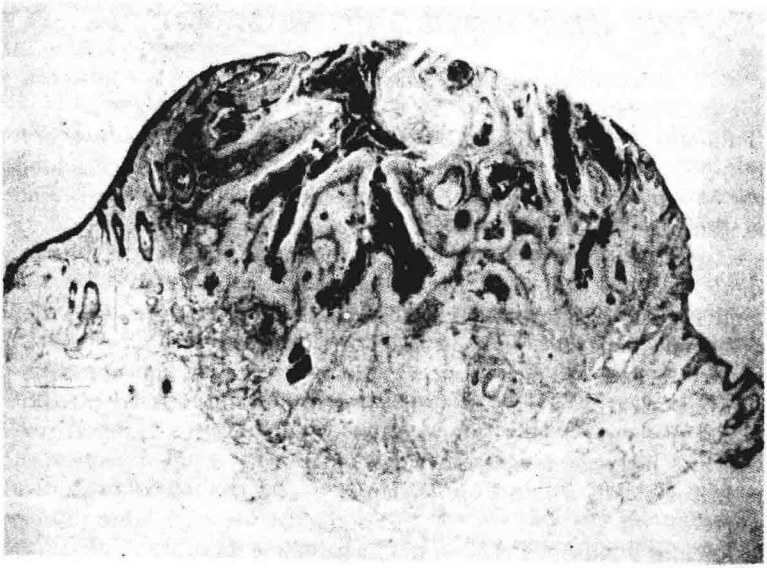

FIG. 1/1. Molluscum sebaceum. Lesion about 7 weeks old, with growth practically completed and keratinization beginning to be extensive. Note that the overlying epidermis is nearly normal, and that the lesion extends to just the same depth as the sebaceous glands on the right. H. & E. × 15.

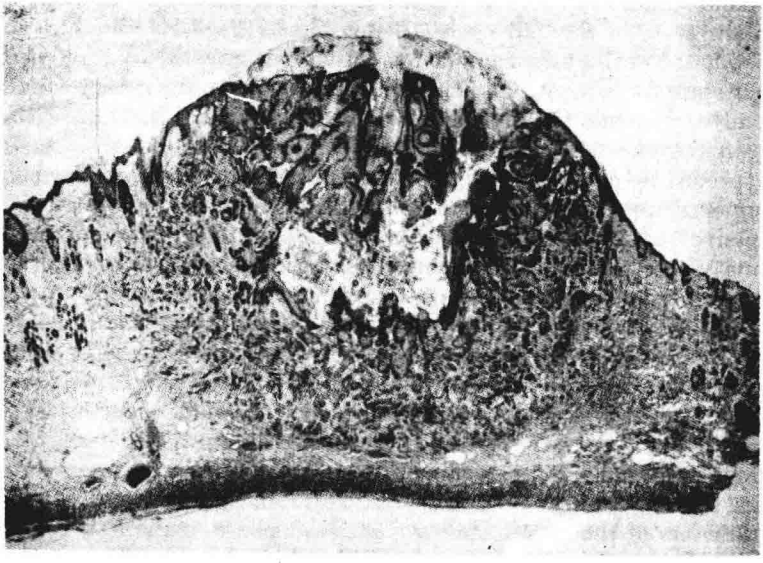

FIG. 1/2. Molluscum-sebaceum-like lesion in a rabbit painted with methyl cholanthrene. *From a slide lent by Dr. R. J. Whiteley.* H. & E. × 15.

layer of inactive squamous epithelium, which later lines the shrinking cavity left behind when the core falls out.

Tumours of the skin can be divided fairly accurately into two groups: those which occur especially in the exposed areas (face and back of hand chiefly) and whose incidence rises steeply with age, and those in which both site and age incidence are more widely distributed. The first group includes the common malignant tumours, rodent ulcer and squamous carcinoma, the second most of the remainder. The first group are those due to the common external carcinogens, especially light, which act chiefly on the exposed areas and have a long latent period. On these grounds molluscum sebaceum may clearly be suspected of being due to an external carcinogen, for it occurs chiefly (but not exclusively) on the exposed surfaces, and its incidence rises steeply with age (though I have seen one histologically convincing specimen from a child of two). Its occurrence on the forearm of tar and oil workers (Beare, 1953; Birkley and Johnson, 1955) points in the same direction.

Experimental Reproduction. It has long been known that when experimental animals (especially rabbits) are painted with carcinogens, a substantial proportion of the skin tumours produced regress. Whiteley (1957) and Ghadially (1958) have shown that this is not simply a matter of chance. The regressing and non-regressing tumours differ from the start, and which is to appear depends largely on the state of the hair cycle. If one plucks the whole flank of a rabbit, the entire area commences active hair growth, continues in that state for a month and then relapses into inactivity for several months. If in addition the flank is painted throughout this time with a carcinogen, such as dimethylbenzanthracene in lanoline, the cycle is speeded up and the inactive phase reduced to two or three weeks. Tumours appearing during an active phase are nearly all true progressive tumours, either squamous carcinoma or squamous papilloma: those that arise in an inactive phase are predominantly regressing lesions which closely resemble human mollusca (Fig. 2).

During the inactive "telogen" phase the empty follicle retracts and the essential cells which will form the matrix for the next cycle lie near the surface. It seems that in this stage the carcinogen may excite the hair germ to a sudden burst of irregular growth. The growth is in part tumour-like, in that it is excessive, invasive, irregular and unaccompanied by differentiation into any of the complex structures of the fully developed hair follicle: but it also retains characters of the corresponding "anagen" phase of the hair cycle, in that invasion is strictly limited to the territory normally invaded

by the newly awakened hair follicle, growth continues only for a strictly limited time (rather shorter in fact than in the normal follicle in the rabbit, and even more so apparently in man) and the final event is the keratinization of the remaining active epithelium and its discharge, though in one case the keratin is fully organized as a hair whereas in the other it is a mere disorganized plug. The resemblance between molluscum sebaceum and Whiteley and Ghadially's rabbit lesions is so close that it is most unlikely that they are not essentially similar. There is nothing new in the concept that a carcinogen stimulates cells to a distorted and exaggerated version of their normal mode of growth, but the idea, which seems to follow inescapably from these facts, that the cyclic mode of growth of the tissue affected may also be imposed on the neoplastic growth has a considerable air of novelty. In the field of hormone-dependent tumours it is not hard to find fairly close analogies. The rare cervical tumours which appear in pregnant women and disappear after delivery (Martin and Kenny, 1950) are a good example and so are the regressing breast tumours of mice (Foulds, 1956). But the hair follicle cycle does not depend on a hormone, and nothing quite like this has yet been described. It is grossly over-optimistic to suggest that if we knew just what stops the molluscum growing we might be able to use the knowledge to devise means of stopping the growth of other tumours: but it would be worth knowing all the same.

Diagnostic Difficulties. It is perhaps worth sounding a note of warning on the diagnosis of these tumours. It is not easy, and a mistake means either severe over-treatment of a benign lesion or potentially fatal under-treatment of a malignant one. Given a sufficiently generous biopsy, the histological appearance of a typical molluscum is highly characteristic, especially under the low powers of the microscope (Fig. 1), and various features have been pointed out as specially helpful—the absence of pre-malignant changes in the surrounding epidermis, the acute angle of junction between epidermis and tumour epithelium at the edge of the crater, the central keratinous mass, the pallor of the active epithelium, the frequency of an inflammatory infiltrate that involves the epithelium. Nevertheless, no purely histological criterion will suffice for confident diagnosis, and correlation with an accurate history is indispensable. One must be able to say, "This lesion is so many weeks old, and its features correspond with those of a molluscum of that age." Continued active growth beyond the age of nine weeks must always excite the greatest suspicion. It is true that there exist occasional molluscа which grow for a few weeks longer than the normal span,

sometimes reaching an unusual size (35 mm. is the largest I have seen) or recurring after excision; but these are rare exceptions, and unless both clinician and pathologist have considerable experience with such lesions and are prepared to watch the lesion closely till it regresses, it is well to take the nine-week rule as absolute.

The self-healing multiple squamous carcinoma of Ferguson-Smith (Currie and Smith, 1952) is almost certainly a distinct lesion, unrelated to molluscum sebaceum.

References

BAUMANN, ALICE, and LENNOX, B. (1954). *Schweiz. Z. Path.*, **17**, 326.
BEARE, J. M. (1953). *Brit. J. Surg.*, **41**, 167.
BIRKLEY, G. W., and JOHNSON, H. H. (1955). *Arch. Derm. Syph. (Chicago)*, **71**, 66.
CALMAN, C. D., and HABER, H. (1955). *J. Path. Bact.*, **69**, 61.
CURRIE, A. R., and SMITH, J. F. (1952). *J. Path. Bact.*, **64**, 827.
FOULDS, L. (1949). *Brit. J. Cancer*, **3**, 345.
GHADIALLY, F. N. (1958). *J. Path. Bact.*, **75**, 441.
LINELL, F., and MÅNSSON, B. (1957). *Acta. radiol. (Stockh.)*, **48**, 123.
MCCORMAC, H., and SCARFF, R. W. (1936). *Brit. J. Derm.*, **48**, 624.
MARTIN, R. T., and KENNY, MEAVE. (1950). *J. Obstet. Gynaec. Brit. Emp.*, **57**, 608.
ROOK, A., and WHIMSTER, I. (1950). *Arch. belges Derm.*, **6**, 137.
WHITELEY, H. J. (1957). *Brit. J. Cancer*, **11**, 196.

THE PLEOMORPHIC ADENOMATA

It is becoming increasingly evident that the tumours of a very large group of glands, of which the most important are the salivary and sweat glands, produce tumours with many similarities. The tumours are mostly rare or at least not very common, and many of the glands lie in specialist fields, and this has led to a diversity of names and descriptions which has obscured some essential resemblances. In an attempt to describe them with reasonable brevity, I have had to confine myself to little more than a dogmatic statement of the views I regard as most probably correct, and in particular to use the names I prefer without even mentioning most of the alternatives. For other views, especially on the crucial salivary tumours, see Foote and Frazell (1953), Willis (1953), Ranger *et al.* (1956), Azzopardi and Smith (1959).

The term "pleomorphic adenoma" has been borrowed from Willis, who, however, restricted its use to the salivary glands. This group will be described first, and then their occurrence traced

through the various glands, and the tumours (not pleomorphic adenomata) which are peculiar to each gland type discussed in passing.

The Pleomorphic Adenomata

I would define these as a group of tumours, generally of low malignancy, occurring with only minor differences in all or most of the members of a large group of glands. No general description of their histology is possible; it is better to attempt to describe the principal varieties.

The "Mixed-salivary" Variety. This is the familiar "mixed parotid" tumour of the students' text-book. After long and bitter argument it seems to be increasingly accepted that this curious-looking tumour is simply an adenoma of the salivary-gland epithelium, modified by two things: first, the inclusion in the proliferating epithelium of myoepithelial elements (Sheldon, 1951) which are epithelial in origin but often tend towards a more connective-tissue-like appearance, and, second, the secretion of a labile and variable mucin (Lennox, Pearse and Richards, 1952) which combines with or modifies the stroma sufficiently to give rise to a variety of changes, of which the appearance of cartilage is the most important (Figs. 3 and 4). (It is often very poor cartilage, but it is undoubtedly good enough to be accepted by the body as cartilage, for it may occasionally—as Professor D. F. Cappell has demonstrated to me most convincingly—ossify by the process of fully-developed enchondral ossification.) These tumours are slow-growing and essentially benign, and nearly always single, but they have a most deceptive and dangerous tendency to form a single well-defined and apparently well-encapsulated mass from which small soft projections, unrecognizable except with the microscope, run into the surrounding tissue. The result is that in an area such as the parotid, where wide excision is surgically difficult, such small and inconspicuous projections are frequently left behind and serve as the origin of recurrences which are often multiple. True malignancy with metastasis may supervene, especially in tumours of long duration, but this is exceptional (Foote and Frazell, 1953).

Mucoepidermoid Variety. This is a strikingly variable group, and the identity between tumours seen at different sites is less well established than in the other two principal varieties. Typical examples consist of two main cell types. (*a*) Large pale-staining cells, sometimes containing glycogen, referred to as epidermoid from their

FIG. 1/3. Mixed-salivary variety of pleomorphic adenoma, from the parotid gland. H. & E. × 65.

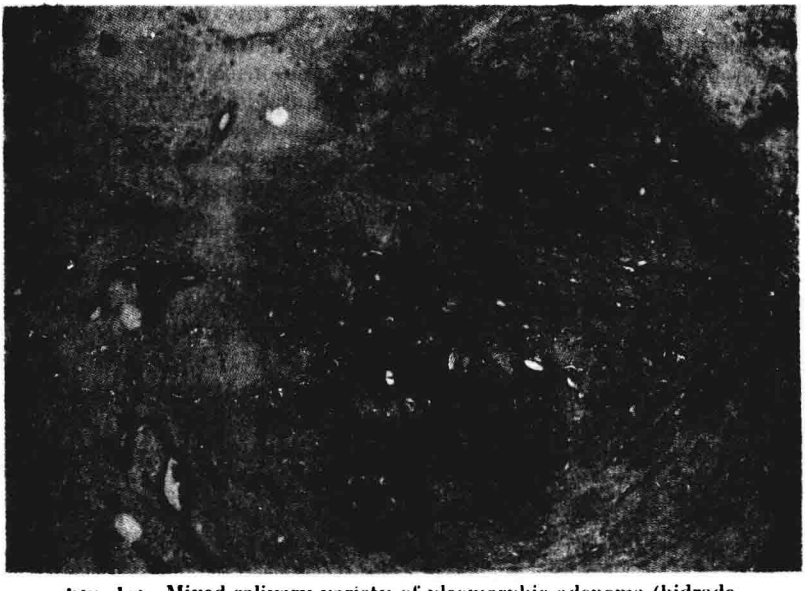

FIG. 1/4. Mixed-salivary variety of pleomorphic adenoma (hidradenoma) from the skin of the leg. H. & E. × 65.

resemblance to the cells of some squamous tumours, but never keratinizing and not certainly related in any way to squamous epithelium. (*b*) Mucin-secreting cells, sometimes columnar, sometimes goblet-cell-like, sometimes massively swollen, sometimes even signet-ring-like as in a mucoid carcinoma. On the whole, the "epidermoid" cells tend to form solid masses, and the mucin-secreting cells to line spaces within the tumour. The tumours are distinctly more often malignant than the mixed-salivary group.

Cylindromatous Variety. (I can find no better name than "cylindroma" for the group, though few members contain any cylindrical structures.) These tumours consist in their most benign form of masses of deeply staining small cells within which lie more or less numerous small ducts, lined by columnar cells with no basement membrane. (The basement membrane of the whole cell mass is sometimes densely hyaline, and some at least of the original "cylinders" were just this.) In the more rapidly growing forms the ducts disappear, and instead groups of spherical holes within the masses of small dark-staining cells give the tumour a "cribriform" pattern (Figs. 5 and 6). The "*cribriform cylindroma*" (which is also the adenoid cystic carcinoma of Foote and Frazell) is by far the most malignant of the pleomorphic adenomata; except in areas where thorough excision is easily carried out the prognosis is bad; recurrence is almost invariable and metastasis frequent. It is a singular fact that the emergence of the cribriform pattern is associated in this variety with a steep rise in malignancy. Though strikingly more malignant than other members of the pleomorphic adenoma group, its progression is usually slow compared to that of the majority of adenocarcinomata (taking as standard, for instance, the adenocarcinomata of stomach or pancreas).

For completeness, it is as well to recognize here the existence of **frankly malignant tumours** of the same glands that give rise to the pleomorphic adenomata. They may be undifferentiated carcinomata, straightforward adenocarcinomata and even (not very rarely) squamous carcinomata. Histological diagnosis is peculiarly difficult in this group, and it is a useful rule to assume with a histologically malignant-looking tumour of, say, the parotid, that if it is recognizably salivary in origin it is likely to show only the relatively minor degree of malignancy characteristic of the less well-behaved pleomorphic adenomata, and that only if it is so uncharacteristic of the parotid that one cannot be certain on histological grounds that it is not a metastasis from elsewhere can one be confident that it will be as malignant as it looks.