PATHOLOGY OF THE UPPER RESPIRATORY TRACT

By

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To

BETTY JEAN

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PREFACE

' But even obscurities arising from other causes than the abstruseness of the argument, may not be always inexcusable. Thus a subject may be treated in a manner, which all along supposes the reader acquainted with what has been said upon it, both by ancient and modern writers; and with what is the present state of opinion in the world concerning such subject. This will create a difficulty of a very peculiar kind, and even throw an obscurity over the whole before those who are not thus informed; but those who are, will be disposed to excuse such a manner, and other things of the like kind, as a saving of their patience.'

JOSEPH BUTLER.

(Preface to ' Fifteen Sermons Preached at the Chapel of the Rolls Court.')

This book is based on the specimens sent for histological examination from the operating theatres at the Ear, Nose and Throat Infirmary, Liverpool, from the middle of 1951 until the middle of 1961. During that time I have been responsible for the morbid anatomy from this hospital with two exceptions. When I have been on holiday or ill the work has been undertaken by Dr. J. S. Elwood. During the years 1956 and 1957 I was in Madras, South India under the Colombo Plan and my place in Liverpool was taken by Dr. Hilda Harris. Thus for a number of the specimens included here the diagnosis was made by Dr. Elwood or Dr. Harris. My work in India was not connected with the pathology of the upper respiratory tract.

In writing I have had two classes of readers in mind. One is the postgraduate student of otorhinolaryngology who needs a systematic treatise on which to base his clinical work. The other class is the pathologist whose experience in the special field is limited. The E.N.T. surgeon sees many cases, but from the point of view of the pathologist most of these fall into a restricted group and many of the problems on which the surgeon seeks his help deal with conditions which are relatively rare and of which neither of them is likely to have seen many examples. Tonsils are seldom sent for section, but tumours of the nasopharynx are invariably. In fact this book deals largely with rarities and this is inevitable. A brief perusal of the literature of the subject soon shows that the pathology of the upper respiratory tract has been largely in the hands of clinicians for some time with, of course, certainly very notable exceptions. This also is inevitable, partly on account of the rarity of many of the diseases of interest and importance, but has the unfortunate result that pathologists and surgeons often speak with different voices on the same subject and misunderstandings persist because neither specialist can follow what the other is trying to say. In such subjects as tumours of the nasal cavity or chronic inflammation of the middle ear, textbooks of general pathology and of special surgery are particularly at variance. The same terms are sometimes used by the two groups for different things, while different names are given to the same phenomenon.

With these two classes of readers in mind much material that will be only too familiar to one and of little importance to the other has been omitted, even when of fundamental importance for the specialist surgeon. Thus embryological detail is not considered unless it is of immediate reference to diagnosis. Discussion of many of the subvarieties of inflammation has been cut to the minimum, since these may be of great importance to the clinician, but of little use to the histopathologist unless clear-cut subdivisions can be recognised using his techniques. The spread of tumours to the base of the skull is of great importance, but here it can be dealt with in the most general terms since the histopathologist need not even know the source of the specimen in which he can find malignant tissue in a nerve sheath, while the surgeon should need no reminder from me of the fine anatomy involved. I have indeed tried to restrict myself to the questions that have been posed to me by surgeons of experience. They are surely the best judges of the nature of the problems to be faced. For a similar reason I have omitted all discussion of diseases of the inner ear. Specimens are never sent to me for an opinion and I have thus never needed to equip myself to apply the special techniques of study that would be required.

With regard to references, these are fairly numerous and include many sources for further information which do not necessarily recount original work. These are distinguished in the text. Most of the papers quoted are from specialist surgical journals and the necessity for this underlines that it is the clinicians nowadays who report original observations on so much of the pathology of this region of the body, though many quote the opinion of a pathologist, even without naming him. Most of the references given are from journals which are recent, are available in most medical libraries of importance, are in English and were often chosen as giving the key to more important earlier work that is more difficult of access. With respect to papers in languages other than English, these have been quoted only when it appeared necessary to do so and all have, of course, been read, even if perhaps not understood.

No attempt has been made to include the most recent publications simply because they are the most recent. In the whole field few fundamental advances could be recorded by doing this; indeed the fundamentals have been unchallenged for some years. Even when considering inflammation of the middle ear and mastoid the remarkable 'recent' advances have been made over about ten years. The most actively growing point probably concerns the development of the series of the reticular-lymphatic cells; some really recent references are required and these will certainly be outdated by the time of publication.

For help in obtaining journals I must thank the Librarians and their staff of the Royal Society of Medicine, of the Cohen Library of the University of Liverpool and of the Liverpool School of Tropical Medicine. In common with many other authors I am especially grateful for the help of Mr. W. Lee, M.A. and Mr. G. T. Evans of the Liverpool Medical Institution.

I must certainly thank my surgical colleagues for their co-operation and understanding. They have agreed to my using their cases here, that acknowledgements for the use of individual cases quoted need not be made separately and that they will be satisfied by a group acknowledgement. Their names are: H. V. Forster, Mrs. B. M. L. Abercromby, R. J. Martin, J. C. McFarland, I. A. Tumarkin, J. Siegler and R. Pracy. In addition a special note of respect must be made for the late J. McGibbon and the late P. Garson. Many of their cases are included here also.

1963. R. E. REWELL.

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CHAPTER I

INFLAMMATIONS OF THE NASAL CAVITY AND ACCESSORY SINUSES

ALL these structures form one system for the pathologist, despite the great differences in their anatomical relations. Even from the theoretical aspect they have the same origin as progressive outgrowths from one cavity. The relations of the different parts certainly have important practical consequences in that many structures may be involved when disease spreads from these cavities, so that bones, nerves, blood vessels and even muscles may become damaged to produce very diverse effects. These, however, are clinical problems and exercises in applied anatomy, are not strictly within the province of pathology and so will not be considered here. The same remarks apply to most diseases that may spread in the reverse direction from surrounding structures into the cavities, *e.g.* from the teeth or orbit, although some conditions when established may present in several sites at the same time and it may be neither useful nor possible to determine where the disease actually started. From considerations of simple convenience we are more likely to obtain for examination samples of disease processes as they occur in the more accessible parts of the system, the nasal cavity and antra, than in the ethmoid, sphenoidal or even frontal sinuses. We must also remember the difficulty of drainage of some of the cavities due to the anatomical arrangements of the natural outlets and also the marked variations in the degree of development attained by some, *e.g.* the frontal sinuses, not only with respect to age and sex, but in regard to the marked differences that may be present between individuals of the same sex and age. These points are elementary and obvious, but must be mentioned here even if only to avoid having to stress them in the following discussions of individual lesions.

NORMAL HISTOLOGY

The underlying bone and cartilage surely need no detailed description either. Overlying these is a variable amount of fibrous tissue which constitutes the periosteum and contains nerves, lymphatics and blood vessels. These last are sufficiently well-developed

in places to warrant the term 'erectile tissue' being applied to the whole layer. The fibrous tissue is very loose in structure so that oedema fluid in large amount may collect within it and cause marked enlargement. Apart from the vestibule of the nares the whole area is lined by the characteristic 'upper respiratory' or 'stratified columnar' epithelium, as also are the nasopharynx and the larynx in much of their extent. The distinguishing features of

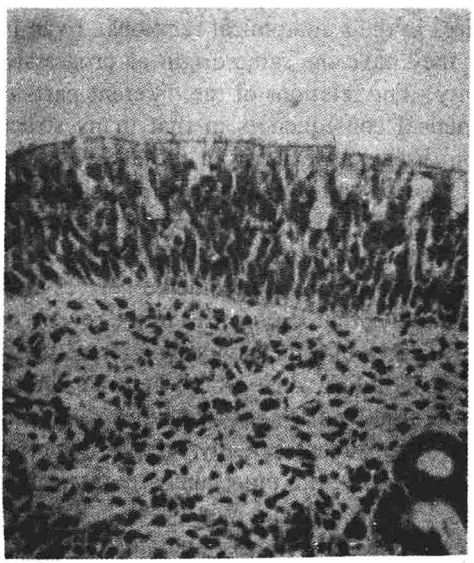

FIG. 1
Upper respiratory mucosa. ×240.

this membrane are: (1) a superficial, single layer of mucus-secreting columnar cells which overlies (2) a layer of epithelial cells of the 'transitional' type. The thickness of the latter layer is variable (Fig. 1). The columnar cells are tall and narrow with elongated nuclei placed at a variable distance between the base of the cell and the free border. This free border bears cilia, but these are frequently missing, vanishing with sometimes the slightest degree of inflammation. The amount of mucus excreted by the cells or found within them varies markedly and may be very great in some types of inflammatory response (Fig. 3d).

The transitional cells are more difficult to describe. They may be of polygonal form or flattened, with rounded nuclei that are rather small so that the cytoplasm appears abundant. The long axes

of the cells may be parallel to the free surface, at right angles to it, or irregular in arrangement, so that the cells form sheets or whorls beneath the layer of columnar cells. Sometimes a definite ' basal ' layer is formed with the long axes of the cells at right angles to the free surface, but this is seldom as marked as in stratified squamous epithelium, nor do the cells forming it take on as cuboidal a shape as true basal cells. Characteristically there are no ' cell

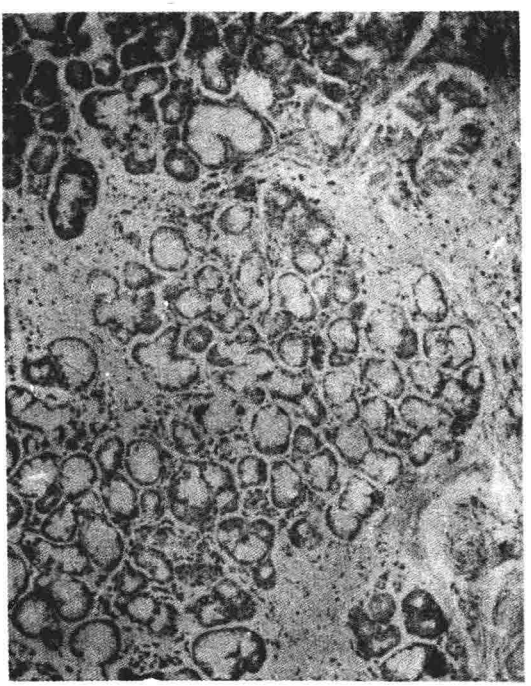

FIG. 2
Sero-mucinous glands as found in most areas beneath the mucosa. ×52.

bridges ' between the cells, nor do they form keratin. To do these things is virtually the definition of a squamous cell.

This type of epithelium is very widespread throughout the animal kingdom, its double layer lining the upper respiratory tract in widely different species. Negus (1956) describes it in many different ones and has a figure showing it from even the slow worm, *Anguis fragilis*, a lizard.

Sero-mucinous glands occur in groups beneath the epithelium (Fig. 2).

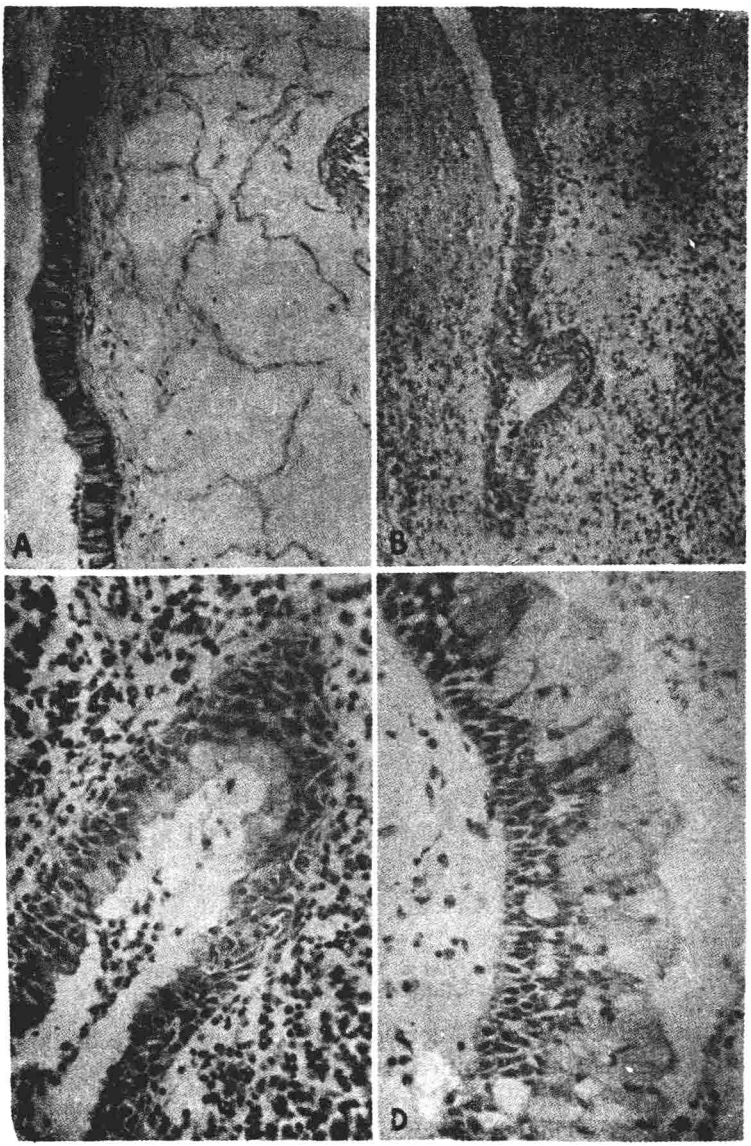

FIG. 3

Variations in the mucosa. (A) Transitional cells are few; there is oedema of the submucosa. ×104. (B) Ulceration in the depths of a fold from inflammation. ×104. (C) Under the columnar layer the cells are tending towards a squamous form, also with inflammatory exudate beneath. ×240. (D) Hypersecretion of mucus. ×240.

SQUAMOUS METAPLASIA

As described in Chapter II many malignant tumours of this area are of squamous structure and these must have arisen in areas of metaplasia. However, such metaplasia is by no means always malignant. It usually follows inflammation, but must be discussed under a separate heading as it is found in association with inflammations of different types and because of its relationship to malignancy. The frequency of its occurrence is illustrated by the work of Schönemann (1902). In eighty-three consecutive necropsies on adults dying from many different causes, squamous metaplasia was found over the turbinate bones in no less than seventy-three. However, none was found in thirty newborn children.

Metaplastic squamous cells appear in scattered, unconnected areas. No two observers would agree as to where to draw the line between squamous and transitional cells. The presence of cell bridges is unequivocal evidence of squamous change, but is not necessarily present in undoubted squamous cells. Figure 31b (p. 93) is of the abdominal skin of a newborn child. There is marked formation of keratin, but the cells are not really arranged in layers, there is no marked basal layer, the cells are of rather rounded form and certainly no cell bridges are present. They are indeed very like transitional cells and lack some of the characteristic squamous features. The body from which this specimen was taken was very fresh, indeed still warm. Once more it may be very difficult to draw the line between squamous and transitional cells and one observer may regard as change towards squamous form what another would term simply non-specific inflammatory response. When much inflammatory change itself is present the decision may be especially difficult since the characteristic features of developed squamous cells may be lost under such conditions.

Metaplasia is essentially a change whereby one tissue takes on the features of another. This supposes reversion to a more primitive form and redevelopment, or rather respecialisation, along new lines (Nicholson, 1923). The widespread occurrence of such a change throughout the body under many different conditions renders invalid the contention that once a cell has assumed its final form the progressive specialisations involved cannot be undone and a new series subsequently undertaken (Willis, 1958). Some tissues are so specialised that they do not undergo metaplasia, *e.g.* the parenchyma of the liver and above all the nerve cells, but many do. Transitional

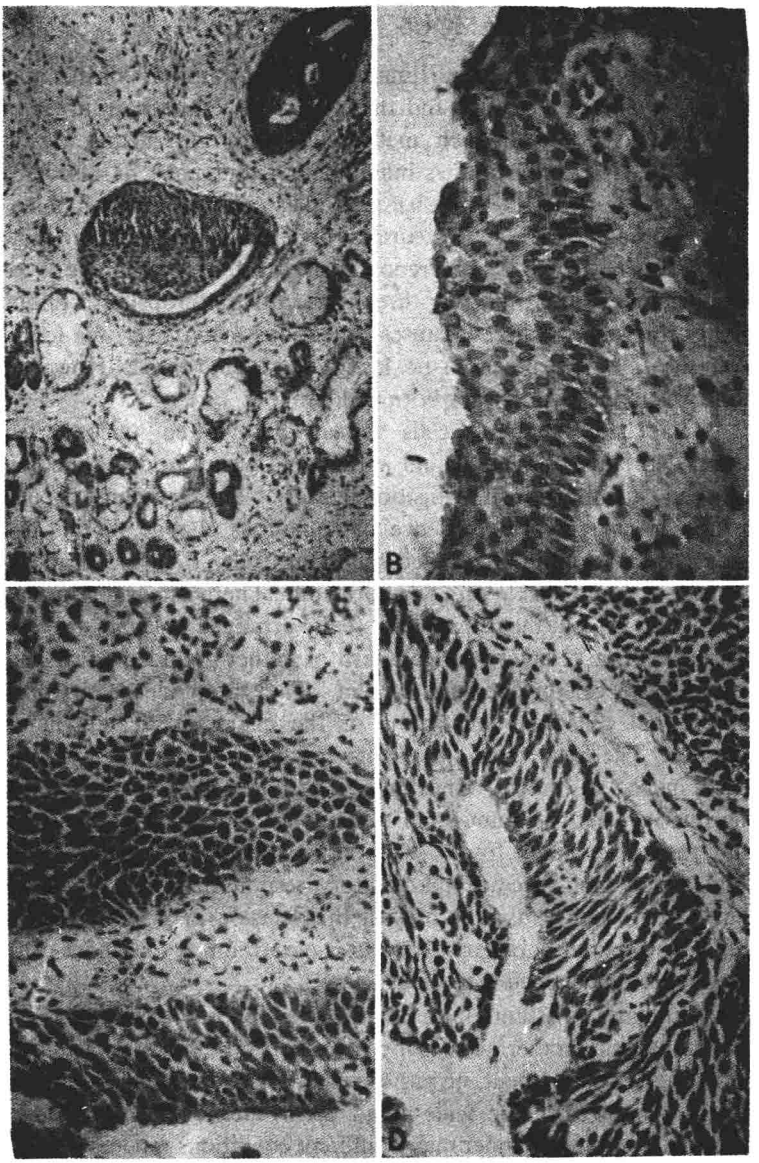

FIG. 4

Squamous metaplasia in upper respiratory mucosa. (A) In a sero-mucinous gland. (B) Columnar cells of the mucosa have vanished and those remaining take on a rounded form. (C) The shape of rather irregular squamous cells has been attained on the surface of an inflamed turbinate. (D) Variation has here produced more of a basal pattern. (A) × 52. All others × 240.

cells may indeed be regarded as epithelial cells which are on their way to specialisation as squamous cells, but in which the process has been arrested more or less permanently. Certainly squamous metaplasia takes place in them easily, *e.g.* in the urinary tract for which system the idea of partial development was first put forward (Schridde, 1907). On such a theory squamous metaplasia would be a process of increasing specialisation within transitional cells, certainly not the dedifferentiation usually considered characteristic of malignancy. The baby's skin shown in Figure 31b could be considered as composed of such partially-differentiated cells on their way to form squames and already with the functional specialisation of keratin formation fully developed. Adult skin can, however, show similar appearances. We must indeed realise that the two appearances may be interchangeable and that such change occurs frequently. Conventional rigid descriptions of fixed cell types are thus often invalid in fact.

Squamous metaplasia is encountered in a number of situations in the upper respiratory tract, *e.g.* in the sero-mucinous glands found in many parts, also in the middle ear cavity; accordingly some characteristics of the change may be considered that are not of immediate reference to what is found in the nasal cavity. Its occurrence in the sero-mucinous glands is shown in Figure 4a. In these, as in other situations throughout the body, a layer of cells arises beneath a columnar epithelium which may remain on the surface, at any rate for a time. They may be removed by inflammation in their turn. The new cells resemble transitional cells at first and may remain in that form, especially if actually invaded by inflammatory exudate, but often proceed to complete identity with squamous cells, including such points as formation of keratin, of cell bridges between them and of glycogen within their cytoplasm. These points require special emphasis as it has often been stated that metaplastic cells do not behave in this way, but always remain incomplete squamous cells in essential particulars. It is thus argued that cells showing these developed features cannot have arisen by metaplasia, while cells that do not show them are held not to be true squames, *i.e.* such differences as they may show from their cells of origin are not regarded as steps towards the squamous form. This last point can also be contradicted categorically. Many cells within squamous membranes lose such characteristics under the influence of inflammation and indeed it is impossible to say in any instance

whether or not one is dealing with cells of non-squamous form on their way to undoubted squamous features, or cells of squamous origin that have been damaged by inflammation. Other parts of the tissue usually, of course, provide the answer. It is a matter of convenience whether we call such doubtful cells ' degenerate ' or regard them as undergoing dedifferentiation or redifferentiation, but we must be careful in any one instance not to prejudge by the terminology used the process that may be going on. The accompanying Figures should make clear the points mentioned. Once more it must be stressed that the structure of a surface epithelium is often more fluid and alterable than is admitted in standard descriptions.

When squamous cells appear beneath a columnar epithelium their origin is sometimes clear in the transitional epithelium that normally lies beneath it, *e.g.* in the nasal cavity. In, say, Bartholin's gland (Fig. 5b) they may be imagined as spreading in from transitional epithelium lying close by in the ducts, although whether or not they indeed do so is doubtful. In other situations, *e.g.* in the endocervix, it has been postulated that undifferentiated ' reserve cells ' lie between the columnar cells and are ready to proliferate and take on squamous form when stimulated to do so (Carmichael and Jeaffreson, 1939). There has been some debate on this point, some observers agreeing that they can identify these reserve cells and others (including the author) being unable to do so. If they did exist we could on theoretical grounds regard them as an extremely reduced complement of the transitional cells that underly the columnar cells over so much of the upper respiratory tract. The early stages of squamous metaplasia at all sites certainly produce transitional cells, but once more the final result is fully-formed squamous cells unless these are damaged by the process responsible for the metaplasia, *e.g.* by inflammations.

Squamous metaplasia from respiratory epithelium is of especial importance in the bronchial tree itself, since it is from such metaplastic tissue that the common squamous carcinoma of the lung must arise. The points discussed here are well illustrated for the bronchus in the paper by Auerbach *et al.* (1956). They stress especially that the squamous epithelium formed by metaplasia cannot be distinguished at any point from the tissue as it occurs naturally. This occurs also when an adenocarcinoma shows squamous metaplasia within the well-established malignant tissue. This happens in the endometrium, the so-called adenoacanthoma, and in the ovary.

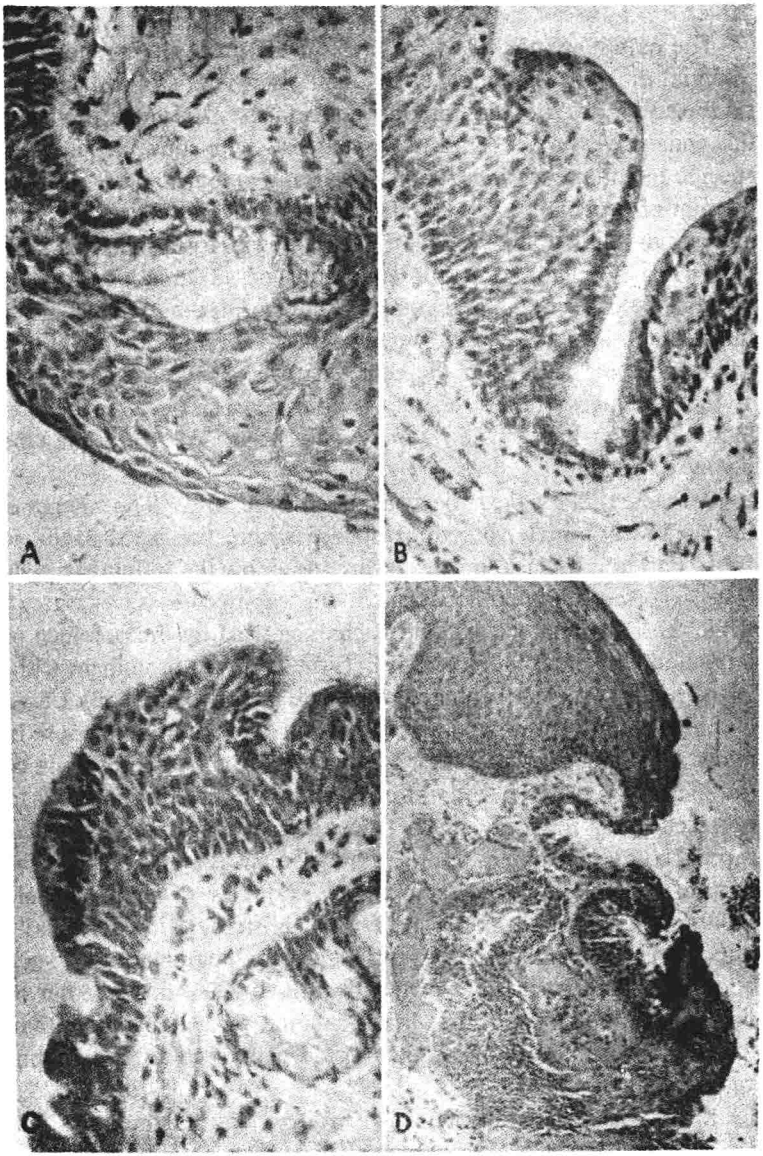

FIG. 5

Metaplasia under the influence of inflammation at different sites producing squamous cells of different degrees of perfection. (A) In the endocervix. × 240. (B) In Bartholin's gland. × 240. (C) In the ethmoid. × 240. (D) On the surface of the nasal polyp. × 104.

NON-SPECIFIC INFLAMMATIONS

The pathology of these conditions in the nasal cavity shows no essential differences from what is found elsewhere, so little description need be given of the familiar appearances. In acute processes the connective tissue beneath the mucosa will show acute, non-specific inflammatory infiltration of varying amount and a variable amount of oedema fluid will collect in its interstices. The overlying epithelium will show very variable changes from necrosis and ulceration (Fig. 3b) to minor conditions of swelling of the cells through a very variable and complex series of degenerative changes the form of which depends on the severity of the noxious agent which must be acting on the cells. Figures 3 and 4 show some of these changes. Severe degrees are usually associated with bacterial invasion and a wide variety of well-known forms may be involved.

Allergic rhinitis must be considered here also. The allergans involved vary widely, but the response within the nasal cavity is fairly constant. Much mucus is produced by the columnar cells (Fig. 3d), the degree of oedema of the submucosa is very great, while the inflammatory exudate is characterised by the presence of large numbers of eosinophile cells. These are most prominent within the tissue covering the middle turbinate (Gristwood, 1959). Large numbers are present in the watery fluid which pours from the nose in many cases. This is a useful diagnostic test. The marked oedema of the lining tissues leads to nasal obstruction of sudden onset and to obstruction of the drainage of the accessory sinuses, but yields rapidly to antihistamines. An allergic element is well known to be part of the disease process in many examples of more chronic inflammation in this region, *e.g.* sinusitis. Histologically it is usually impossible to disentangle the parts played by inflammation as such and by allergy, but it is always worthwhile to determine whether or not the inflammatory exudate in the submucosa contains more than the proportion of eosinophils that would be expected in uncomplicated inflammation.

More chronic manifestations of non-specific inflammation are less common in the nasal cavity itself than in the accessory sinuses, *e.g.* the antrum. The inflammatory exudate has the characteristics of the subacute type, fewer of the cells being polymorphs, but plasma cells and lymphocytes appear, while fibroblasts will do so if the condition persists for long enough. The overlying epithelium