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MORPHOLOGICAL CHANGES IN SMOKERS' LUNGS*

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IN RECENT YEARS statistical evidence has been accumulating that there may be a direct relationship between smoking and the development of bronchogenic carcinoma.[1-3] Certainly there is no doubt about the increasing incidence of carcinoma of lung,[4] and one must accept the possibility that not only tobacco smoke, but also the smoke and fumes in the atmosphere of big cities, may be etiological factors of importance.

Despite the emphasis on the importance of smoking given by the statistical investigations, there have been remarkably few attempts to determine whether or not there is any histological evidence to implicate smoke as an irritant, and possibly a carcinogen, in man. Experimental work would suggest that tobacco smoke may act as a carcinogen in susceptible animals.

The purpose of the present investigation was to determine whether or not any changes in the bronchial epithelium could be related to smoking. Morphological changes in bronchial mucosa have been well described,[5-8] and related to chronic inflammation in some cases. No new morphological alterations have been encountered in this study, but there is suggestive histological evidence that smoking may be a factor in inducing hyperplasia of bronchial epithelium. The relationship of this to the development of carcinoma cannot be elucidated.

MATERIAL AND METHODS

Selected autopsy cases were studied; they were collected from the autopsy service of the Toronto General Hospital, and the remainder from Toronto Western and Sunnybrook Hospitals. They fell into three groups (Table I).

1. *Carcinoma of lung.*—In this group there was usually an adequate history of the smoking habits of the individual. On the theory that whatever noxious influences may have caused the development of carcinoma in one lung probably also affected the opposite lung, the uninvolved bronchial tree and lung were taken for study.

2. *Smokers' lungs.*—It proved to be very difficult to obtain adequate histories of smoking for patients coming to autopsy without overt pulmonary disease. Nonetheless, over a period of time, 15 such cases were found.

3. *Control lungs.*—It also proved difficult to collect a series of cases in which one could be sure there had been no exposure to tobacco. However, 20 such cases were finally obtained in which the data appeared sufficiently reliable.

TABLE I.

	Total No. of cases	Age		Sex		Smoking history				
		Between	Average	M.	F.	Light 0 - 20	Moderate 20 - 40	Heavy 40+	Amt. not known	No history
Carcinoma of lung.....	30	45 - 81	61.3	28	2	6	6	12	1	5
Smokers.....	15	39 - 77	57.8	14	1	10	5			
Control.....	20	29 - 83	59.6	18	2					

The procedure in all three groups was the same. It was found that the best results were obtained when the trachea and lungs were removed together at autopsy and immediately perfused with 10% formalin, through the trachea. Alternatively, it was almost as satisfactory to remove the bronchial tree and immerse it in 10% formalin. In both instances, after fixation the bronchi were dissected free and opened longitudinally posteriorly. Gross inspection of the mucosa failed to give any indication of changes subsequently seen on microscopic examination. Attempts to remove mucus by washing usually rendered the mucosa unsuitable for histological study. Whereas in the first group, carcinoma of lung, the uninvolved opposite lung was taken for study, in the second and third groups the right lung was arbitrarily chosen. Blocks were taken transversely, and in each case from the same sites, notably the main bronchus, primary bronchi to upper, middle and lower lobes, and secondary bronchi. In all a minimum of six blocks was examined from each lung. Paraffin sections

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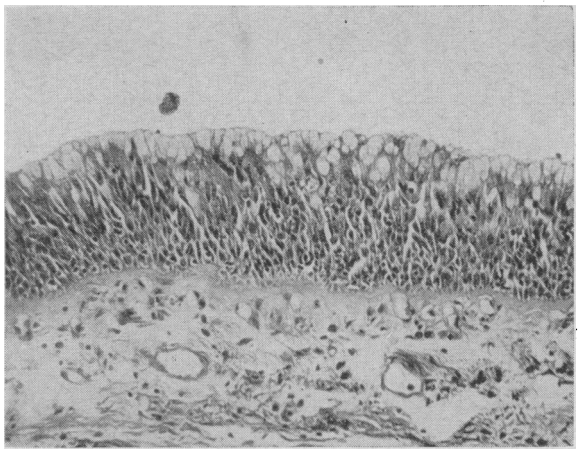

Fig. 1.—Marked basal cell hyperplasia. Note the uniformity of the proliferating cells and the relatively slight inflammatory infiltrate in the underlying tissues (× 240).

were cut at 5 μ. and stained with hæmatoxylin and eosin. Frequently additional blocks were obtained in order to determine the extent of the histological alterations seen.

OBSERVATIONS

The normal epithelial lining of the tracheobronchial tree has been described as mucous membrane consisting of pseudo-stratified ciliated columnar epithelium. Usually three types of epithelial cells are recognized, i.e., ciliated columnar cells, goblet cells, and basal cells. Interspersed between the ciliated cells are goblet cells, while the basal cells rest on a thin basement membrane, often forming a single but interrupted layer.

In the course of this study five types of morphological alteration in the lining epithelium of the bronchi were observed. For the most part these changes were focal and not extensive, and were recorded as extensive only when seen in every block studied and involving at least 70% of the circumference of the bronchus. The terms used to designate the alterations in the epithelium are meant to be descriptive only, and not physiological.

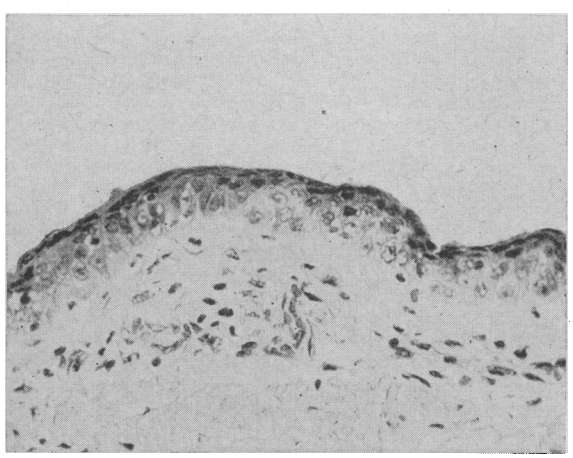

Fig. 2.—Stratification. The lining cells are flattened and the columnar ciliated cells have disappeared (× 480).

1. *Basal cell hyperplasia.*—Generally the basal cells form a single layer on the basement membrane, and have scant cytoplasm and round or oval nuclei. Increase in the number of layers of these cells was termed basal cell hyperplasia, and this was graded quantitatively as light, moderate and marked. Although the number of layers formed was the basis of gradation, it was felt that rigid adherence to the number of cell layers as proposed elsewhere[9] was not justifiable or possible in every case. In the majority of cases where basal cell hyperplasia was encountered it was focal, but occasionally was extensive. The basal cells were always uniform in size, shape and staining qualities, and the overlying columnar epithelium possessed cilia and appeared normal. Goblet cells were interspersed in the usual manner. In distribution, basal cell hyperplasia often extended into smaller branches of the bronchi (Fig. 1).

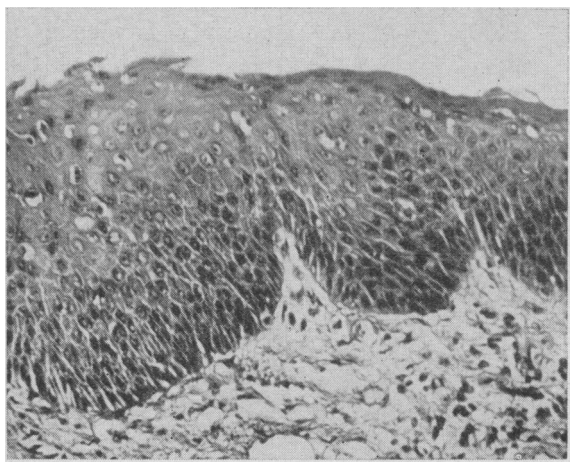

Fig. 3.—Squamous metaplasia. Well-marked area with stratification and flattening of cells, but no keratin formation (× 360).

2. *Stratification.*—This change was characterized by a uniformity of structure, in that the epithelium was composed of several layers of flattened cells, arranged parallel to the surface and to each other. There was a resemblance to squamous epithelium, but intercellular bridges were never seen. Neither ciliated cells nor goblet cells were present in these foci (Fig. 2).

3. *Squamous metaplasia.*—This change requires no description other than to state that the epithelium resembled the squamous non-keratiniz-

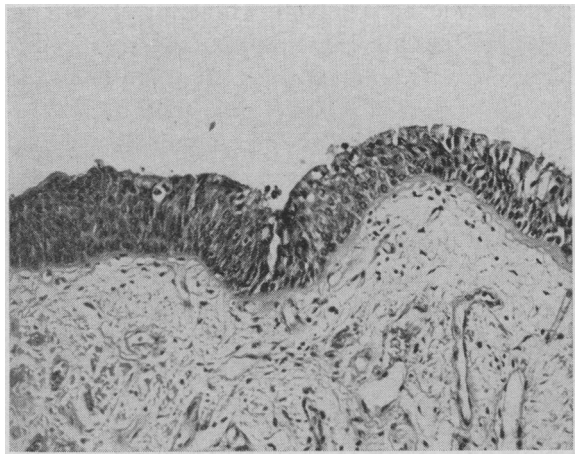

Fig. 4.—Transitional metaplasia. Stratified low columnar or cuboidal cells with absence of ciliæ. Note the gradual change to normal epithelium on the right-hand side (× 240).

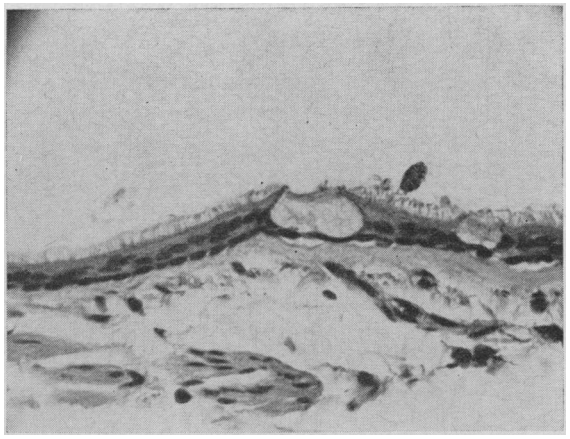

Fig. 5.—Intermediate change. Markedly thin epithelium with flattened, closely packed cells 2-3 layers deep. Note the presence of ciliæ (× 485).

ing epithelium of the oral cavity. Intercellular bridges were well developed, and ciliated columnar cells and goblet cells were absent. Keratinization was never seen. In comparison with stratification as described above, the areas of squamous metaplasia were thicker, being composed of more cell layers (Fig. 3).

4. *Transitional metaplasia.*—In this type of alteration the epithelium was stratified, composed of somewhat irregular cuboidal or low columnar cells with round or slightly oval nuclei. The cells were quite closely packed, presenting the same appearance as the transitional epithelium of the urinary tract. Again ciliated and goblet cells were absent (Fig. 4).

RESULTS

In Table II the incidence of the above described series of morphological changes is given. With few exceptions these alterations were found to be most frequent in Group 1, slightly less frequent in Group 2, and least frequent in Group 3.

TABLE III.

	Smokers 45 cases		*Non-smokers 20 cases*	
	No.	*%*	*No.*	*%*
Basal cell hyperplasia	37	82.2	8	40
Stratification	15	33.3	4	20
Squamous metaplasia	12	26.6	3	15
Transitional metaplasia	14	31.1	7	35
Intermediate change	19	42.2	4	20

TABLE II.

	No. of cases	*Basal cell hyperplasia*								*Stratification*		*Squamous metaplasia*		*Transit'l metaplasia*		*Intermed. change*	
		Slight		*Moder.*		*Marked*		*Total No. present*									
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Carcinoma of lung	30	23	76.6	12	40	8	26.6	24	80.0	12	40	9	30	8	26.6	14	46.6
Smokers	15	11	73.3	9	60	7	46.6	13	86.6	3	20	3	20	6	40.0	5	33.3
Control	20	8	40.0	6	30	5	25.0	8	40.0	4	20	3	15	7	35.0	4	20.0

5. *Intermediate change.*—This is a rather inadequate term used to denote a type of alteration which appeared to be a simplification of structure such as the stratification, and yet cilia and mucous secretion were not lost. In the areas affected the epithelium consisted of one to three layers of flattened cells having oval or elongated nuclei lying parallel to the surface, and scant cytoplasm. Nonetheless cilia were present on the surface, and occasional mucous vacuoles could be seen (Fig. 5).

Basal cell hyperplasia was most often encountered in all three groups. If one considers Groups 1 and 2 as both representing smokers' lungs, and this seems justifiable to us (see Table I), then the relative incidence of the various changes in smokers and non-smokers as shown in Table III is better demonstrated.

Whereas the predominance of basal cell hyperplasia is striking, in that it occurred in over 80% of the lungs of smokers and of those with carcinoma, as opposed to 40% of the non-

smokers, the other changes described do not really show a statistically significant increase in the smokers' and carcinoma groups. There is, however, a distinct trend towards a higher incidence in these latter cases, as well as a more extensive involvement by the change in question.

DISCUSSION

Although it was stated earlier that no significant functional alteration should be ascribed to the terms we have used to denote morphological alteration, one cannot escape from inferring that some physiological transformation had resulted in an altered growth and maturation pattern in the epithelium of the cases described. The appearance of basal cell hyperplasia, an increase in the number of cells, implies an increased rate of growth. Stratification suggests not only an increased rate of growth, but an alteration in maturation, in that the cells have lost the power to develop cilia and to secrete mucus. Squamous metaplasia, and transitional cell metaplasia, would imply an alteration in maturation carried beyond stratification. The last change described, intermediate change, is open to two interpretations: firstly that it represents regenerating epithelium and, secondly, that it represents regression and a diminution of physiological function. The term intermediate is meant to be non-committal with regard to the physiological state this may represent. It was, however, most frequently seen over small areas, and at times was not associated with inflammatory cellular infiltrates. It was seen most frequently around the openings of small ducts of mucus-secreting glands. In only two cases was this change seen over a wide area, and we have no explanation to offer regarding its nature. It is possible that intermediate change represents a variant of the Type I metaplasia of Wittekind and Strüder.[10]

All of the above changes may be interpreted as being in response to abnormal stimulation. The difficulty lies in determining the nature of the stimulus. The same changes are found in smokers and non-smokers, the only difference being one of degree. One may argue that the non-smokers may either have smoked at some time and the histories were inaccurate, or that even non-smokers were exposed to the smoke-polluted urban atmosphere of a large industrial city. Unfortunately our histories are inadequate, and do not give sufficient data regarding place of abode during adult life. However, it must be admitted that the smoky atmosphere of a city may be a factor in inducing the morphological changes described. This supposition would indeed help to explain the findings in the groups of cases studied in this report. The increased incidence of morphological alteration, and especially basal cell hyperplasia, in the smokers' and carcinoma groups, could then be due to the added factor of tobacco smoke. The above interpretation does parallel the statistical evidence implicating atmospheric pollution and tobacco smoke as causal factors in carcinoma of lung.[11]

There are other possible stimuli which must be considered. Inflammation of the bronchial tree has long been known to cause alterations in the lining epithelium. Basal cell hyperplasia and metaplasia have been described in chronic bronchitis, repeated upper respiratory tract infections, and some generalized infections in childhood.[10] Acute inflammation of short duration does not produce any significant alteration in the bronchial epithelium.[6]

In the selection of our cases an attempt was made to exclude all those in which there was, at autopsy, evidence of chronic pulmonary infection, such as bronchiectasis, tuberculosis and lung abscess. Nonetheless, in the majority of those instances where morphological alterations were seen in the epithelium, the underlying bronchial wall was infiltrated with varying numbers of lymphocytes, plasma cells and macrophages. Such inflammatory cellular infiltrates accompanied basal cell hyperplasia as well as the other changes described, but not in every instance, which suggests that the stimulus causing the epithelial alteration was not necessarily the same as that causing the inflammation. Other investigators, notably Wittekind and Strüder,[10] deny any connection between smoking and bronchial metaplasia, and relate such a change to chronic inflammation. These authors do not, however, mention basal cell hyperplasia. Auerbach,[9] on the other hand, finds a high incidence of the same types of epithelial change, notably basal cell hyperplasia, metaplasia, etc., in smokers' lungs and in carcinoma of lung. He does not, however, find as high an incidence as in the present series.

Although, as stated earlier, the incidence of stratification and squamous and transitional metaplasia was not significantly greater in

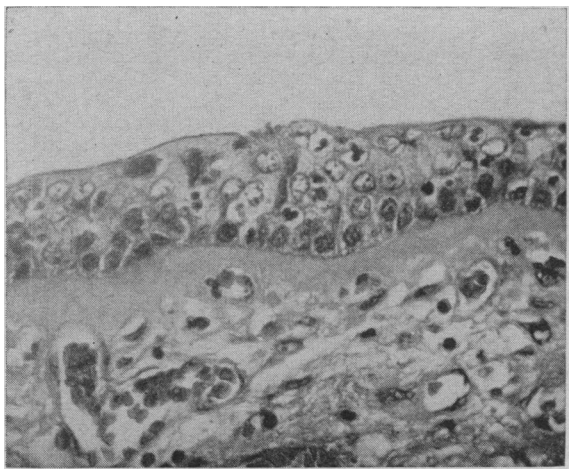

Fig. 6.—"Carcinoma-in-situ" of bronchus. Note the rather pronounced cellular pleomorphism, mitotic figures and scattered atypical hyperchromatic nuclei. (From a case of carcinoma of the opposite lung.) (× 480)

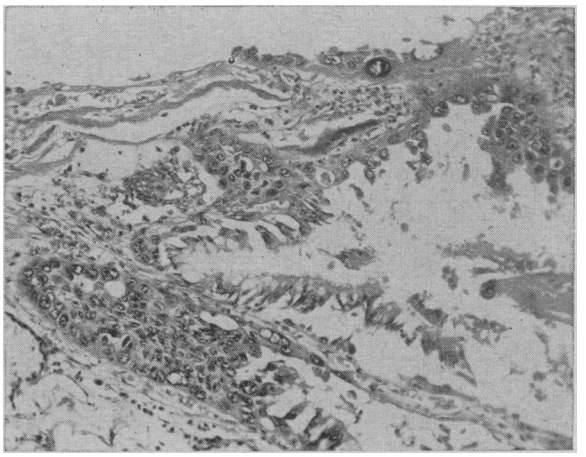

Fig. 7.—"Carcinoma-in-situ". The atypical epithelium shows shedding of superficial layers, but the change extends into the dilated ducts of mucus-secreting glands (× 100).

smokers, it was more extensive, and showed at times a tendency towards cellular pleomorphism. In two cases only, in which there was carcinoma in the contralateral lung, was "carcinoma-in-situ" found (Figs. 6 and 7). This does lend some support to the theory of multicentric origin of bronchogenic carcinoma.[12, 13]

This brings forward the relation of the histological changes described to carcinoma of the bronchus. We have no evidence whatsoever to suggest that any of the changes herein described, including basal cell hyperplasia, stratification, squamous and transitional metaplasia, and intermediate change, are pre-cancerous. It was noted that these changes were often not clear-cut or sharply defined, but merged one into the other, for example, stratification into squamous metaplasia. In two instances carcinoma-in-situ was encountered, localized to a small area in one case, but transformation from any preceding alteration could not be traced. In the second case, the whole of the lining epithelium appeared atypical, and no association with a preceding alteration could be found.

Our data do not lend themselves to any further analysis of etiological factors which may have induced the morphological alterations, and the only fact which has emerged is that basal cell hyperplasia of bronchial epithelium is more common in smokers, but we cannot ascribe this change to smoking alone, nor can we suggest that it has any relationship to cancer.

SUMMARY

The bronchial tree of one lung in 65 cases was examined, and the right lung was arbitrarily chosen. In cases of carcinoma of lung, the opposite lung was used.

These cases were divided into three groups: 30 cases of carcinoma of lung; 15 cases of smokers who did not develop carcinoma; and 20 cases of non-smokers.

Five types of epithelial change were seen: basal cell hyperplasia, stratification, squamous metaplasia, transitional metaplasia, and intermediate change.

The commonest finding was basal cell hyperplasia, which was more extensive and was encountered in a significantly higher percentage of smokers' lungs, including those with carcinoma. Furthermore, the other changes showed only a slightly higher incidence in the above-mentioned groups.

With the exception of basal cell hyperplasia, the changes described in bronchial epithelium have been observed in association with chronic inflammatory changes in the bronchial wall. However, the significant difference in incidence and extent of basal cell hyperplasia in cases of carcinoma of lung and in smokers can not be explained on the basis of inflammation.

It is felt that the results of the present series confirm some of the previous observations and warrant further studies.

The authors wish to express their indebtedness to Dr. W. Stanley Hartroft, who had the original idea for this study, but left Toronto to become Professor and Head of the Department of Pathology at Washington University.

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RÉSUMÉ

L'arbre bronchique du poumon droit de 65 sujets fut soumis à l'examen histopathologique. Dans les cas où ce poumon était cancéreux, l'autre fut examiné. Les sujets divisés en trois catégories, comprenaient 30 cas de cancer du poumon, 15 fumeurs dont les poumons n'étaient pas cancéreux et 20 non-fumeurs. Cinq genres de modification de l'épithélium furent observés: une hyperplasie basocellulaire, de la stratification, de la métaplasie pavimenteuse, de la métaplasie de transition et des altérations intermédiaires. L'observation la plus fréquemment notée fut l'hyperplasie basocellulaire qui prit plus d'ampleur et fut retrouvée avec une fréquence distinctement plus marquée chez les fumeurs, y compris ceux qui avaient un cancer, que chez les non-fumeurs. Les autres altérations ne furent que légèrement plus fréquentes dans le premier groupe. A l'exception de l'hyperplasie basocellulaire les altérations décrites dans l'épithélium bronchique se retrouvent dans l'inflammation chronique des bronches. Cependent l'ampleur et la fréquence accrue de cette hyperplasie basocellulaire dans les poumons cancéreux et dans ceux des fumeurs ne peut s'expliquer par une cause inflammatoire. Ces résultats semblent confirmer des observations antérieures faites à ce sujet et justifier une étude plus approfondie.

THE VALUE OF CHLOROQUINE IN RHEUMATOID DISEASE
A FOUR-YEAR STUDY OF CONTINUOUS THERAPY

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THE TREATMENT of rheumatoid disease with adrenal glucocorticoids has made it very clear that what is still required for its successful management is a drug that will control the systemic disease itself, not merely the inflammation in the target-organs, i.e. the joints. The ideal for long-term control would be a drug of very low toxicity, to which tolerance does not develop—so that it may be given safely and effectively over the many years of ebbing-and-flowing inflammatory activity that characterize the natural history of the average case of rheumatoid arthritis.

Parenteral gold was the first agent that appeared to arrest the systemic disease itself—but the rather high incidence of toxicity made it of long-term value in only a small proportion of patients. The data to be presented herein suggest that chloroquine may be the best approach at present available towards the ideal drug for the long-term management of rheumatoid arthritis, including the prophylaxis of relapses.

MATERIAL

One hundred and twenty-five private patients with rheumatoid disease have been carefully followed up personally, some of them for over four years after chloroquine therapy was instituted.

The aim was to keep them on continuous therapy for at least a year longer than the disease had existed at the start of chloroquine therapy, in the same fashion as the author had previously employed parenteral gold.

Four patients had less than six months' treatment but are included because toxicity necessitated withdrawal. All the rest had eight months or more of continuous therapy, 75% for more than one year, 50% for more than two years and 20% for more than three years.

During the first two years of this trial, only serious "problem" cases were chosen but, since then, all patients seen in whom a firm diagnosis of rheumatoid disease could be made, were started at once on chloroquine. Thus 55 (45%) had been under other (intensive) treatment for more than four months and up to six years before chloroquine, while 55% had less than five months' prior treatment. Of the 125 patients, 94 (75%) are still under treatment at the time of analysis (and 90% of those still under treatment show Grade I or II improvement). None of these 125 patients has been lost, so that the study is complete.