

PRIMARY CARCINOMA OF THE LUNG.

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## INTRODUCTION.

Adler, in 1912, apologised for writing a monograph on so rare a condition as "Primary malignant growths of the lung and bronchi" as he was able to collect only 374 cases from the world's literature. But since then, there has probably been no other pathological condition which has received as much attention in the medical literature.

In 1935, Gazayerli searched the post mortem records of Edinburgh Royal Infirmary and found 212 cases of intrathoracic neoplasms in a period of 31 years (from 1904 through 1934). He noticed that there was a gradual increase in the incidence of the disease in the last few years of his series but as there was a similar increase in some previous years, he felt that "to conclude that there was a real increase in the incidence of intrathoracic neoplasms in Edinburgh Royal Infirmary would be premature and the condition requires further investigation for several years."

Since that study was made, an increasing number of cases of carcinoma of the lung was encountered, not only in Edinburgh Royal Infirmary, but also in other hospitals and in particular the Eastern General Hospital where a thoracic unit was established.



The establishment of this thoracic unit resulted in great advances in thoracic surgery and also, as a consequence, in hundreds of bronchoscopic biopsies, specimens of sputa and pleural fluid, etc. etc. being sent to the Pathology Department for examination.

It was felt that it would be of benefit to continue that study started by Gazayerli in order to arrive at a conclusion regarding the incidence of carcinoma of the lung in Edinburgh, to find out the relative frequency of the histopathological types and to assess the value of bronchoscopy and cytological examination of the sputum in the diagnosis of the disease.

Though few cases of "bronchial adenoma" were encountered, it was possible to trace some of them for some time and get an idea about the natural course of this tumour and therefore a separate chapter was included.

No definite conclusion could be arrived at, with regard to aetiological factors, from study of the relative frequency of the disease among the various occupations. Therefore the question of aetiology is not considered in the present study.

INCIDENCE:-

This is a long-debated question about which there are many different opinions. Weller (1929) expressed the situation accurately when he said: "No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lung, for within a generation it appears to have become one of the common forms of malignant disease instead of the rarity which it was believed to be at the beginning of the century."

Dorn (1943) estimates that between 450,000 and 500,000 people in the United States are under medical care for cancer, of which about 13,000 are being treated for primary cancer of the bronchus. Approximately 8,000 new cases of primary bronchogenic carcinoma are diagnosed and receive medical care for the first time each year.

Harnett (1943) found that whereas the total number of cancer deaths in the British Empire had increased 22%, cancer of the respiratory tract has increased 120% and the deaths from carcinoma of the lung in males from 1921 to 1930 was 25.1 per million as contrasted with 100.9 per million in 1937.

From Edinburgh, Robertson (1943) stated that statistics show that each year the number of deaths registered as due to this disease is gradually increasing. In Scotland alone the total death-rate from pulmonary cancer in the year 1935 was 437 whereas by 1940 the toll had gradually mounted to 559, the increase in the five years having been fairly regularly supplemented by about 25 additional registrations each year.

Much of the literature on carcinoma of the lung has been devoted to whether the increased incidence is real or apparent. The problem may appear to be only of academic importance; but its resolution, however, may have a greater significance because if the increase is real and absolute attention can be directed to the elucidation and perhaps the ultimate elimination of the responsible factor or factors in the environment and therefore the control of pulmonary carcinoma would be partly solved by prophylaxis.

The authors who are in favour of the idea that the increase is real and absolute point to the steady increase in the incidence of reported cases out of proportion to the increase in the incidence of cancer in general.



Thus Edwards (1939) found that in the London Hospital there was an increase far in advance of that of all other forms of cancer and of all regions of the body. The proportion of deaths from cancer of the lungs in relation to other varieties of cancer rose from 2.4 to 3.2%, that is a rise of 30%.

Rosahn (1930) summarised most of the available autopsy statistics in 1930 and found that lung carcinomas increased 102% in the period from 1920-1928, as compared to the period from 1910-1919 while in the same periods carcinoma in general increased only 30%. He cited this as a proof of an absolute increase. Again in 1940 he analysed the factors often cited as evidence that cancer of the lung has shown only a relative increase and stated that improved methods of diagnosis had increased only the ante mortem diagnosis of pulmonary cancers.

Perrone and Levinson (1942) came to the conclusion that there has been a relative and absolute increase in the incidence of the disease. They also stated that Simons (1937) in his monograph has reached the following conclusions regarding incidence:

1. Incidence of the disease has increased



absolutely and relatively.

2. Continued suggestions that such an increase is only apparent and not real are denied by the facts.

3. The increases were gradual until the early 1900's, since when the gradient of the increase has become constantly steeper.

4. In many localities the greatest incidence seems to have been reached in 1924, whereas in others the frequency still is advancing.

A panel on lung cancer in the "National Cancer Conference" in U.S.A. (1949) reported: "All agreed that the incidence of cancer of the lung is apparently increasing rapidly and that it is one of the most common cancers in men. Also, the absolute incidence is increasing in both sexes, but apparently much more so in the male sex."

One of the strongest arguments favouring the conclusion that the increase is real, as stated by Klotz (1938) is to be found in the reports of increased incidence coming from institutions which have been under the same supervision and have required the same standards of diagnosis for a number of years.

Weller (1929) expressed the same idea when he

said: "If, however, one tabulates the statistics of successive periods in the same institution and that one in which there is continuity of diagnostic standards and often even of personnel, and finds there an increase in the incidence of carcinoma of the lung, one must give the increase more serious consideration."

These conditions and standards are fulfilled to the utmost degree in the Pathology Department of Edinburgh University and as will be shown later the data compiled therefrom show an undoubted and steady increase in the incidence of carcinoma of the lung which started and became more apparent from the late 1920's and onwards.

Several reviews, however, have been published - many of them doubting that there is a real increase. Thus Macklin (1942) thinks that "diagnosed" lung cancer is increasing but this is because it is being diagnosed in more cases in which it exists than was formerly the case and will be increasing no doubt because persons of lung cancer age are having fewer diseases to die of to-day than they had before, and hence must die in ever increasing numbers of the ones which remain.

Peery (1940) stated that one should hesitate in concluding that primary carcinoma of the lung is increasing in its frequency and that statistics in this field are probably misleading for the following reasons:

1. Prior to 1900 primary carcinoma of the lung was probably diagnosed less frequently than it actually occurred, even after autopsy, because of the belief then current that the tumour was exceedingly rare. Most of the tumours of this type occurring at that time were considered metastatic, probably erroneously.
2. Possibly the diagnosis of cancer of the lung is made more frequently now than is justifiable. Involvement of the bronchial mucosa, generally considered to be one of the criteria for the diagnosis, is not reliable, since metastases to the bronchial mucosa are relatively common.
3. The virtual abandonment of the diagnoses "endothelioma of the pleura", "oat cell tumour of the mediastinum" and "tumour of the superior pulmonary sulcus" and the placing of all the tumours formerly designated by these terms in the classification of primary carcinoma of the lung has enlarged the group considerably.

Peery believes that these tumours are



correctly diagnosed as primary carcinoma of the lung but that the change has swollen the statistics rather than increased incidence of the disease. He adds that undoubtedly primary carcinoma of the lung is quite common, but that the alarming apparent increase in the incidence of the tumour in the reported statistics cannot justifiably be accepted as an actual increase until due allowances are made for the pendulum to come to rest.

Among other authors who believe that the increase is more apparent than real is Jaffe (1935) who, in two separate reports from different parts of the world done in an interval of 20 years, found an almost similar incidence on each occasion.

Willis (1948) in his "Pathology of Tumours" says "..... For the foregoing reasons, comparisons of early and recent clinical or necropsy estimates of incidence, or comparisons of the findings in different hospitals, must be quite unreliable. So much depends on the personal experience of the clinicians and pathologists concerned, and current journals contain evidence enough that a uniformly high standard of diagnosis has not yet been attained by either. Now that



the properties of the disease are becoming better known, however, its true frequency and trend in a given community or institution might be ascertainable by meticulously careful and complete necropsies performed by skilled pathologists on all fatal cases over a period (probably 20 or 30 years) sufficient to obviate chance fluctuation."

Heady and Kennaway (1949) criticised what Willis states about the incidence of bronchial carcinoma in such an elaborate way that I cannot refrain from quoting it here. They said: "One might suggest that Willis is placing upon the material of Passey and Holmes (1935) a significance which it is not fitted to bear. For many years some students of this subject have wondered whether the (alleged) absence of any evidence in their data of an increase in cancer of the lung was not due to the fact that the great bulk of the increase took place after the period studied by Passey and Holmes. Willis does not point out that between the last year of that period (1928) and the year in which, presumably, he wrote (1947) the deaths attributed annually to cancer of the lung in England and Wales rose no less than ninefold (from 814 to 7667) and those of women from 314 to 1620; one might expect some comment

upon this enormous increase.

Thus the data recorded in the very careful and elaborate study of Passey and Holmes when put 20 years later as representing the state of our knowledge today, appear to show the unavoidable defect that the investigation ended in 1928, when the rapid increase of the last 20 years was just beginning.

Bonser has published three papers (1929, 1934, 1938) on this subject, dealing with the cases of intrathoracic cancer coming at autopsy at Leeds General Infirmary during three periods (1) 1891-1927 (2) 1928-1932 (3) 1933-1937. Though she noticed no increase in the 1st period of 35 years and a very slight increase in the 2nd period "which is unlikely to be of significance unless sustained for several more years" she recorded that there had been a considerable increase in the last 10 years which was more noticeable in the last 5 years and was seen whether intrathoracic cancers were recorded in relation to total post mortems or total admissions to hospital."

... ..

Now to discuss in a little more detail the arguments put forward by various authors against

the idea that there is a real increase in the incidence of carcinoma of the lung. These authors explain the recognised increase in the incidence of the disease by one or more of the following factors:-

1. Improvement in diagnosis, whereby a larger proportion of the actual number of cases is detected in life; and an increase in the number of autopsies performed.
2. The increase is due to the increase in the life span so that more individuals now reach the cancer age and so fall victims to the disease i.e. ageing of the population.
3. An increased interest in carcinoma of the lung on the part of the physicians and thoracic surgeons resulting in an increase in the number of cancers of the lung diagnosed ante mortem. In many of these cases in which the disease was suspected but was not definitely diagnosed, post mortem examination was made, hence the increased incidence of this type of tumour in autopsy statistics.
4. Changes have occurred in the histologic classification of primary lung tumours and many of the cases which were regarded as "mediastinal sarcomata" or "secondary" carcinomata in the past



are now classified as primary lung carcinomata.

5. Persons of lung cancer age are having fewer diseases to die of to-day than they had before and hence must die in ever increasing numbers of the ones which remain.

(1) & (4) IMPROVEMENT IN DIAGNOSIS AND CHANGES IN THE HISTOLOGIC CLASSIFICATION:-

There can be no doubt that with the advent of X-rays, bronchoscopy, etc. and also the fact that physicians are more aware nowadays that carcinoma of the lung is not the rare disease it was thought to be, that the diagnosis is made much more commonly in recent years. But it must be realised that this resulted mostly in an improvement in the clinical or "ante mortem" diagnosis of the disease and did not influence to any similar degree the diagnosis of carcinoma of the lung in the autopsy room. It might be argued that even post mortem diagnosis had improved because pathologists were under the wrong notion expressed by Virchow that most tumours of the lung were secondary and not primary and also because many of the "oat cell" carcinomas were regarded as mediastinal sarcomata.

Again if we take it for granted that these two factors did improve the P.M. diagnosis as



well, this would be applied only to a period not later than the late 1920's or early 1930's when the medical profession became fully aware of the condition and the nature of the oat cell tumour of the mediastinum was realised after Barnard in 1926 published his paper.

Another important point which must not be forgotten is the fact that the data I am going to present and compare are not only compiled from the same institute but that the standards and criteria of diagnosis are also the same since during the whole period Professor A.M. Drennan - who was always interested in the subject - was in charge of this Department.

To obviate any possible error still due to this factor of improved diagnosis, all cases of intrathoracic neoplasms (apart from those obviously arising from the oesophagus etc.) were included in both of these series. Rosahn (1940), in trying to evaluate the role of the factor of the change in the histologic classification of primary lung tumours in the incidence of the disease, found only two instances in which the anatomic diagnosis altered after restudy of the slides of the older cases.

(2) INCREASE IN LIFE EXPECTANCY:-

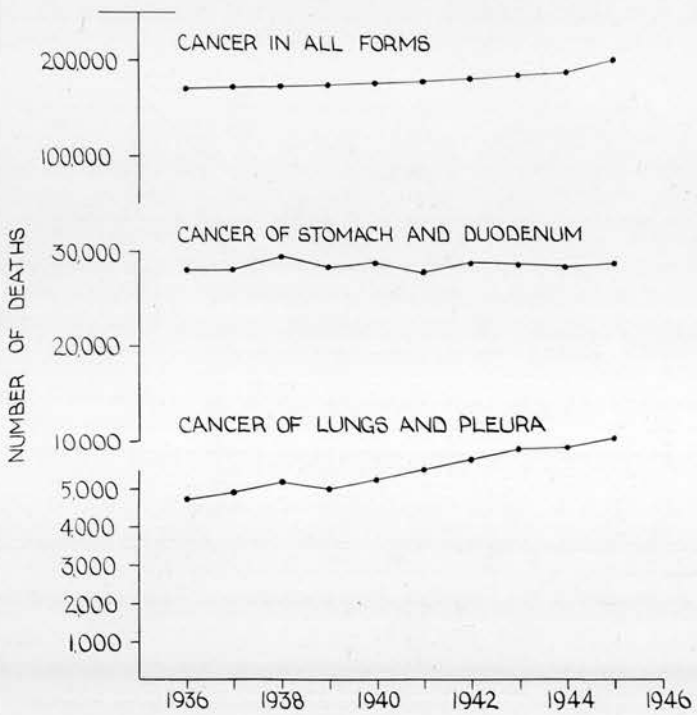
A point which is usually raised against a

real increase in the incidence of the disease is that because of the ageing of the population in general, more persons nowadays live in the cancer age than in the previous decades and so there should be many more deaths from cancer.

If this is true, we should then find a similar increase in all types of cancer because admittedly this factor of the ageing of the population will not affect cancer of the lung alone. But if we analyse the deaths from cancer of the lung and those from cancer in other internal viscera e.g. the stomach, we are struck by the fact that whereas cancer of the stomach did not show any appreciable increase, cancer of the lung continued to rise over the whole period. This was confirmed in many countries. In U.S.A., the mortality from cancer in the ten year period (1936-1945) was analysed and from the data obtained the following graph was constructed (graph 1). In Germany, Jeuther et al (1947) found even more striking results in a period of 50 years from 1894-1943) (graph 2.)

Though the following data which were extracted from the annual reports of the Public Health Department concerning the City and Royal Burgh of Edinburgh are unfortunately lacking the figures from 1939-1945 (the war period), it is quite

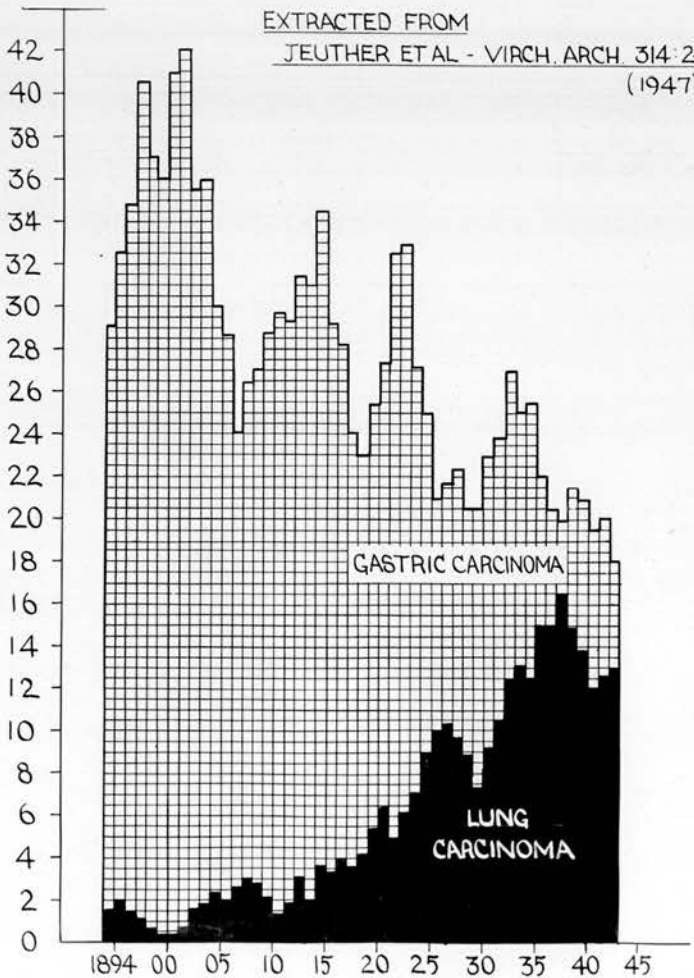
MORTALITY OF CANCER IN THE UNITED STATES FOR A TEN YEAR PERIOD



GRAPH 1.

EXTRACTED FROM 'PANEL ON LUNG CANCER'  
PROCEEDINGS OF THE NATIONAL CANCER CONFERENCE 1949 (p.189-206)

EXTRACTED FROM  
JEUTHER ET AL - VIRCH. ARCH. 314: 242  
(1947)



GRAPH 2.

PERCENTAGE RATIO OF LUNG CARCINOMATA (BELOW)  
AND GASTRIC CARCINOMATA (ABOVE) TO ALL CARCINOMATA



evident from the table that while deaths from carcinoma of the stomach and oesophagus showed very slight variation, those due to carcinoma of the lung have shown nearly a five-fold increase (table 1.)

TABLE 1.

| YEAR | Deaths from Ca. lung |    |      | Total Ca. deaths | Deaths from Ca. Stomach & Oes. | Ca. death rate per 1000 |
|------|----------------------|----|------|------------------|--------------------------------|-------------------------|
|      | M.                   | F. | Both |                  |                                |                         |
| 1935 | 15                   | 22 | 37   | 806              | 201                            | -                       |
| 36   | 20                   | 21 | 41   | 809              | 211                            | 1.7                     |
| 37   | 44                   | 20 | 64   | 854              | 206                            | 1.8                     |
| 38   | 42                   | 24 | 66   | 883              | 228                            | 1.9                     |
| 39   | -                    | -  | -    | 884              | -                              | 1.9                     |
| 1940 | -                    | -  | -    | 891              | -                              | 2.08                    |
| 41   | -                    | -  | -    | 934              | -                              | 2.17                    |
| 42   | -                    | -  | -    | 972              | -                              | 2.29                    |
| 43   | -                    | -  | -    | 971              | -                              | 2.33                    |
| 44   | -                    | -  | -    | 913              | -                              | 2.18                    |
| 1945 | -                    | -  | -    | 1013             | -                              | 2.37                    |
| 46   | 91                   | 23 | 114  | 955              | 204                            | 2.08                    |
| 47   | 98                   | 23 | 121  | 969              | 191                            | 2.00                    |
| 48   | 143                  | 33 | 176  | 1018             | 209                            | 2.08                    |

(3) AN INCREASED INTEREST IN THE DISEASE:-

As regards increased interest in this disease on the part of physicians and thoracic surgeons this must suppose a constantly increasing awareness of this condition to the present time and it would be necessary to assume also that in the same time the attention to and the interest in tumours of other organs were maintained at a constant level.

(5) PEOPLE WHO LIVE TO THE CANCER AGE HAVE FEWER DISEASES TO DIE OF, ... etc.

Some authors remark that because of the decrease in the mortality from infectious diseases like pneumonia, etc. within recent years due to the advent of chemotherapy, people have to die in increasing numbers from other diseases. I think that this point is no argument against the real increase in deaths from lung cancer. In fact it means that these authors agree that the deaths due to this disease have increased but they are trying to explain why this increase took place.

To conclude then: it would seem that all arguments put forward to prove that the rise in the incidence of lung carcinoma is apparent and not real, are not valid and have no real basis.

... ..

Now, I proceed to the actual statistical study of the incidence of the disease in the R.I.E. In order to ascertain, as far as possible, the actual state of affairs, and to make it easier for comparison, it was decided to carry on with the investigation and analysis of the data on the same lines as those followed by Gazayerli in his study which covered the period from 1904 to 1934 inclusive.

Therefore the P.M. records from 1935 through 1947 were carefully searched and every case where a primary intrathoracic neoplasm was reported has been noted and considered (excluding, as he did, those obviously arising from the oesophagus, cases of Hodgkin's disease, etc.)

The admissions to the hospital wards, the total of deaths, the number of post mortems performed and the number of malignant tumours in all sites - were also recorded and the data obtained are shown in Table 2.

Though a glance at this table is not very impressive in showing a striking rise in the incidence, yet when these data are plotted in one graph together with the previous ones, it will be quite evident that an undoubted increase has occurred in the incidence of intrathoracic neoplasms



in Edinburgh Royal Infirmary. This rise started nearly from 1929 and continued, with some yearly fluctuations, up to the present time.

TABLE 2.

| YEAR | ADMISSION | DEATHS | AUTOPSIES | % OF AUTOPSIES TO DEATHS | ALL TUMOURS | LUNG TUMOURS | % OF TUMOURS TO AUTOPSIES | % OF INTRATHORACIC TUMOURS TO |           |                      |        |
|------|-----------|--------|-----------|--------------------------|-------------|--------------|---------------------------|-------------------------------|-----------|----------------------|--------|
|      |           |        |           |                          |             |              |                           | ALL TUMOURS                   | AUTOPSIES | ADMISS <sup>NS</sup> | DEATHS |
| 1935 | 19801     | 1314   | 696       | 52.8                     | 114         | 14           | 16.3                      | 12.2                          | 2.0       | 0.07                 | 1.1    |
| 1936 | 20675     | 1354   | 623       | 46.0                     | 99          | 9            | 15.8                      | 9.1                           | 1.4       | 0.04                 | 0.7    |
| 1937 | 20995     | 1369   | 616       | 45.0                     | 111         | 24           | 18.0                      | 21.6                          | 3.9       | 0.11                 | 1.7    |
| 1938 | 21883     | 1362   | 630       | 46.2                     | 115         | 17           | 18.2                      | 14.8                          | 2.5       | 0.08                 | 1.2    |
| 1939 | 20937     | 1306   | 599       | 45.8                     | 104         | 14           | 17.3                      | 13.4                          | 2.3       | 0.06                 | 1.1    |
| 1940 | 18182     | 1375   | 551       | 40.0                     | 99          | 16           | 17.9                      | 16.2                          | 2.9       | 0.09                 | 1.2    |
| 1941 | 20056     | 1353   | 496       | 36.6                     | 78          | 13           | 15.7                      | 16.6                          | 2.6       | 0.06                 | 0.96   |
| 1942 | 19726     | 1266   | 467       | 36.8                     | 87          | 19           | 18.6                      | 22.9                          | 4.0       | 0.10                 | 1.5    |
| 1943 | 20249     | 1419   | 485       | 34.1                     | 69          | 14           | 14.2                      | 20.3                          | 2.9       | 0.07                 | 0.98   |
| 1944 | 20205     | 1339   | 426       | 31.8                     | 70          | 15           | 16.4                      | 21.4                          | 3.5       | 0.07                 | 1.1    |
| 1945 | 21002     | 1504   | 482       | 32.0                     | 100         | 27           | 20.7                      | 27.0                          | 4.9       | 0.12                 | 1.8    |
| 1946 | 22282     | 1664   | 649       | 39.0                     | 140         | 35           | 21.5                      | 25.0                          | 5.4       | 0.15                 | 2.1    |
| 1947 | 22148     | 1459   | 610       | 41.8                     | 125         | 22           | 20.4                      | 17.6                          | 3.6       | 0.10                 | 1.5    |

If we analyse the previous table in some detail we find the following:

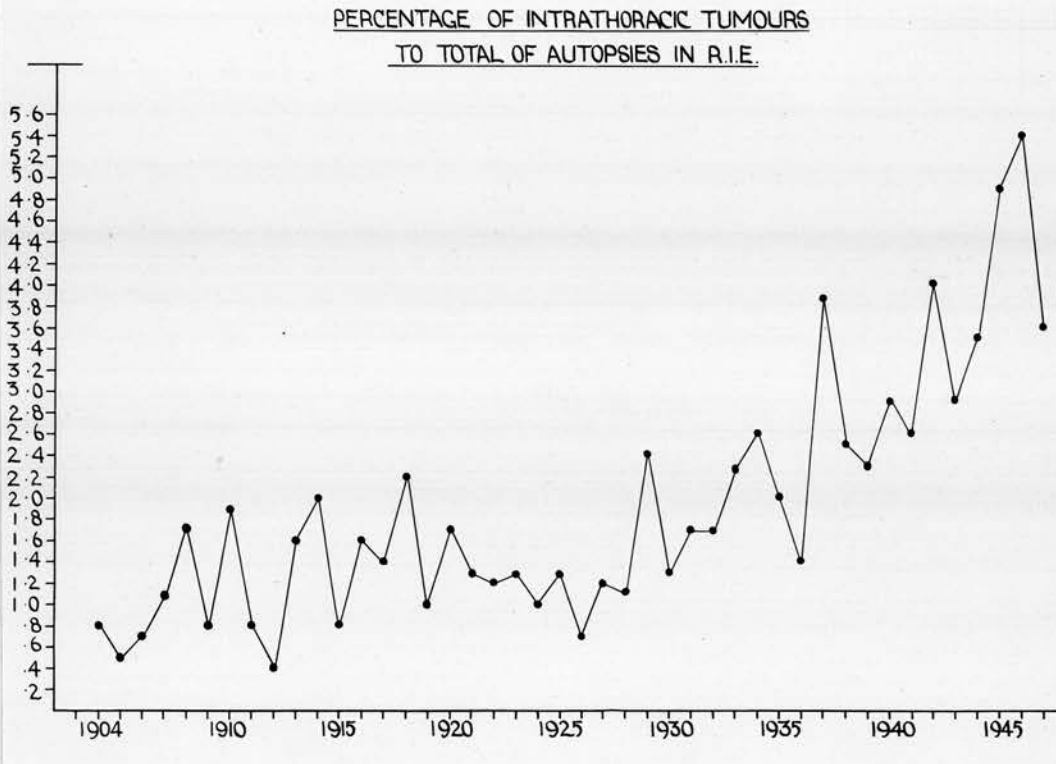
(a) % of Intrathoracic Tumours in relation to

Autopsies:-

During the 31 years from 1904 to 1934, 212 cases of intrathoracic tumours came to the post mortem room at the Royal Infirmary. This represents an average ratio of intra-thoracic tumours to all autopsies of 1.3%. In the next 13 years (from 1935 to 1947 inclusive) the number of cases of intra-

thoracic tumours in the post mortem records is 239 representing an average ratio of 3.3% (intra-thoracic tumours to autopsies). See table 2, column 9, and graph 3.

GRAPH 3.



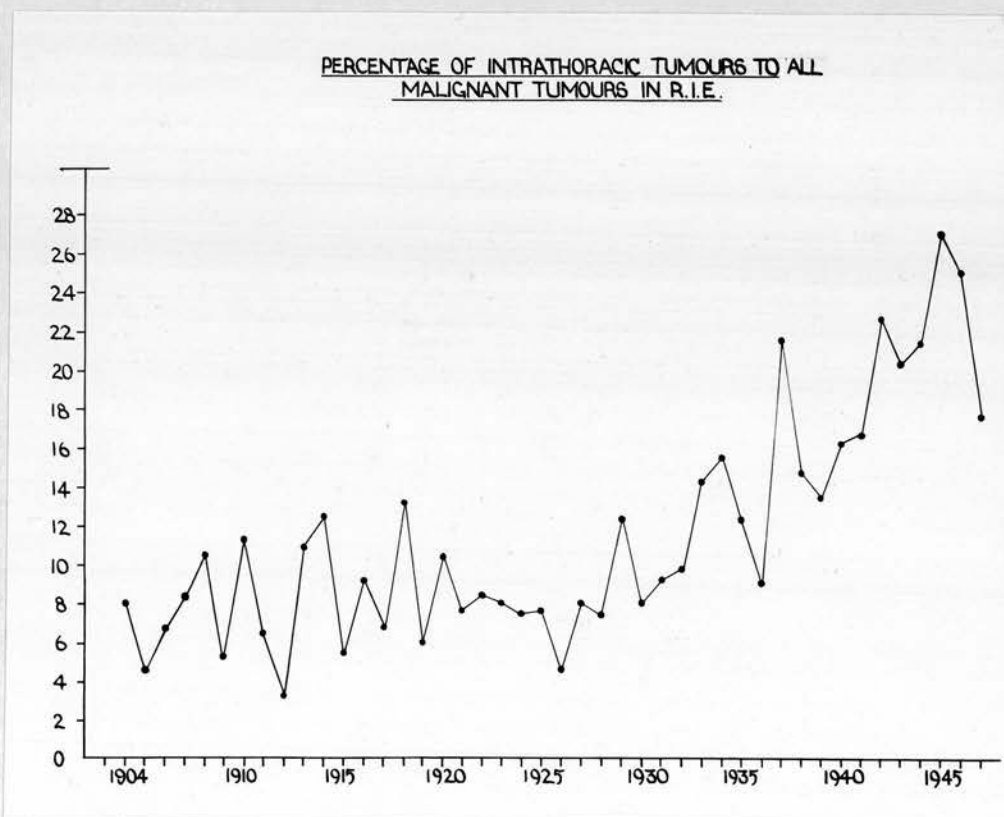
In graph 3, the % of intrathoracic neoplasms to the total of autopsies in the whole period covered by the two series is shown. It will be clearly seen that the "gradual but evident rise" which Gazayerli noticed in the last few years of his series but which was not sufficient for him to conclude that there had been a real increase

in the incidence of the disease, was not only maintained but actually progressed during the following years up to the present time.

(b) In relation to malignant tumours in all sites:-

All cases of malignant tumours found amongst the autopsies were recorded and then the percentage ratio between intrathoracic neoplasms and these tumours was plotted as shown in graph 4.

GRAPH 4.



The average ratio up to the year 1934 was 8.3% while in this new series of cases this ratio has gone up to 18.2%. This shows that even if the total number of malignant tumours among the



population has increased within recent years because of the increase in the life span, this increase is not distributed equally among cancers in the various sites but that intrathoracic tumours in particular have increased.

(c) In relation to Admissions:-

The third method recommended by many investigators for the estimation of the incidence of intrathoracic tumours is by means of finding out their relation to the number of cases admitted to the hospital wards. In the case of the R.I.E. this is certainly a recommended method because it is a "general" hospital and it cannot be argued that there might have been more interest in intrathoracic neoplasms among the staff of the hospital. In graph 5 this relation is represented and it will be noticed that the rise which started about the year 1929 is maintained and has actually progressed during the following years.

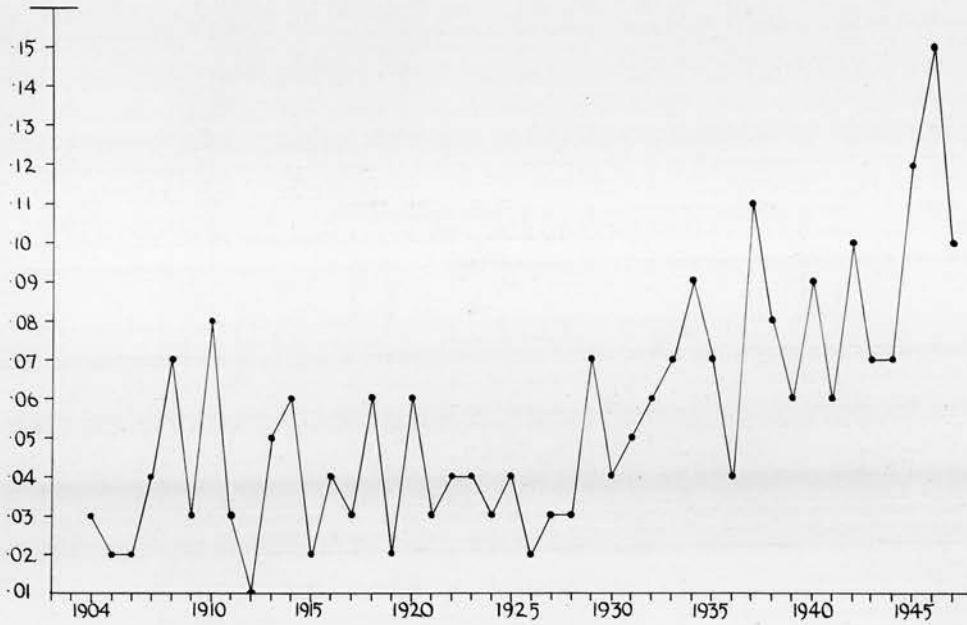
The % of intrathoracic tumours in relation to the total of admissions up to 1934 was 0.04 whereas from 1935 to 1947 this percentage is 0.086.

(d) In relation to Deaths:-

The percentage of intrathoracic tumours to the total number of deaths was also calculated and

GRAPH 5.

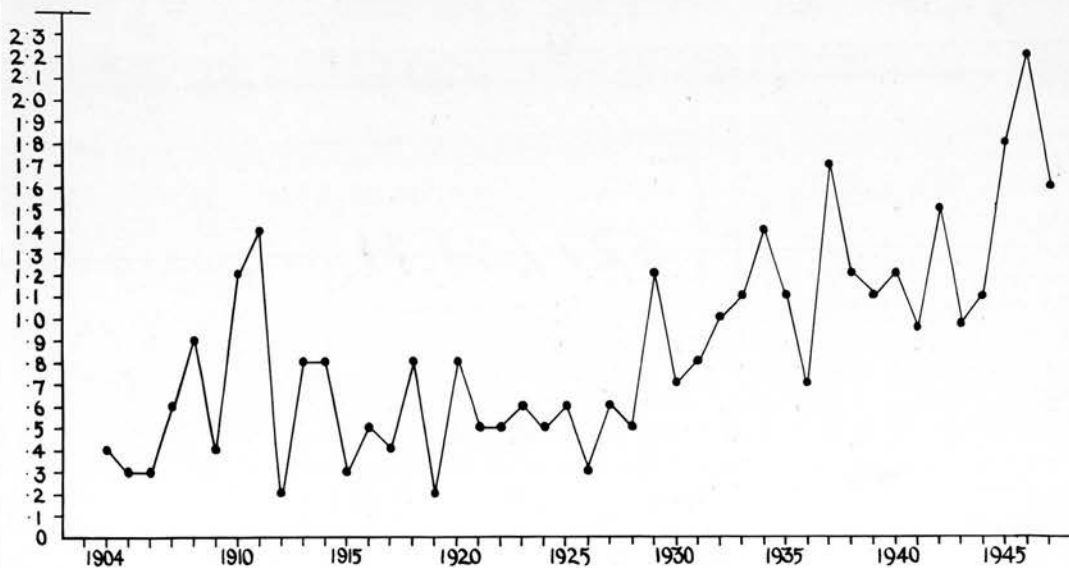
PERCENTAGE OF INTRATHORACIC TUMOURS TO TOTAL OF ADMISSIONS IN R.I.E.



the result is shown in graph 6.

GRAPH 6.

PERCENTAGE OF INTRATHORACIC TUMOURS TO TOTAL OF DEATHS IN R.I.E.



It shows clearly that the rise noticed in the last few years of Gazayerli's series has progressed during the following years. The average % in the period 1904 - 1934 was 0.6, but in 1935 - 1947 this percentage is 1.3.

... ..  
 ... ..

In conclusion it is quite clear from the above data that during the last two decades especially, carcinoma of the lung has shown a real and obvious increase in its incidence. The various suggestions that this increase is only apparent have been discussed and it can be seen that they have no real foundation.

If so, then we must look for some factor or factors in our environment which may have caused this rise in the incidence of the disease. The geographical distribution of the cases gives general support to the view that the incidence of carcinoma of the lung is higher in industrial areas than it is in rural zones, and therefore we have as Fulton (1949) said "to peer into the shadows to see what lies behind: to strive constantly to solve the riddle of why this disease should be a man-killer and why, indeed, it should occur at all".

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AGE INCIDENCE:

There were two cases only among the 239 cases of intrathoracic tumours in the R.I.E. in which the age was not recorded. The highest incidence was in the decade 50 - 59 years and the majority of cases occurred in the age period 40 - 69 years, as shown in the following table (table 3), which is represented graphically in graph 7.

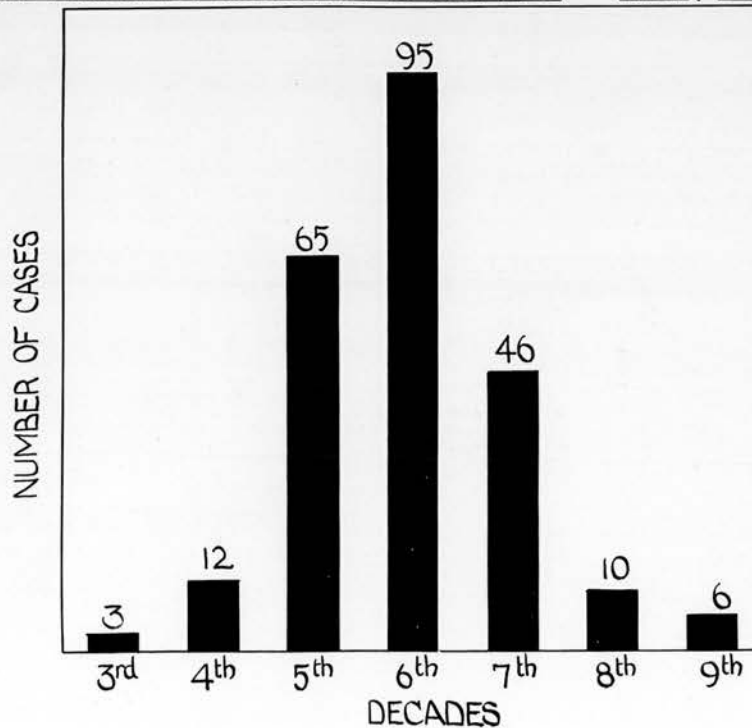
GRAPH 7.AGE INCIDENCE ACCORDING TO DECADES. R.I.E. (237 CASES)

TABLE 3.

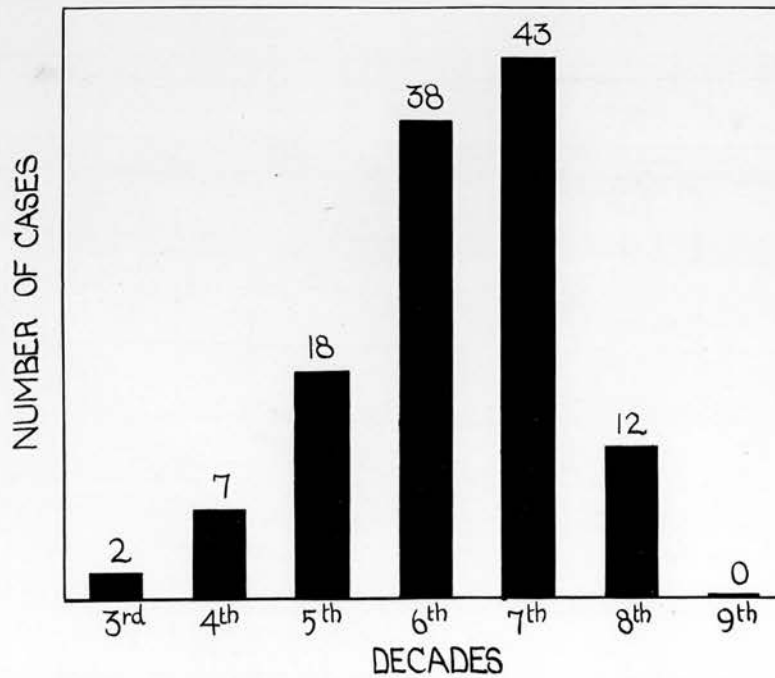
| Decade | Number of Cases |
|--------|-----------------|
| 20-29  | 3               |
| 30-39  | 12              |
| 40-49  | 65              |
| 50-59  | 95              |
| 60-69  | 46              |
| 70-79  | 10              |
| 80-    | 6               |
| Total  | 237             |

The youngest was a man of 23 years and the oldest victim was a man of 84 years. It will be noticed that 206 cases out of the 237 i.e. 86.9% occurred in the age period 40-69 years. This agrees with the majority of published series.

In the records of the Municipal Hospital Autopsies (M.H.A.) from 1936 - 1947 there were 121 cases of intrathoracic neoplasms (almost entirely lung cancers). In one case only the age was omitted and the age distribution of the cases according to the decades is as follows: (Table 4 and graph 8).

TABLE 4.

| Decade | Number of Cases |
|--------|-----------------|
| 20-29  | 2               |
| 30-39  | 7               |
| 40-49  | 18              |
| 50-59  | 38              |
| 60-69  | 43              |
| 70-79  | 12              |
| 80-    | 0               |
| Total  | 120             |

GRAPH 8.AGE INCIDENCE ACCORDING TO DECADES. M.H.A. (120 CASES)

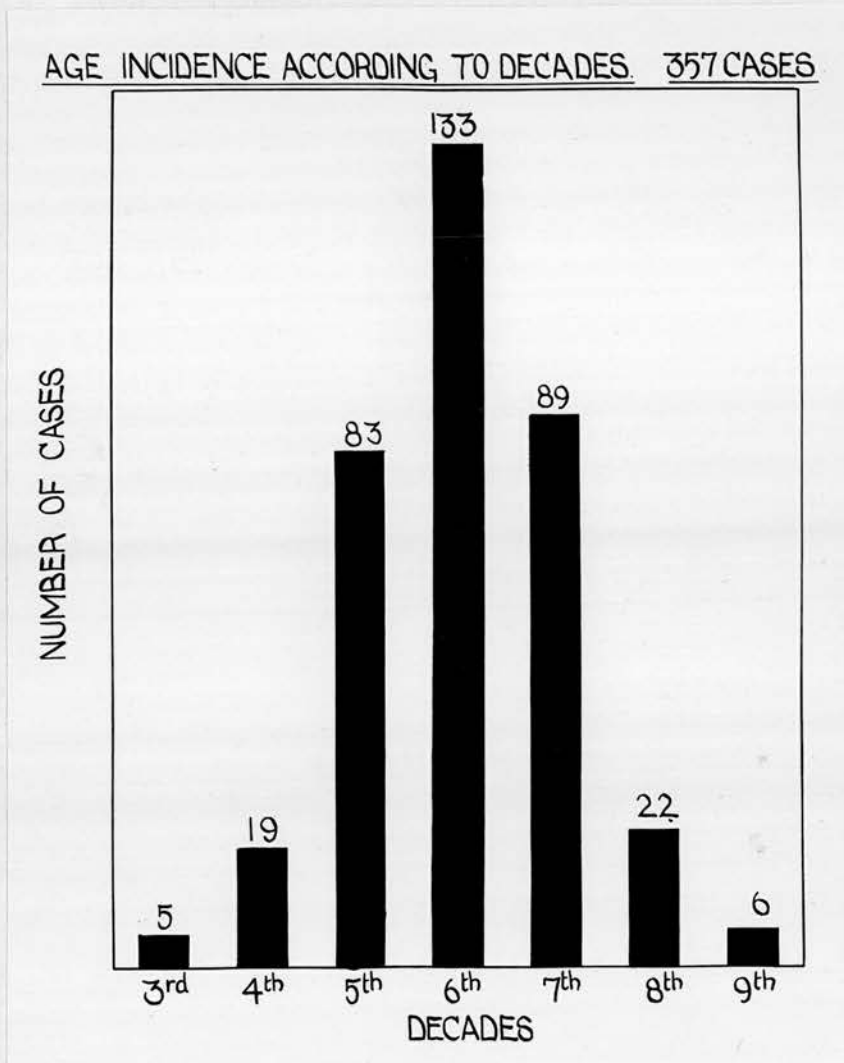


The youngest in this series was a female of 24 years and the oldest was a man of 79 years. Again, the majority of cases occurred between 40 and 69 years. Thus, out of the 120 cases 99 or 82.5% occurred in this age period.

If the 2 series are compiled together as in Table 5 and Graph 9, it will again be seen that more than 85% of cases (305) occurred in the age period 40 - 69 years. This is, as we mentioned before, in agreement with most published series on the subject.

TABLE 5.

| Decade | Number of Cases |
|--------|-----------------|
| 20-29  | 5               |
| 30-39  | 19              |
| 40-49  | 83              |
| 50-59  | 133             |
| 60-69  | 89              |
| 70-79  | 22              |
| 80-    | 6               |
| Total  | 357             |

GRAPH 9.SEX INCIDENCE:-

When the sex incidence among these cases was studied, it became clear that the general impression that carcinoma of the lung affects males much more commonly than females is true. Among the 239 cases in the R.I.E. there were 191 males and 48 females with a ratio of 3.97:1.

These cases were distributed as follows:

TABLE 6.

| Decade | Total | Males | Females |
|--------|-------|-------|---------|
| 20-29  | 3     | 2     | 1       |
| 30-39  | 12    | 9     | 3       |
| 40-49  | 65    | 56    | 9       |
| 50-59  | 95    | 77    | 18      |
| 60-69  | 46    | 34    | 12      |
| 70-79  | 10    | 7     | 3       |
| 80-    | 6     | 4     | 2       |
| Total  | 237   | 189   | 48      |

Note: There were 2 cases in which the age was not recorded.

In the Municipal Hospital Autopsies series, there were 99 males and 22 females among the 121 cases with a ratio of 4.5 males to 1 female. Their distribution among the different age periods is as follows (Table 7).



TABLE 7.

| Decade | Total | Males | Females |
|--------|-------|-------|---------|
| 20-29  | 2     | 0     | 2       |
| 30-39  | 7     | 5     | 2       |
| 40-49  | 18    | 15    | 3       |
| 50-59  | 38    | 34    | 4       |
| 60-69  | 43    | 34    | 9       |
| 70-79  | 12    | 10    | 2       |
| 80-    | -     | -     | -       |
| Total  | 120   | 98    | 22      |

Note: In one case the age was omitted.

It is interesting to note that in this series the few cases occurring in the young age periods show a relatively higher incidence among females.

If both series are grouped together, then there will be a total of 360 cases, of which 290 are males and 70 are females with a ratio of 4.1 males to 1 female.

It is interesting to note that there is practically no difference as regards the sex incidence between this series and that of Gazayerli, which covered the period 1904 through 1934. Therefore the idea expressed by some that the disease is becoming commoner amongst females is not supported by our data.

HISTOPATHOLOGY.

According to Ewing (1940), the earliest microscopic studies of lung tumours were by Landhans, Marchiafava and Malassez (1871 to 1876). From a histologic standpoint, Adler assigned the majority of cases to the carcinoma group. It was Barnard's paper in 1926 which clarified the origin of the "oat cell tumour of the mediastinum" and revealed its carcinomatous nature.

It is the custom to try to divide lung carcinomas according to the cell type of which they are composed. There are thus three chief groups: adenocarcinoma, squamous cell carcinoma, and the undifferentiated carcinoma (including the oat cell variety).

Though this seems to be the most convenient way of classifying the disease into histological types, the majority of observers remark that in most cases there is more than one type in the same tumour and even in the same slide, and that if different parts of the tumour are examined, more than one type is usually encountered.

This, I think, explains the marked difference in the figures given by various authors regarding the relative frequency of these three histological

types. Weller (1929) stated that satisfactory figures are not available in regard to the incidence of the various cell types and explained this by differences in individual opinion, the existence of intermediate types and especially because of the fact that the degree of differentiation may vary in different portions of the same neoplasm.

Anderson(1948) remarks that when statistics of incidence of various histological types are quoted, one wonders whether the same material might not be differently classified by another histopathologist and whether a different chance selection of tissue for microscopic examination might not have yielded different percentages even by the same examiner.

From some institutions the figures published have indicated that squamous cell carcinomas constitute the greatest number, from others, the undifferentiated types. Most writers agree that the cylindrical cell form is the least common of the three main groups.

On the whole, my impression is that the majority of classifications based on study of post mortem material give a high proportion of the undifferentiated types, while those based on



the study of surgically resected cases and bronchoscopic biopsies tend to show a higher proportion of the squamous cell variety.

Classifications based on the study of exfoliated cells in sputum and bronchial secretions are, in my opinion, very inaccurate seeing that even in histological sections one frequently finds some difficulty in labelling the correct type especially in a tumour which shows such a polymorphic structure as carcinoma of the lung. E. Jackson et al in a recent article (1951) state that it is their opinion that the recognition of the type of neoplasm by the study of exfoliated cells is not possible because exfoliated cells are subject to degenerate changes.

There was a feeling among some colleagues that there might have been a change in the relative frequency of the histological types within recent years as they seem to be diagnosing more cases of squamous cell carcinoma than they used to do in previous years.

Therefore I tried to find out if this idea was justified by comparing the more recent data with those obtained in the previous study by Gazayerli.

There were 208 cases in which the histopathological type of the tumour was either recorded

or could be found out from examination of slides kept in the files. The classification of these cases is shown in the following table (table 8).

| Histological Type | Number of Cases | %    |
|-------------------|-----------------|------|
| Undifferentiated  | 130             | 62.5 |
| Squamous          | 37              | 17.8 |
| Adenocarcinoma    | 36              | 17.3 |
| Mixed             | 5               | 2.4  |
| Total             | 208             | 100  |

Table 8.

The percentage given by Gazayerli as a result of studying 95 cases was as follows (table 9.)

| Histological Type | Number of Cases | %    |
|-------------------|-----------------|------|
| Undifferentiated  | 74              | 77.8 |
| Squamous          | 7               | 7.3  |
| Adenocarcinoma    | 14              | 14.7 |
| Total             | 95              | 99.8 |

Table 9.

If we compare these two tables we notice that in the older series there is a greater number of the undifferentiated tumours and a smaller number of the squamous variety. But the change is not very striking and still the great majority of cases are of the undifferentiated types (spheroidal and oat cell types).

In addition to the 208 cases from the Royal Infirmary quoted above, there were 110 cases of carcinoma of the lung among the Municipal Hospital Autopsies (in the period studied) in which a histopathological diagnosis was recorded. These cases were subdivided as follows (Table 10).

| Histological Type | Number of Cases | %    |
|-------------------|-----------------|------|
| Undifferentiated  | 66              | 60   |
| Squamous          | 21              | 19.1 |
| Adenocarcinoma    | 18              | 16.4 |
| Mixed             | 5               | 4.5  |
| Total             | 110             | 100  |

Table 10.

The above table shows nearly similar percentages to those found among the autopsies in the



Royal Infirmary during the same period - and again it shows the great preponderance of the undifferentiated types.

There is only one point which attracted my attention in studying the histopathology of the tumour and which, I think, is worthy of record. I found that there was a relatively high percentage of females in the group of adenocarcinoma. Thus, out of 54 cases which occurred in both series examined (tables 8 and 10), there were 34 males and 20 females with a proportion of males to females of 1.7:1. If it is remembered that the proportion of males to females as regards all types together is 4:1, it will be realised that there is an undoubted sex predilection in this group. The significance of this difference may be appreciated when it will be shown in a later chapter that "bronchial adenoma" occurs more in females than in males or at least that it occurs with equal frequency in both sexes. Whether this will be taken as a further proof that "bronchial adenoma" is potentially malignant and that many cases progress to adenocarcinoma will be the subject of further comment later.

Having worked out these percentages among the autopsies, I thought it might be of interest

to find out the relative frequency among the bronchoscopic biopsies. Therefore I searched out the Municipal Hospital Biopsies for 100 consecutive positive bronchoscopies. In the current reports starting from M.H.B. 2000 till M.H.B. 4163, the percentages found among these 100 bronchoscopic biopsies were as follows. (Table 11.)

TABLE 11.

| Histological Type | Number of Cases | %   |
|-------------------|-----------------|-----|
| Undifferentiated  | 54              | 54  |
| Squamous          | 39              | 39  |
| Adenocarcinoma    | 7               | 7   |
| Total             | 100             | 100 |

This table shows that the impression which was expressed before (page 34) was justified because the percentage of squamous cell carcinoma in the bronchoscopic biopsies is more than double that found amongst the autopsy cases.

This fact, however, does not impress me as being of much significance because as we know (and this is generally accepted) various parts of the tumour may show different histological

appearances and the tiny portion taken for microscopy during bronchoscopic examination cannot be regarded as representing the true histological pattern of the tumour. Secondly, these percentages are based only on the positive bronchoscopies and do not take into account those cases of lung cancer which gave a negative result on bronchoscopic examination (about 30%). A third factor which may account for the relatively low percentage of adenocarcinoma in the biopsy series is that adenocarcinomata usually tend to be located more in the periphery of the lung rather than towards the hilum and so they are more out of reach of the bronchoscope than the hilar tumours. Again the larger bronchi which are more exposed to irritants are liable to undergo squamous metaplasia and if this continues over a considerable time, it may progress to a squamous carcinoma.

Therefore, it would seem that to judge the relative frequency of the histological types of lung cancer from material obtained during bronchoscopic examination is bound to be inaccurate and that autopsy material is more suitable from this point of view.

Even then, to obtain a correct idea it would be necessary to examine various blocks from every



tumour. If this is done, a higher percentage of "mixed" types will, most probably, be found.

Philips et al (1950) studied "tissue mounts" from resected specimens of bronchogenic carcinoma and found a predominance of squamous cell carcinoma. They found also that any combination of cell types may exist in the same tumour. In 22.5% of their cases both adeno and squamous cell type carcinomas were present in the same tumour. Anyhow, they came to the conclusion that no correlation between type of tumour cell or location of tumour within the lung and the prognosis was demonstrable. Neuhof and Aufses (1948) came to the same conclusion and stated that the microscopic features of cancer of the lung bear no significant relation to the ultimate prognosis.

On the other hand Koletsky (1938) concluded that "the histologic classification of primary carcinoma of the lung may be correlated with essential differences in the growth, dissemination and prognosis of each tumour."

It can be said that at present there is no unanimous opinion regarding the value of the histologic classification of primary cancer of the lung in estimating the prognosis - although many

authors claim that the undifferentiated carcinoma is highly malignant and offers a poor prognosis while, on the other hand, the squamous carcinoma is slowly growing, locally invasive and relatively a non-metastasizing growth. In the case of adenocarcinoma they state that surgical intervention is less favourable, since the tumour, while locally invasive, shows more frequent and more extensive lymph node involvement and metastasizes by the blood stream.

It seems to me, however, that the important factor is not the histological type of the growth whether it is differentiated or undifferentiated; but the important thing is the early diagnosis of the case. If there is no undue delay in diagnosing the case, and it is recognised during the early stages of the disease, then there is a better prognosis no matter what the cell type of the tumour is.

Therefore, we have to find out every possible means to enable us to diagnose this condition as early as possible. Though Galen, in the second century, was the first to make the echoing statement: "Early diagnosis is necessary if cancer is to be cured.", today, after nearly two thousand years, we are still repeating this slogan.

This leads us to an important part of this study: namely, the evaluation of bronchoscopy and cytological examination of the sputum in the diagnosis of lung cancer.



BRONCHOSCOPY.

The earliest record found of bronchoscopy dates back to 1910 when Renon removed a piece of tissue from the left bronchus which on section proved to be a carcinoma. Since then bronchoscopy has gone ahead by leaps and bounds owing to the work of Killian in Germany and of Dr. Jackson and his co-workers in Philadelphia. Now, bronchoscopy occupies a secure place in thoracic surgery.

The first published account of endoscopy in Edinburgh was in 1913, when Dr. Logan Turner and Dr. J.S. Fraser published in the Edinburgh Medical Journal (1913) an account of the "direct method of examining the larynx, trachea, bronchi and oesophagus" with some illustrative cases. The authors suggested the use of laryngoscopy in diseases of the larynx, and oesophagoscopy in certain tumours of the oesophagus, but they considered bronchoscopy to be mainly of use in the removal of foreign bodies from the bronchus and mainly performed through a previous tracheotomy opening.

In 1924 Dr. G. Ewart Martin read a paper before the Edinburgh Medico-Chirurgical Association on the application of the bronchoscope in diagnosis and treatment of certain affections of

the chest (1924).

The most important function of the bronchoscope in establishing the diagnosis of bronchogenic carcinoma is the obtaining of tissue for biopsy. As is well known, the majority of lung cancers are "central" in position - taking origin from the major bronchi or their branches. Therefore such tumours are within the reach of the bronchoscope and tissue can be easily obtained for microscopic examination. Even in the more peripherally located tumours which are beyond bronchoscopic vision, mucus can be aspirated from the suspected bronchus or saline washings sucked out and these are examined for the presence of "tumour cells."

Betts (1941) remarks that a patient with a change in bowel function rightfully deserves a proctoscopic examination and that abnormal urinary symptoms often indicate the desirability of cystoscopic studies. Likewise the patient with unexplained pulmonary symptoms cannot be considered fully investigated without a bronchoscopic inspection of the trachea and bronchial tree. He obtained a pre-operative diagnosis of cancer from biopsy specimens in 74% of 62 patients with histologically verified primary neoplasms

of the lung.

In a series of 300 cases, Kramer and Som (1930) proved the diagnosis by bronchoscopic biopsy in 222 or 74%. Clerf (1937) obtained a positive tissue diagnosis in 98 or 68.5% of 143 proved cases of bronchogenic carcinoma. In Jackson's statistics bronchoscopic biopsy was possible in 75% of the cases of bronchial carcinoma and Overholt (1938) obtained a specimen for microscopic study in 28 of the 32 cases of his series.

Ochsner et al (1948), however, state that though bronchoscopy with biopsy is the most accurate method of diagnosis, it provided a positive diagnosis in only a little more than one third of the cases and explained this by the location of the tumours. They concluded that bronchoscopy has definite limitations as a diagnostic procedure and that a large proportion of patients with carcinoma of the lung would be denied proper treatment if operations were limited to those with positive results of biopsy.

The bronchoscopic findings, positive or negative, are always of value. As stated by Overholt (1935), bronchoscopy should inform the surgeon as to the presence <sup>or</sup> of absence, and, if present, the location and extent, of a tumour



in the accessible bronchi; the mobility or fixity of the tracheobronchial tree (of value in deciding the operability of the tumour); and the histologic character of the lesion where biopsy is possible.

In order to evaluate the position of bronchoscopy as an aid to the diagnosis of bronchogenic carcinoma in Edinburgh, I decided to follow up some of the cases from whom a bronchoscopic biopsy was taken on the assumption that a bronchial neoplasm was a possibility. Cases on which bronchoscopy was performed to prove other lesions and in which cancer was out of question, e.g. tracheobronchial tuberculosis, were not included.

Therefore I searched the records of 2000 consecutive municipal hospital biopsies (from M.H.B. 2000 to M.H.B. 4000) for such cases. These biopsies were received during the period from April 1947 to February 1949. They comprised 217 bronchoscopic biopsies from patients suspected of having primary bronchial malignancy. On analysis of the reports of these cases the result was as follows:-

- (a) 114 cases were reported as negative.  
 (b) 96 " " " " positive.  
 (c) 5 " " " " inconclusive.  
 (d) 2 " " " " bronchial adenoma.

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217 Total.

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The majority of these cases were received from the Thoracic Unit of the Eastern General Hospital and through the kindness of Mr. Logan and his office I had access to the records of these patients and could follow them up.

The total number of cases which proved to be bronchogenic carcinoma among this group was 131. Therefore out of 131 cases of primary carcinoma of the lung 96 were correctly diagnosed bronchoscopically. This is equal to 73.3%.

Out of 114 cases reported as showing no evidence of tumour, 34 proved later on to be cases of carcinoma of the lung. Calculated in relation to the negative cases this gives a false negative of 29.8%, but if calculated in relation to the whole series of cases, which is the proper way to do, the percentage of false negative reports will be only 16%.

Five inconclusive reports were issued. Of these: three proved to be negative, one positive

and in one the diagnosis remained incomplete.

As mentioned before, two cases of this series were classified as "bronchial adenoma".

These results are summarised in the following table (Table 12.) in which, for convenience, cases of cancer are recorded as positive and non cancerous cases are recorded as negative.

TABLE 12.

| No. of cases reported | Original report   | No. of cases followed up. | Result of followup |               |                         |
|-----------------------|-------------------|---------------------------|--------------------|---------------|-------------------------|
|                       |                   |                           | Posi-<br>tive      | Nega-<br>tive | Incon-<br>clus-<br>ive. |
| 114                   | negative          | 114                       | 34                 | 67            | 13                      |
| 96                    | positive          | 96                        | 96                 | 0             | 0                       |
| 5                     | incon-<br>clusive | 5                         | 1                  | 3             | 1                       |
| 2                     | adenoma           | 2                         | 2                  | -             | -                       |

To conclude then it is evident that bronchos-  
:copic examination with biopsy was of value in  
establishing the diagnosis of cancer of the lung  
in 73.3% of cases. This compares favourably with  
reports of other workers and verifies the undoubted  
value and essential role played by bronchoscopy  
in the diagnosis of carcinoma of the lung.  
Taylor (1939) made the statement "confirmation  
of lung tumours is not usually available pre-  
:operatively". Though this statement may have



been true at the time, it need not be true to-day if all patients with unexplained pulmonary symptoms are studied bronchoscopically.

Bronchoscopy in experienced hands is an easy and minor procedure that can be done with very slight inconvenience to the patient and it remains to be the most important method available for the sure diagnosis of carcinoma of the lung.

A CRITICAL STUDY of the VALUE of SPUTUM EXAMINATION  
in the DIAGNOSIS of LUNG CANCER.

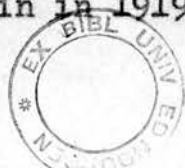
"To be exploited prematurely in practice is the common fate of all new scientific facts. Not content to wait for full knowledge, men hastily draw conclusions from imperfect data!"

William Osler.

. . . . .

Review:

The story of cytologic diagnosis begins over one hundred years ago when Pouchet (1847) first examined unstained preparations of vaginal fluid in an attempt to analyse the normal sexual cycle. But attempts to identify cells from a neoplastic source date back to 1860 when Beale (1860) noticed large multinucleated cells, single and in clumps, in unstained smears of sputum from a case of carcinoma of the pharynx. Hampeln (<sup>1876</sup>~~1887~~) reported finding a shred of tissue in the sputum of a patient, one of whose extremities had been amputated for sarcoma three years before. Examination of the shred revealed sarcoma, and brought to his attention the importance of the search for minute particles of tissue in fluid specimens. Again in 1919 Hampeln recorded two



cases in which the sputum was examined morphologically following a large haemoptysis. In both these instances he found cells which he considered to be diagnostic of malignant growth but no details were furnished of the technique employed.

Bezancon and De Jong (1913) were the first to report on the application of rapid fixation to wet films of sputum. They described the non malignant cellular elements, discussed their origin and compared their appearance with that of malignant cells. Though their technique was accepted by several European writers, Ridge and Treadgold (1913) remarked that the stain was uncertain and that the films were impermanent.

But it was not until 1928, when Papanicolaou reported his original work on a simple method of fixing vaginal smears by which good cytologic details could be obtained, that some interest was aroused in Hampeln's report. Even then, seven years elapsed before Dudgeon and Wrigley (1935) reported that they had utilised cellular study of sputum for the diagnosis of carcinoma of the lung and demonstrated its feasibility. They reported that they were able to make a positive diagnosis of carcinoma of the bronchus from cytologic examination of the sputum in 68% of their proved



cases of carcinoma. Their report stimulated a great deal of interest and favourable reaction, especially among European observers. Further reports of the use of this technique followed and in particular a monograph by Wandall in 1944.

The present revival of interest in the examination of sputum and bronchial secretions for cancer cells is due primarily to the work of Papanicolaou. He applied the smear technique to the study of sputum for the detection of cancer in 1946 and in the same year Herbut and Clerf (1946) studied bronchial secretions by the same method. Woolner and McDonald (1949) stained smears of sputum and bronchial secretions with haematoxylin and eosin.

Mathews (1948) reported his results using paraffin sections of sputum fixed in Bouin's fluid and stained with H & E. Richardson et al (1949) collected bronchial secretions or sputum which they fixed in formalin and picric acid and filtered. From the sediment they made paraffin sections which were stained by a modified Papanicolaou stain.

By these various methods, correctly positive results were obtained in from 68 to 89% of cases. On the other hand, many authors obtained

completely different results. Thus Craver (1940) made a diagnosis from examination of the sputum in only 2 of 175 cases of bronchogenic carcinoma, in each case by sectioning gross tissue fragments found in the sputum. Balogh (1943) described this test as being worthless and Stahelin (1942) had only one positive result in 115 cases. Fischer (1949) stated that the diagnosis of carcinoma of the lung by means of examination of the sputum is possible only in very few cases. He believes that the positive results are not usually based on solid diagnostic and histological criteria.

The recent literature concerning the cytologic method of cancer diagnosis is impressive in its extent. Even the press and popular magazines have featured the method as a public health measure par excellence. In the recent medical literature several large series of cases have been published and evaluated.

Despite a mass of evidence, the value of cytologic diagnosis of tumours is not widely acknowledged. The greatest scepticism is found among pathologists themselves. The failure of whole-hearted acceptance of the principles laid down by the enthusiastic workers in this field is due, at least in part, to an unwillingness to

forego the sacred dicta of the founding fathers of pathology. Rudolph Virchow, himself a great iconoclast, taught that invasion was essential for absolute proof of the malignancy of a tissue. A blind acceptance of this principle would necessarily rob the cytologic method of the detection of cancer cells of its very foundation, based as this is on the study of exfoliated cells which, though they may occur in histoid patches, evidently do not reveal any cellular invasiveness.

A more trenchant criticism is the apparent fact that histologically one encounters a great diversity of individual cellular changes in inflammatory or benign neoplastic lesions which apparently mimic the changes observed in the so-called cancer cell.

#### The Cancer Cell.

The question as to whether or not there is such an entity as a cancer cell has occupied many competent observers. The very existence of such specifically altered cell has been strenuously denied. The prestige of the older pathologists has long retarded speculation in this field. Ludford (1942) succinctly restates this problem as follows: "No specific morphological criterion of malignant cells has been discovered, but it



would be erroneous to conclude that there are no cytological differences between malignant cells and their non malignant prototypes. Cancer cells are not simply cells which have acquired rapidity of growth. They are specifically altered cells." Adams (1948) thinks that the transplantability of tumours both in animals and in tissue culture over long periods of time with essential preservation of the characteristic features, would support this statement. Hauptmann (1948) remarks that although there is a great difference between Borst's statement (1928), "Die Geschwulstzelle, auch die bosartige, hat weder in morphologischer, noch in chemischer, noch in irgend einer anderen Hinsicht etwas absolut charakteristisches an sich" (The tumour or cancer cell has no absolute morphological, chemical or any other characteristic to itself.) and that of MacCallum (1940), "No doubt, in time we shall have a reliable morphological criterion by which we may say definitely that an isolated cell is a cancer-cell or a normal cell", both indicate that the problem of single cell diagnosis of cancer is still to be settled.

Many pathologists are of the opinion that there is no sign which characterises the non

malignant tumour cell, that there is also none for the malignant cell and the destructive growth is the only characteristic of malignant tumours. Others state that there is only one biologic characteristic of differentiation from normal cells, and that is that the carcinoma cell and the normal cell do not differ qualitatively but quantitatively.

Repeated microscopic studies of fresh tissue cells has convinced McCarty and Haumeder (1933) that quantitative changes in malignant cells are evident; the relative average increase in nuclear size and more particularly in nucleolar size, is well marked.

Numerous workers have attempted to find absolute criteria of malignant cells. However, such morphological criteria have not been found and points of distinction between the cells of malignant tumours and benign lesions have been relative differences requiring interpretation. Hauptmann (1948) recently was unable to find any common denominator in cell types characteristic of carcinoma. He came to the conclusion that many cellular changes suggest malignancy but are neither sufficiently constant nor sufficiently prominent to establish their diagnostic significance.

He added that "when seen in a smear, they should, however, awaken the suspicion of the observer."

Granting the non-specificity of morphological changes according to present methods, pathologists have nevertheless long described concomitant cellular changes in tissue preparations such as increased nuclear cytoplasmic ratio, nuclear hyperchromatism, the presence of mitotic figures, etc. and these will be described in more detail later on.

#### The Old Series.

The general opinion among pathologists in Edinburgh as regards the value of sputum examination in the diagnosis of lung cancer was one of scepticism. Hundreds of specimens of sputa were examined for tumour cells, but only very rarely was the pathologist able to report their presence with confidence. The specimens were usually sent fixed in Zenker's fluid and slides were prepared in the usual routine way after embedding in paraffin, sectioning, etc. One of the major difficulties about this method of diagnosis is the uncertainty about the nature of some of the cells and the apparent similarity between some of the cells from inflammatory and benign conditions and those derived from malignant



neoplasms. This is due, as mentioned before, to the lack of any absolute criterion which distinguishes the cancer cell from other cells.

Before starting this study on sputum examination by the fresh smear method, I decided to find out first the actual results obtained previously by employing the block and section technique. Therefore I studied carefully the 2000 consecutive municipal hospital biopsies mentioned before in relation to the evaluation of bronchoscopy as an aid to the diagnosis of cancer of the lung, i.e. from M.H.B. 2000 to M.H.B. 4000. Among these biopsy reports no less than 455 were concerning specimens of sputa sent for examination for tumour cells, i.e. about 23% of all biopsies. Though the majority of these were received from the Eastern General Hospital, there were some from both the Western and the Northern General Hospitals as well. From analysis of the reports issued it was found that,

|       |        |   |   |   |   |                                 |
|-------|--------|---|---|---|---|---------------------------------|
| 437   |        |   |   |   |   | were reported as being negative |
| 16    | "      | " | " | " | " | positive                        |
| 2     | "      | " | " | " | " | doubtful or inconclusive.       |
| <hr/> |        |   |   |   |   |                                 |
| 455   | Total. |   |   |   |   |                                 |

I traced the subsequent history of these cases by studying their case records in the

hospitals. The result of this follow up was as follows:

280 cases were found negative  
 144 " " " positive  
 25 " " incompletely investigated.  
 6 miscellaneous (adenomas and secondary  
 tumours).

455 Total.

Then I tried to check on the accuracy of the reports issued and the result is shown in the following table. (Table 13).

TABLE 13.

| Original Report | No. of Cases | Follow up. |          |            |               |
|-----------------|--------------|------------|----------|------------|---------------|
|                 |              | Negative   | Positive | Incomplete | Miscellaneous |
| Negative        | 437          | 277        | 132      | 25         | 3             |
| Positive        | 16           | 3          | 10       | -          | 3             |
| Doubtful        | 2            | -          | 2        | -          | -             |

Therefore out of 144 cases of primary lung carcinoma only 10 were diagnosed correctly by means of examination of the sputum. This gives a positive result in less than 7% of cases. Three cases reported as positive were considered to be cases of secondary tumours in the lungs from primaries elsewhere in the body. The remaining three reports

were regarded as false positives but there was a possible mix up of specimens in one of the cases.

It was only natural that there had been a general feeling that the examination of sputum for tumour cells was not really worth the trouble and though there were many reports in the literature stressing its value and claiming excellent results, these were regarded with some doubt.

#### Method.

The method which was used before, as already mentioned, was the ordinary block and section technique and as many of the investigators who claimed good results had employed the fresh smear method in their studies, it was thought that it would be better to employ that method in trying to assess the value of sputum examination in the diagnosis of cancer of the lung.

As regards staining, many writers claimed that the Papanicolaou stain was superior to others. But as there is nothing in any method of staining that will with certainty identify cancer cells, and, as the ordinary haematoxylin and eosin stain gives very adequate detail as will be shown later, this stain was used by preference. It is always the acquired experience of the pathologist with a particular stain (and even with a particular



microscope) that yields the necessary accuracy in cytological studies; and since the writer is much more used to the haematoxylin and eosin method of staining, that stain was the one used.

Fresh specimens of sputa were collected and delivered to the laboratory in wide mouthed, glass specimen-bottles. No preservative or fixative was added because there was only an interval of few hours between the collection of the specimens and their receipt in the laboratory. As soon after receiving the specimens as possible, fresh smears were prepared, fixed and stained in the following way:-

(1) The sputum was inspected carefully by the naked eye and representative portions were picked with the aid of a clean sterilised platinum loop. Usually solid particles or blood streaked or pigmented bits were preferred when found. On very few occasions solid bits of tissue were encountered which were difficult to spread properly on the slide. These were embedded in paraffin and sectioned in the usual way; but from these cases fresh smears were prepared as well. After some experience one can usually avoid food debris and be able to pick out the most suitable portions of the sputum for smears.

(2) The preparation of the smear is a very important step and the time spent and interest taken in preparing a homogeneous thin smear is very well worth the trouble. In the early part of this study, relatively thick smears were prepared and the result was that

(a) Many portions of the smear used to be washed away during the staining process. This obviously reduces the chances of finding tumour cells in specimens which do contain them.

(b) The overlapping of the cells prevented clear visualisation of cellular and nuclear details. This interferes materially with the proper interpretation of the smear. An essential part of these cytological studies is a well prepared smear.

As a rule two or three smears each covering an area measuring 2 x 3.8 cms. were prepared from every specimen on clean glass slides bearing the appropriate serial biopsy number.

(3) The smears were fixed at once, i.e. without allowing them to dry, in Schaudinn's fluid. This consists of one volume of absolute alcohol to two volumes of a saturated aqueous solution of mercuric chloride and before use glacial acetic acid is added to the strength of 3%. They were left in the fixative for about 20 minutes or

longer.

- (4) Wash in water.
- (5) Wash in alcoholic iodine for 1-2 minutes.
- (6) Remove excess of iodine by 2% solution of hypo.
- (7) Wash again in water.
- (8) Stain with haematoxylin for about 2 minutes; but it is important not to overstain with haematoxylin as this is apt to give a false impression of hyperchromatism to the nuclei.
- (9) Wash in water.
- (10) Place in a weak solution of lithium carbonate for 1-2 minutes.
- (11) Wash in running water for about 5 minutes.
- (12) Counterstain with eosin (a mixture of equal parts of alcoholic and aqueous eosin).
- (13) Wash well in water.
- (14) Fix in a weak solution of potassium alum for about 2 minutes.
- (15) Wash in water.
- (16) Dry back of slide, its sides and smear carefully with blotting paper.
- (17) Differentiate in methylated spirit to which a few drops of ammonia are added.
- (18) Dehydrate in 74% and then in absolute alcohol.



(19) Clear in xylol or benzene - keeping the slides in the solution until they look very clear and transparent.

(20) Mount in Canada balsam and then cover with a large-size cover slip.

(21) Leave to dry well and then examine.

#### Examination of the Smears.

A thorough systematic examination of the whole smear using a microscope with a mechanical stage is essential. The low power of the ordinary microscope is quite adequate for the screening of the smear; but suspicious groups of cells are to be examined with the high power and, if need be, with the aid of an oil immersion lens as well.

#### Time factor.

Apart from those smears which consist almost entirely of epithelial squames and which represent really nothing more than saliva and post nasal discharge, the examination of one smear would require about 10-15 minutes or more according to the presence <sup>or</sup> of absence of atypical cells which require careful interpretation and consideration. Occasionally, it took the writer much more than this time to examine one slide.

This time factor must be stressed as one important limitation to this method of examination

because unless the pathologist has and is willing to devote the necessary time to the examination of the smears, then it is better not to do it at all. This point will be stressed further later on.

#### Training & Experience.

Then comes the factor of training and experience. This has been stressed by nearly every writer on this subject. Thus Dudgeon (1936) stated that "There is no question that considerable experience in normal and morbid histology is required before the many difficulties are overcome in the recognition of particles of new growth in sputum." Scheffey (1948) said "Unquestionably the personal factor in cytologic interpretation is of far greater import than that which obtains in making a histologic diagnosis of malignancy. Farber et al (1950) emphasised that extensive experience is the most important single factor in cytologic diagnosis. They rightly say that with the development of skill with the technique, both the reliability and the sensitivity of the results will improve. Fermon-Smith et al (1948) stated "The ability to make accurate diagnoses by this method is difficult to acquire, obtainable only by months of intensive

training and perfected through constant use."

The pathologist, before being able to report on smears of sputum, has to familiarise himself first with the usual non malignant cells that are encountered during routine examination of sputum from patients suffering from non neoplastic diseases. He has also to be familiar with artefacts in cells which occur as the result of fixation and staining procedures and also with the changes which occur as the result of degeneration. The writer has observed the most bizarre looking cells with alterations in size, shape and staining properties in polymorphs in which degeneration had started and has usually refrained from giving a conclusive report on any specimen in which degeneration was a marked feature.

Having been acquainted with these non malignant cells, the examiner will be able to recognise easily any atypical or suspicious looking cells with the low power of the ordinary microscope. The nature of these has to be elucidated further with the aid of the high power bearing in mind the various criteria of malignant cells as will be described in detail later.

#### Non Malignant Cells in Sputum

The following is a description of the cells

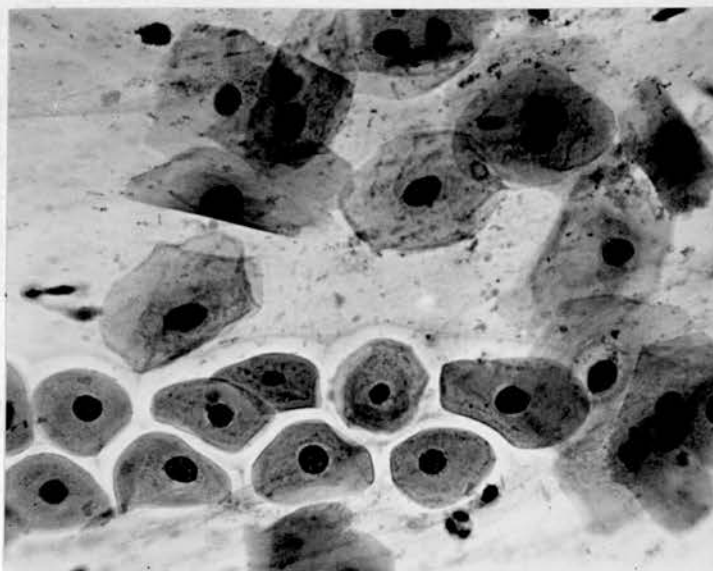


which are derived from non neoplastic sources and which one usually encounters in the routine examination of sputum smears.

(1) Squamous Epithelial cells

or "squames" as they are sometimes called - are very common in sputum smears and are easily recognised. They are usually derived from the mucosa of the mouth, nasal passages, pharynx, etc. and appear as large polygonal cells with abundant cytoplasm which usually takes a homogeneous light eosin stain. Their nuclei are usually relatively small, round and central, but they may be slightly ovoid. They may show a tiny nucleolus. The size of these "squames" varies a great deal according to their site of origin, but on the whole they tend to show these characteristics with minor alterations e.g: some of them may appear "folded" on their sides, etc.

(Fig.1)



Occasionally one finds small squamous epithelial cells, with relatively large nuclei which take a deeper stain with haematoxylin. These cells are found either singly or in sheets and they are supposed to indicate squamous metaplasia of an epithelial surface lined by columnar cells. They may cause some difficulty in interpretation but on the whole they tend to be regular in size and shape and there is a reasonable amount of cytoplasm surrounding the nuclei and though the latter may be deeply stained, they are rather uniform in appearance.

An occasional finding is a "cell-nest-like" appearance of some of the mature squamous cells (Fig.2).



Fig. 2.

X500

These are benign structures and do not have the same significance as the cell nests or epithelial pearls seen in keratinising squamous cell carcinoma. They consist of compressed, elongated and oval epithelial cells surrounding a squamous epithelial cell which shows some keratinisation, affinity to the eosin stain and starting degeneration of the nucleus in the way of pyknosis and fragmentation.

## (2) Columnar Epithelial Cells

These are the cells that are shed off from the respiratory passages. They are not uncommon and occasionally they are found in large numbers in smears. When lying separately they are easily recognised; but sometimes they overlap each other and as their nuclei are oval and relatively large, they may cause some difficulty in interpretation as then they resemble tumour cells from an oat cell carcinoma.

These cells, which are usually derived from tracheal and bronchial mucosa, are cylindrical elongated cells whose base tapers to a sharp point and the distal end is usually flat and covered with cilia (Fig.3.)

The nucleus is ovoid in shape, relatively large when compared with that of the squamous



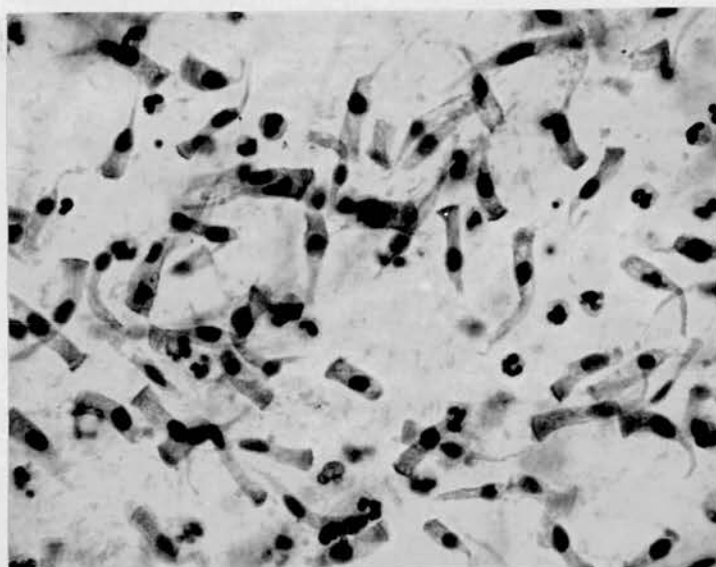


Fig 3. X 500

cell and its chromatin shows fine stippling.

Minor alterations in the shape of these cells sometimes occur. Thus the cytoplasm may appear vacuolated or show evidence of degeneration.

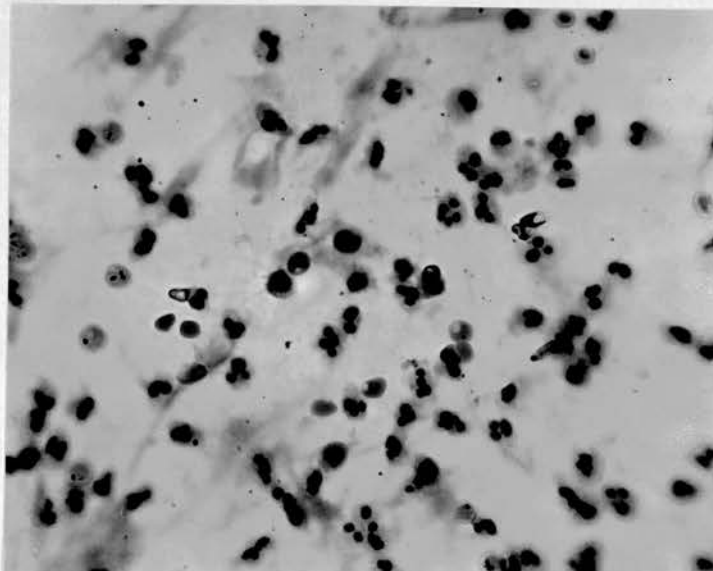
The cell may take a rounded rather than an elongated form and in these cases the cytoplasm is usually relatively scanty and the cells have to be differentiated from tumour cells by the regularity in the size and shape of the nuclei, the absence of histoid arrangement of the cells, etc.

Recently on reviewing a case which was reported as positive but which was thought, on clinical grounds, not to be a case of cancer, i.e. a false positive, it was thought that the deceptive cells could be a group of these cells closely packed together with the thin tapering end either obscured

or cut away this resulting in a group of cells which look very much like tumour cells.

(3) Polymorphonuclear and other Leucocytes.

Polymorphs are seen in the majority of sputa submitted for examination, but their number varies a great deal. In purulent specimens, masses of them in various stages of degeneration are seen. They are easily recognised as small cells with multilobulated nuclei - the number of the lobes increasing with the age of the cell. Their cytoplasm stains poorly with eosin, being mostly neutrophils; but occasionally eosinophils, with intensely acidophilic granules, are encountered. If they are present in large numbers they are usually ascribed to an ashtmatic or allergic origin. (Fig. 4.)



X 500

Fig. 4.

When autolysis sets in, these cells are still easy to identify if the degeneration results only in distension and vacuolation of the cytoplasm and/or fragmentation of the nuclei. But occasionally the autolytic process results in swelling of the nuclei with blurring and obliteration of any lobulated pattern so that we get cells with bizarre shaped nuclei which might look like small carcinoma cells. A point of differentiation, however, if the smear is properly stained, is that these swollen nuclei take a lighter stain with haematoxylin than cancer cells do. But if the smear is overstained with haematoxylin these nuclei may take a deep colour and the examiner has to be careful in the interpretation of his findings as already mentioned.

Scattered amongst these polymorphs or pus cells, occasional lymphocytes may be seen. These are small cells with rounded or slightly indented nuclei which are darkly stained and are surrounded by a thin rim of cytoplasm which may be hardly seen. These lymphocytes are specially seen when there is blood in the sputum, i.e. near red blood corpuscles. I have not as a rule found aggregations of lymphocytes of any size in smears of sputum and apart from the occasional and isolated cells



seen with and amongst inflammatory cells, lymphocytes are rather rare. Groups of small cells, which on a first glance look like lymphocytes but which on more closer examination show variation in their size and shape are, as a rule, small carcinoma cells and not lymphocytes as will be shown later.

(4) Macrophages.

Macrophages, histiocytes or dust cells ... to mention some of their names, are common cells which may have a typical or an atypical appearance. Contrary to some impressions, the majority of these cells are easily recognised and do not offer any difficulty in diagnosis.

They are often present in large numbers. They are much larger than the polymorph leucocytes, tend to be round or oval in shape and their nucleus, which is usually ovoid and eccentrically placed, has a fine chromatin network and a distinct but small nucleolus. Sometimes the nucleus appears kidney or banana shaped and occasionally it is wrinkled or elongated or appears as a bar across the cell - especially in those cases in which there is active phagocytosis.

The cells of this group are easily recognised when the cytoplasm contains carbon particles,

golden brown pigment or fat globules. The amount of engulfed foreign matter, of course, varies greatly and in extreme cases the cell is completely packed with the pigment, e.g. carbon, so that neither cytoplasm nor nucleus can be visualised. (Fig. 5.)

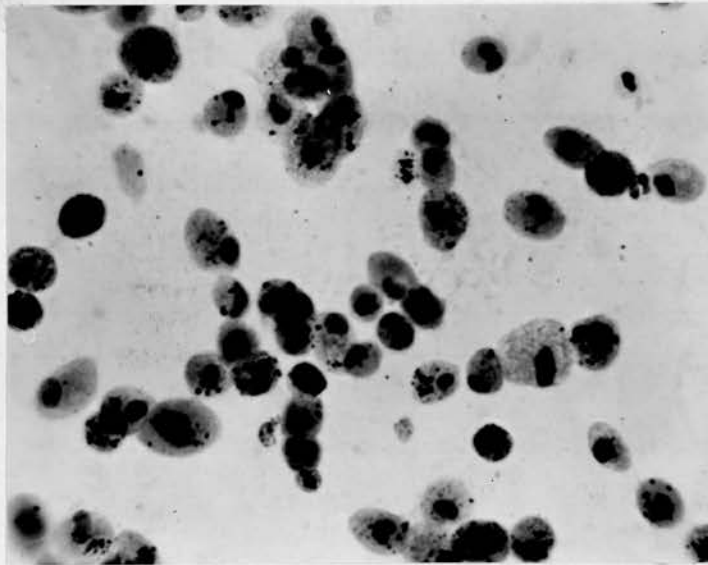


Fig 5.

x 500

Sometimes, however, these cells do not show evidence of phagocytosis and in such cases the cytoplasm is clear and relatively abundant; the nucleus is rounded or oval, with a distinct nuclear membrane and a fine chromatin network. In many cases, side by side with these cells, there are others similar in appearance, but engulfing foreign particles and so render recognition of

the former cells easy. It must be stated, however, that phagocytosis is not confined to these macrophages because tumour cells, too, may exhibit this property - though to a much less marked degree.

Though the cells of this group may show extreme variation in size and shape, not only in the various smears, but sometimes in the same smear, on the whole they tend to retain their characteristics which have been just outlined and so they can be easily identified.

It is not rare to find some giant forms with many nuclei amongst these cells. These are foreign body giant cells and their nuclei are usually centrally located and some of them may overlap. These nuclei are usually similar to macrophage nuclei and the cytoplasm may or may not contain foreign particles or fat globules.

Some histiocyte cells usually seen in sputa from cases of pulmonary tuberculosis look more like epithelial cells than macrophages. Their cytoplasm is pale looking and binucleate forms are common among them. The individual cells are ovoid or slightly polygonal and their nuclei are vesicular and relatively larger in size but they do not show any hyperchromatism. Some of these



cells, too, contain lipoid material in their cytoplasm. These cells are probably the "epithelioid" cells seen in the histological sections from cases of tuberculosis.

... ..

Apart from the cells described above, there may be few other types of cells of non neoplastic origin. There may be few or numerous red blood corpuscles, clumps of organisms, threads of mucus, nuclear and food debris, etc. etc.

#### Malignant Cells in Sputum.

It should be made clear from the beginning that there is no absolute cytologic criterion of malignancy, at least at the present state of our knowledge. Secondly it is not safe to go by cellular hypertrophy, nuclear irregularity and hyperchromatism, nuclear cytoplasmic ratio or nucleolar measurements alone. The third point to be stressed is that it is always advisable to base one's diagnosis on groups of cells and not to rely on isolated single cells. Thus Dudgeon (1936) mentioned that with experience the study of the sputum for the presence of malignant growth is not a great difficulty provided it is realised that it is only possible to recognise malignancy when the cells are present

in clumps or plaques.

Again Liebow et al (1948) stressed that "reliance was placed only upon groups of cells possessing an arrangement suggesting that of tissue, not merely upon individual atypical cells."

Constantine and Shaver (1949) stated: "We feel, and conservative observers emphasise, that the positive diagnoses should rest upon the finding of groups of many frankly cancerous cells" and finally Papanicolaou (1946) said "One should refrain from reaching a final conclusion on the strength of only a few cells."

Luckily, in most positive specimens there is usually more than one criterion on which to base a diagnosis and the various abnormalities that are going to be described rarely occur singly. Such abnormalities, as a rule, occur in combination and as Farber and his co-workers (1950) state, each re-inforces the significance of the others in the total picture.

Now: What are the morphological criteria of malignancy in exfoliated cells??

The characteristics of exfoliated cells that have been found to be of greatest diagnostic value are chiefly nuclear. The nuclei are large

in proportion to the amount of cytoplasm and they vary in size and shape and this is best demonstrated when the cells occur in small groups. They are hyperchromatic. The nucleoli of tumour cells are frequently large and prominent and may be multiple. Nuclear giantism either absolute or in relation to cell size is of considerable diagnostic value in the recognition of detached cancer cells. The characteristics of the cells themselves are less important but may be helpful. The general opinion that cancerous cells are larger than normal cells may be partly true because the majority of carcinomata do have larger cells than those of the tissue from which they arose; but it is impossible to make a diagnosis of malignancy on the basis of the size of a cell seeing that there are "small cell" carcinomata on the one hand and large "benign" histiocytic cells on the other. Again, irregularity of cell shape, atypical staining reactions of the cytoplasm, etc. may be suggestive but are not considered diagnostic of malignancy.

The diagnosis of tumour cells in this series was only made when the following criteria were fulfilled:-

(1) The finding of cells or groups of cells which



are obviously atypical, i.e. not encountered as a rule in the vast majority of smears of sputa from benign and inflammatory conditions. The word "atypical" is used here to designate cells other than the "routine" cells which were described under "non malignant cells in the sputum".

(2) The presence of a distinct and obvious "contrast" between this group of "atypical" cells and the surrounding "non malignant" cells. This contrast I think, should be quite evident with the low power of the ordinary microscope. Fig. 6 represents a unique group of cells in a smear which consisted almost entirely of pus cells.

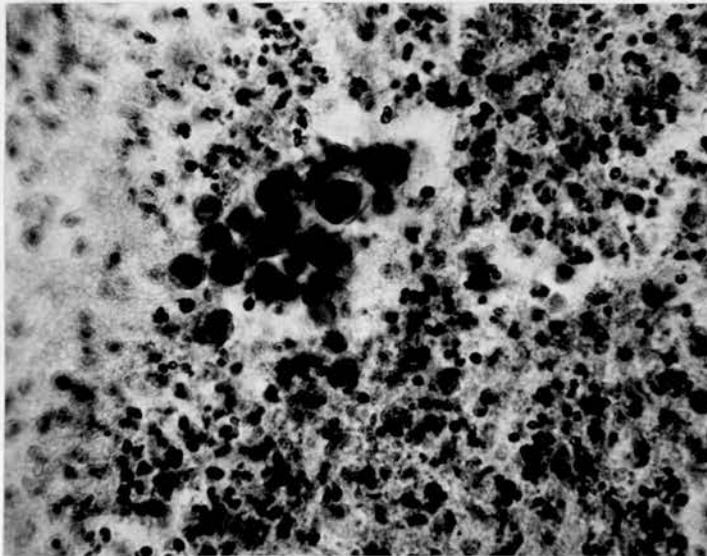


Fig 6.

X 500

Whereas the rest of the smear showed masses of

polymorphs, this group of "atypical" epithelial cells could be easily recognised. On closer examination the cells showed other characteristics of tumour cells and the smear was reported as positive.

(3) The occurrence of these cells in a histoid arrangement similar to, as far as possible, that seen in tissue sections. (Fig. 7.)

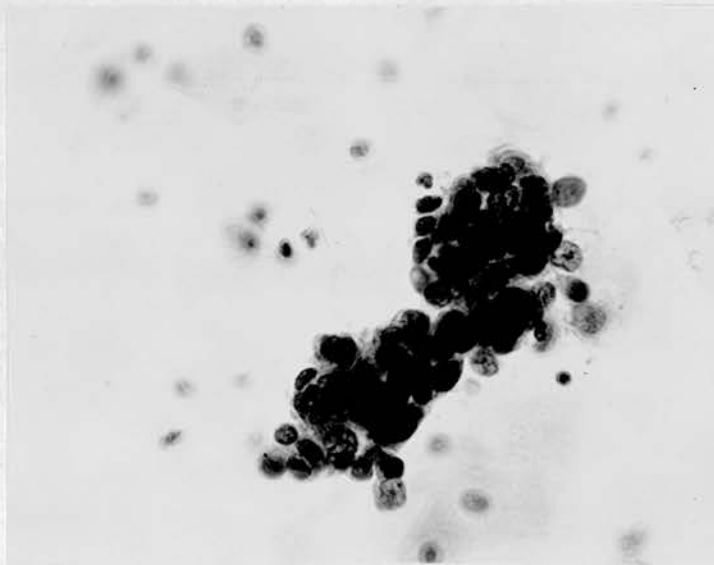


Fig. 7.

X 500

(4) The presence of the various "criteria of malignancy" just described - amongst the individual cells especially nuclear giantism, anisocytosis and hyperchromatism. Fig. 8 shows the obvious contrast between the group of tumour cells in the centre and the polymorphs scattered about. In

addition it shows the variation in size and shape of the cells and their nuclei and shows also variation in the staining properties of the nuclei.

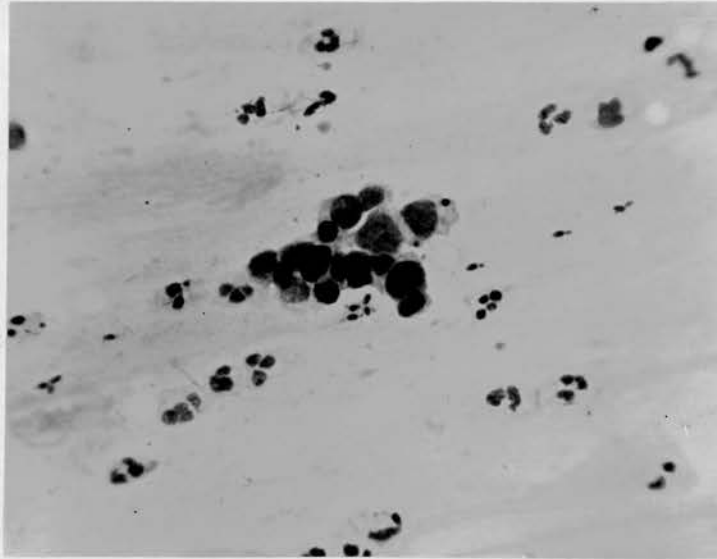


Fig 8.

X 500

Fig. 9 shows a group of epithelial cells with large nuclei which show very prominent and relatively large nucleoli.

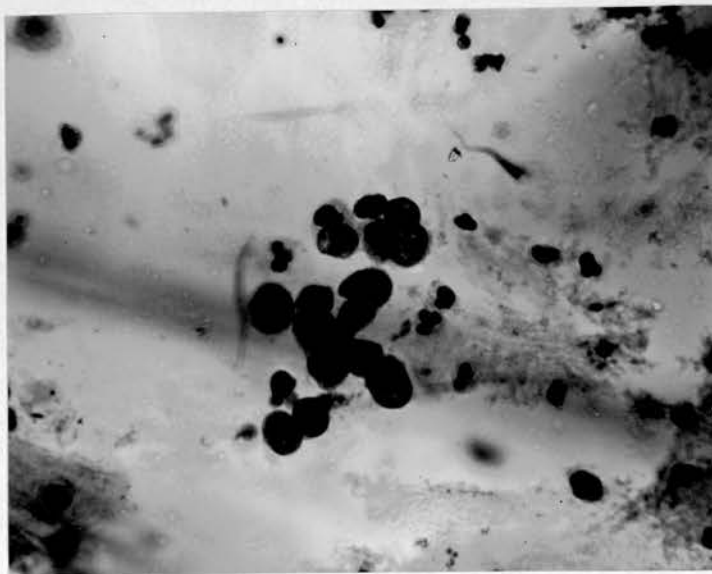


Fig 9

X 500



There is also a suggestion of mitosis in some of the cells.

(5) Additional helpful points are: "clumping" or "overcrowding" of the cells (Fig. 10), the presence of special types of cells like the "bird's eye" cell which is said to occur in cases of keratinising squamous cell carcinoma (Fig.11) and rarely the finding of mitotic figures.

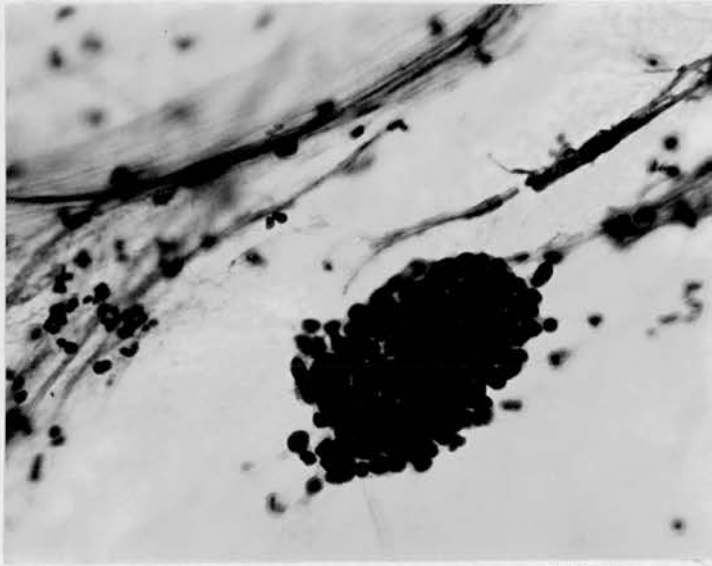


Fig 10 X 500

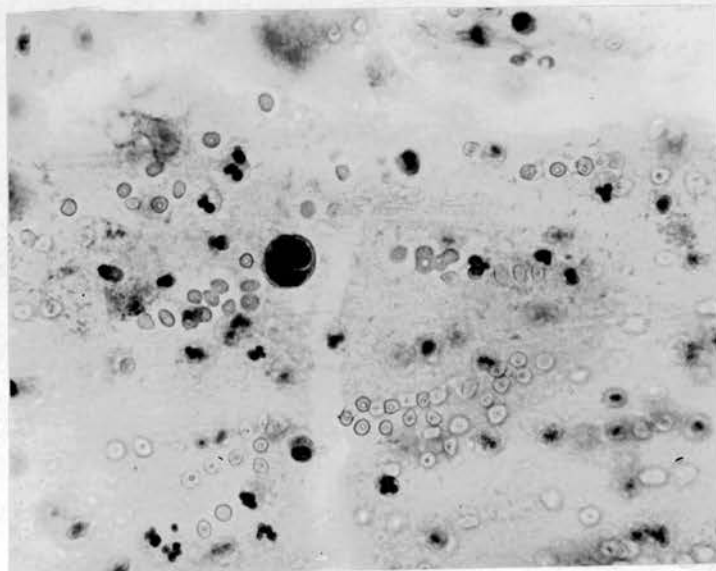


Fig 11 X 500

As mentioned earlier, I was impressed by the rarity of lymphocytes, especially in groups, in smears of sputum. Groups of small cells with nuclei which nearly occupy the whole cell and which take a deep haematoxylin stain and show wide variation in size and shape strongly suggest tumour cells of an undifferentiated type. (Fig.12) Such was also the experience of Constantine and Shaver (1949).

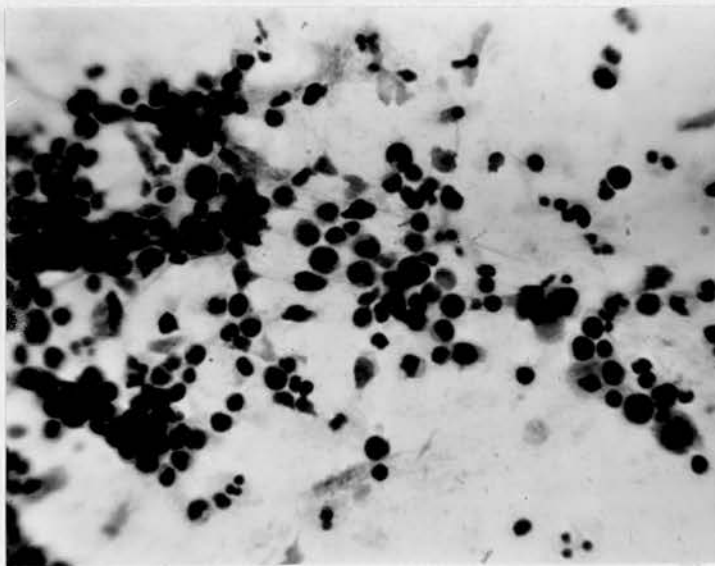


Fig 12

X 500

In describing the method of preparing the smears it was mentioned that occasionally one finds a fragment or a bit of tissue which is firm and rather difficult to spread on the slide. Such bits are better sectioned and stained in the usual

way and this sometimes helps to confirm the diagnosis of an otherwise suspicious smear. Fig. 13 is an example of such a case.

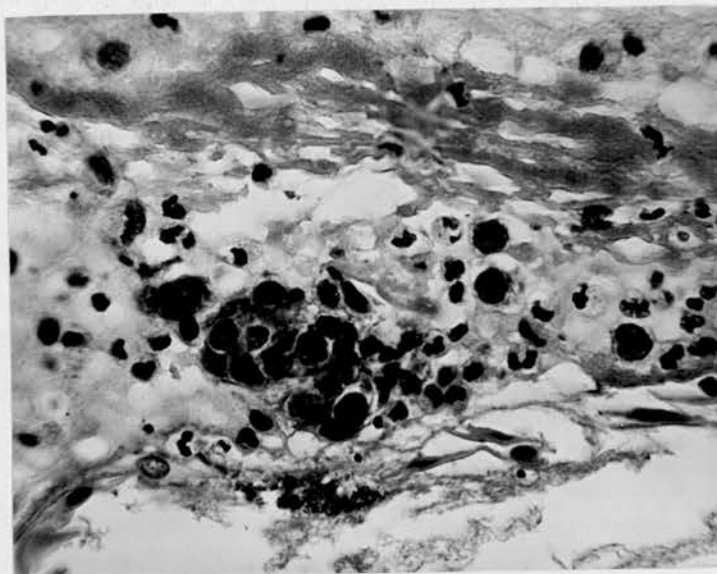


Fig 13

X 500

It is interesting to note that this case in particular had had a negative bronchoscopic biopsy and the diagnosis - which was confirmed later - was based on the sputum report together with the clinical and radiological findings.

It is advisable, if there is doubt concerning the malignancy of a group of cells, not to report them as malignant but to ask for further specimens which might be helpful in the elucidation of the nature of those cells.

If one tries to adhere to these rules, one



will probably miss some cases of carcinoma and so the number of "false negatives" will be increased; but on the other hand, in all probabilities, one will give no "false positive" diagnoses which should be, of course, the aim. The attitude of Papanicolaou toward false positive diagnoses is worth repeating: "Failure to detect malignant cells in a smear is in a way excusable, but the wrong interpretation of findings is apt to be severely criticised and to cause serious doubt as to the accuracy and dependability of the test." It should be borne in mind, of course, that a negative result does not, in any way, exclude the possibility of the presence of a tumour.

#### Material & Results.

This part of the study is based on the personal preparation and interpretation of smears from 480 specimens of sputa received in the period between 29.10.1949 and 19.3.1951. These specimens were examined as unknowns and in many of them even the age of the patient was not mentioned on the request sheet accompanying the specimen. This was thought necessary in the evaluation of such a method of diagnosis because one's decision is likely to be influenced, especially on border line and doubtful cases, by the clinical data.

All specimens received were accepted and examined even if it was obvious that the specimen submitted was no expectorate at all, but merely saliva or mouth secretions. Some authors discard such specimens as being unsuitable for examination e.g: Kjoer et al (1949) who discarded 18% of the specimens as being unsuitable and regarded an additional 3% as less suitable. The reason why no specimen was rejected was that we are trying to assess the value of this method of examination as a practical test and so it must be subject to any defect or weakness that most clinical tests which depend partly on patients, nurses, etc. are liable to. If some of the specimens are rejected, this would give an artificial result as it would certainly reduce the number of negative reports.

From reviewing all the reports given by the writer concerning these specimens it was found that 429 were stated to contain no tumour cells (negative), 32 were reported to contain tumour cells (positive) and 19 were stated to contain cells of a doubtful or suspicious nature and further specimens were requested. Thus from analysis of the 480 reports issued

|     |   |   |              |
|-----|---|---|--------------|
| 429 |   |   | negative     |
| 32  | " | " | positive     |
| 19  | " | " | inconclusive |

480 Total.

The next step was to follow up these cases in order to check up on the results and the accuracy of the reports given. This was done by examining case records and follow-up histories mainly in the Thoracic Unit of the Eastern General Hospital and also in the Western and Northern General Hospitals and in the Radiotherapy Department of Edinburgh Royal Infirmary. Up to the time of writing (April, 1951) I was able to trace a total of 467 out of these 480 cases. The result of this follow-up is as follows:

256 proved to be negative.

185 proved to be or thought to be very probably positive.

22 remained with an incomplete diagnosis.

4 miscellaneous (adenomas and secondaries).

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467 Total checked.

13 not traced.

---

480 Total.

As in the old series I tried to check on the accuracy of the reports issued and the result is shown in the following table (Table 14.)

Therefore out of 185 cases of primary lung carcinoma 29 were diagnosed correctly by examination of the sputum. This gives a positive result in only 15.6%. An additional number of 12 cases or about 6% were reported as inconclusive.



TABLE 14.

| Original Report | No. of cases (traced) | Follow up. |          |            |               |
|-----------------|-----------------------|------------|----------|------------|---------------|
|                 |                       | Negative   | Positive | Incomplete | Miscellaneous |
| Negative        | 417                   | 248        | 144      | 21         | 4             |
| Positive        | 32                    | 2          | 29       | 1          | -             |
| Doubtful        | 18                    | 6          | 12       | -          | -             |

At the time of writing 2 of the cases reported as positive were not confirmed clinically and the possibility of lung cancer was thought to be remote. In a third case the diagnosis was incomplete and though cancer was not proved, it was not dismissed as a possibility. Therefore we might regard 2 of the positive reports as being false.

As regards the negative reports, 144 specimens were reported to contain no tumour cells, but were proved later on to be obtained from patients suffering from primary cancer of the lung. This is equal to 34.5% of all negative reports issued. Other investigators regard such cases as representing "false negative" reports, but the writer is inclined to regard this term as being inaccurate because it gives the impression that such specimens actually contained tumour cells

but these were overlooked by the examiner. While certainly this is a possibility, there is little doubt that many of them were true negative in the sense that they did not contain tumour cells although the patients actually suffered from bronchial carcinoma. Though tumours do exfoliate cells, they do not do this continuously and this is the explanation why "repeat" specimens may give better results than examination of a single specimen.

To summarise: this series gave  
 15.6% positives.  
 34.5% so-called false negatives.  
 0.8% false positives (calculated in relation  
 to negative cases.)

From a glance at this result it is obvious that it does not compare favourably with the numerous enthusiastic reports on the subject by other investigators, e.g. Wandall 84%, Herbut and Clerf 82.4%, McKay et al 74%, etc. etc. On the other hand it is not so gloomy as that obtained by Craver (2 cases out of 175) or Stahelin (1 case in 115).

#### Discussion.

The main object of this study was to try to come to a conclusion about the value of cytologic examination of the sputum in the diagnosis of

carcinoma of the lung. The recent literature abounds with articles concerning the cytologic diagnosis of cancer. A number of monographs too, with many beautiful illustrations have appeared, e.g: those of Wandall (1944), The Staff of the Vincent Memorial Laboratory (1950) and that of Farber et al (1950). Not only the medical literature, but also the daily press and popular magazines have written repeatedly about the new "test" for cancer, its easiness and popularity.

The majority of the mentioned papers and monographs give a high percentage of positive results from this method of examination. On the other hand there are many pathologists who, not only doubt the value of this method, but who state plainly that they cannot diagnose cancer "for sure" from cytologic examination. They doubt if it is possible to tell whether a given cell is neoplastic in origin or not. They stick to the sacred doctrines of the old fathers of pathology in diagnosing malignancy, e.g. if there is evidence of invasion, etc.

Willis (1950) in a review of "The Cytologic Diagnosis of Cancer" by the Staff of the Vincent Memorial Laboratory ..... wrote: "All experienced histopathologists practise "cytologic diagnosis"



in that they search for, and sometimes find, undoubted tumour cells in various body fluids and secretions. Of recent years there has sprung up a group of enthusiasts in this field who claim to have attained a proficiency much superior to that of other histologists and to be able to identify isolated tumour cells with great accuracy." Then after a well reasoned criticism of the results of these authors he concluded by saying "Very probably there is room for improvement in the work of some pathologists in their identification of tumour cells in fluids, but this will be achieved only by those with a sound knowledge of histopathology, both of cancer and non-cancer tissues. Purely "cytologic diagnosis" will always suffer from a high proportion of either doubt or error."

Therefore this series of cases was studied carefully. They included 256 or nearly 60% of cases not suffering from cancer. As mentioned previously no specimen was discarded and all specimens were examined as unknowns. These three points are considered important in the assessment of the value of this method of examination because (1) If all or the majority of specimens came from cases of cancer or suspected cancer of the lung,

a positive diagnosis, even if based on false criteria, will add to the final result of correct positive cases when, as a matter of fact, it was a false positive result.

(2) To accept only specimens which are more likely to yield positive results would give an "artificially" high percentage of positives.

(3) Thirdly, there is little doubt that clinical and radiological data are likely to have an influence on the pathologist in his decision especially in doubtful cases.

The first and third of these points were stressed by Liebow et al (1948) as being essential in the critical analysis of the accuracy of this method. On very few occasions was the writer fairly confident of a positive diagnosis because there is no doubt that "malignant-looking" cells which show the "criteria" of malignancy are sometimes seen in smears from "benign" conditions and, on the other hand, cells derived from a well-differentiated malignant neoplasm may look fairly "benign" and regular.

On the other hand, in some of the positive cases reported, though few as they were, the diagnosis from sputum examination was the only positive pre-operative or ante mortem diagnosis.

Therefore this method can be of value as an adjunct to other well established methods of diagnosis.

Conclusions on the Value of this Method.

As a result of this study and also after studying the various reports on the subject especially those concerned with sputum examination, the writer has arrived at the following conclusions:-

(1) There is no doubt that cytologic examination of sputum for the diagnosis of cancer of the lung is of some value. But there is no doubt too, that this value is a limited one. Thirdly it is clear that the widespread publicity given to this method is rather misleading and premature.

(2) The value of this method of examination is clear from the following facts:-

(a) It is an easy and convenient method which entails no trouble, special preparation or otherwise of the patient.

(b) The ease in obtaining additional specimens if few atypical cells are present and more evidence is required on which to base a conclusive diagnosis, is a very important consideration.

(c) By employing the fresh smear technique, a much quicker result can be obtained than with



tissue biopsies. A report can be given within the space of few hours instead of some days.

(d) In some cases, especially in those in which the tumour is beyond bronchoscopic reach, sputum examination may be the only pre-operative or ante mortem way of verifying the diagnosis of carcinoma of the lung. In such cases the writer feels that a confident report given by a competent examiner can be regarded as a sufficient reason to justify exploration of the chest even in the absence of a positive bronchoscopic biopsy.

(3) To get the best results from this method:-

(a) The technician or pathologist must master the technique of preparing the smears. This point has already been discussed in some detail in a previous chapter.

(b) The pathologist must be well trained in this method of examination besides, of course, his general training and experience as a pathologist. To rely on a diagnosis given by a "cytologist" who is not a pathologist at the same time is a dangerous practice.

(c) He must be willing to spend an adequate time on the examination of his smears. There is no doubt at all that this method is time consuming and one may spend on one case as much time as he would spend in examining ten tissue biopsies.

This time factor is stressed because personally I believe that it is not easy for the general pathologist who has to report on the other routine biopsies, to find enough time to examine such smears thoroughly.

(4) Again this method is not intended, by any means, to replace other established and more reliable methods of diagnosis, e.g. bronchoscopy - but is intended to be an additional method to help to increase the number of correct clinical diagnoses of cancer of the lung so that adequate treatment might be undertaken.

(5) The writer feels that a positive diagnosis should rest upon the finding of groups of frankly cancerous cells and that it is far better to be more conservative and give a diagnosis of "tumour cells" only when such cells are strictly compatible with the established criteria of malignancy than to be more lenient and risk giving a false positive report.

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BRONCHIAL ADENOMA

Bronchial adenoma is widely recognised as a definite clinical and pathological entity. It is still a subject of much controversy and as yet no unanimity of opinion exists regarding its histologic origin, potential malignancy, relationship to cancer of the bronchus and its proper treatment.

History:

It was Laennec who mentioned this tumour for the first time in his treatise on auscultation. He believed that these polypoid tumours or excrescences, as he called them, were rare and that they were similar to the vesicular polyps of the nose, ear and uterine cervix.

In 1882, H. Mueller found a case accidentally at the post mortem examination of a young woman who, for eight years, had been suffering from cough and blood tinged sputum. He found a benign pedunculated tumour occluding the left main bronchus and causing extensive secondary bronchiectasis distal to it. This was the first recorded case and up to 1930 Patterson could find only 26 cases recorded in the available literature. Kramer (1930) reported the first case clinically and bronchoscopically diagnosed and he claimed that



bronchial adenomas arose from the ducts of the mucous glands.

This period which was largely one of post mortem recognition of the tumour continued till 1932, when Wessler and Rabin published their report on 12 bronchial adenomas based largely on bronchoscopic and clinical observations. This report started a period of bronchoscopic recognition and treatment of the tumour and a number of important papers appeared.

Hamperl (1937) described 9 cases and since that time rational therapy is being developed and is based upon more knowledge of the natural life histories of these tumours.

Among the many excellent papers on the subject are those of Foster-Carter (1941), Holley (1948), Brunn and Goldman (1941), Moersch and McDonald (1950), Goldman and Stephens (1941), Womack and Graham (1938), Fried (1947) and Engelbreth-Holm (1944-45).

#### Incidence:

It is generally agreed that adenoma is the commonest "benign" bronchial neoplasm. Lowry and Rigler (1944) and Nacleris and Langer (1948) state that bronchial adenomas account for 80% of benign bronchial tumours. Other authors e.g.

Paterson (1936) state that they account for 50% of these tumours.

They are estimated by Goldman and Stephens (1941) to constitute 6-10% of all primary tumours of the bronchi. Most authors give similar figures but the experience here in Edinburgh is that these tumours are very uncommon. In the series of bronchoscopies recorded in an earlier chapter, there were only 2 cases of bronchial adenomas as compared with 131 cases of bronchial carcinoma. In the post mortem records of R.I.E. too, "bronchial adenoma" is rare. It is interesting that Mr. B. Dick (1950) in a Honyman Gillespie Lecture on bronchial adenoma mentioned that in the three large infirmaries in Glasgow, there is no single case of bronchial adenoma in the post mortem records.

#### Age:

The majority of cases are recognised between the ages of 30 and 40 years, but other age periods are not immune. The age incidence of 18 cases collected by Goldman and Conner (1950), according to decades was as follows:-

| <u>Decade</u> | <u>Number of Cases</u> | <u>%</u> |
|---------------|------------------------|----------|
| 1-10 years    | 1                      | 5.6      |
| 11-20 "       | 1                      | 5.6      |
| 21-30 "       | 4                      | 22.2     |
| 31-40 "       | 6                      | 33.3     |
| 41-50 "       | 6                      | 33.3     |

It may be observed that the majority of bronchial adenomas are thus seen at an earlier age period than that in which most bronchial carcinomata are recognised.

Sex:

The sex incidence is of particular interest because this tumour is commoner in females. About 55-60% of cases occur in women. Among the 18 cases already mentioned there were 10 or 56% females and 8 or 44% males. In all the reported series females either predominate or are nearly equal in number to males. All the few cases I studied occurred in females. On the other hand, all authors agree that bronchial carcinoma is far commoner in males with an average ratio of 4 males: 1 female.

In the section on histopathology of bronchial carcinoma I recorded the observation that adenocarcinoma was relatively commoner among females



- with a ratio of males to females of 1.7:1. If we correlate these two points, i.e. the fact that bronchial adenoma is more common among females and the occurrence of relatively more bronchial adenocarcinomata also in females, we may be justified in thinking that some bronchial "adenomas" may change into adenocarcinoma later on; and if this is so, it may be regarded as a further proof that bronchial adenoma is a potentially malignant tumour.

Site:

The tumour is usually located either in a primary bronchus or near enough to it to be easily accessible to the bronchoscopist. Thus Engelbreth-Holm (1944-45) stated that these tumours are always located in a main bronchus or where the stem bronchus is branching to a lobe and that in no case bronchial adenoma has been seen more peripherically. Foster-Carter (1941) too, made the statement that bronchial adenoma arises invariably in one of the larger bronchi and that there is no record of this tumour occurring in the periphery of the lung. Similar statements were made by Moersch et al (1945) and Willis (1948).

But Maier and Fischer (1947) reported five cases in which the tumour was located in a branch bronchus not accessible to the bronchoscope and

though in four of these cases the tumour was located near the hilar area, in the fifth case the tumour was at the periphery of the lung close to the diaphragm.

The distribution of 70 bronchial adenomata studied by Foster-Carter (1941) is as follows:-

| <u>Right side</u> (44 cases) | <u>Left side</u> (26 cases) |
|------------------------------|-----------------------------|
| Rt. main bronchus .... 18    | Lt. main bronchus .. 14     |
| Rt. lower lobe " .... 21     | Lt. lower lobe " ... 8      |
| Rt. middle " " .... 4        | Lt. upper " " ... 4         |
| Rt. upper " " .... 1         |                             |
| —                            | —                           |
| 44                           | 26                          |
| —                            | —                           |

The location of 85 cases studied by Moersch and McDonald (1950) is as follows:-

| <u>Right side</u> (47 cases) | <u>Left side</u> (38 cases) |
|------------------------------|-----------------------------|
| Rt. main bronchus .... 15    | Lt. main bronchus ... 14    |
| Rt. lower lobe " .... 19     | Lt. lower lobe " ... 15     |
| Rt. upper " " .... 7         | Lt. upper " " ... 9         |
| Rt. middle " " .... 3        |                             |
| Both lower & middle .. 3     |                             |
| —                            | —                           |
| 47                           | 38                          |
| —                            | —                           |

It is seen from these two series of cases that the tumour is found more on the right side

than on the left and that together with the main bronchi, the right lower lobe bronchus is a particularly common site.

Gross Appearance:

The tumour is a pinkish white vascular body which may be sessile or pedunculated and bleeds readily on touching. The tumour may advance towards the lumen of the bronchus or towards the parenchyma of the lung. It appears as a rounded, well demarcated growth, about 1-3 cms. in diameter arising from the bronchial wall and often surrounded by a fibrous capsule. (Figs. 14 and 15).

Goldman and Stephens (1941) describe three morphologic types of bronchial adenoma: endobronchial, intramural and extra-endobronchial. They believe that the incidence of intramural and extrabronchial types is greater than previously reported.

At first the tumour usually appears as a wart-like prominence which is firm and sessile; later it becomes pedunculated and hangs by a constricted neck. Its tendency to project upwards is attributed to the expulsive efforts of coughing.

Occasionally the mass hardly projects into the bronchial lumen but grows mainly outside the bronchial wall into the lung. There it forms a



well circumscribed mass and the lung damage that follows is not due to the tumour per se but to the mechanical obstruction that follows.



Figs. 14 & 15.

Usually the bronchial mucosa is pushed by and covers the tumour. It is not ulcerated as is usual with bronchial carcinoma. It may, however, become metaplastic as a result of irritation, circulatory and inflammatory disturbances.

Histopathology:

Excellent descriptions of the histologic appearances of these tumours can be found in articles by Hamperl (1937), Brunn and Goldman (1941), Holley (1946) and others.

Many authors divide these tumours into various histological types. This division, however, is not new. Hamperl (1937) classified the tumours into bronchial carcinoids and cylindromas. Laff and Neuburger (1944) also recognised a carcinoid-like pattern and a cylindromatous one. Hazel et al (1949) divided them into a large group of adenomas and a smaller one of cylindromas. Goldman and Conner (1950) went as far as describing 4 histological variants viz: (1) the carcinoid, (2) the mixed tumour and cylindromatous types, then (3) the glandular and (4) myoepithelial types.

Though the classification of these tumours into carcinoids and mixed tumours is advocated

by many observers, neither is accepted by many pathologists. Justification for the term carcinoid is weakened by the fact that silver positive granules, found in most carcinoid tumours, could not be demonstrated in the cells of the bronchial tumours.

The designation mixed tumour has been also opposed because although epithelial elements are similar to those in mixed tumours, other components of the latter, such as neoplastic myxochondroid elements, are often lacking. The cartilaginous tissue sometimes found is considered as a residue of the bronchial wall.

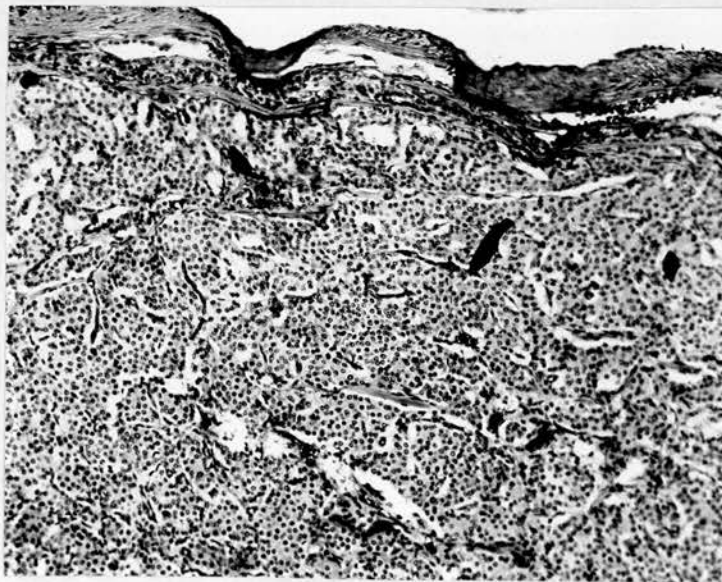
Though the histological pattern varies from tumour to tumour in a marked degree, the individual tumours are usually uniform and the striking histological characteristic is the uniformity of the cells: in size, shape and staining properties.

Next to a fibrous capsule, the tumour is found to be composed of closely packed small cells which are either cubical or cylindrical in shape and are supported by a vascular fibrous tissue stroma. The cytoplasm is usually scanty and clear and the nuclei are large, round or oval in shape. They are uniform in size, deeply stained



but very rarely do they show any mitotic figures or show the marked irregularity in size and shape commonly displayed in sections from bronchial carcinoma.

The arrangement of the cells varies a great deal and in this study I have met with at least four patterns of growth. In Figs. 16 and 16A the cells are aggregated in solid acini with no attempts at glandular formation. The structure is fairly uniform throughout the sections examined and the stroma is rather scanty. The individual cells are similar, their nuclei are relatively large and darkly stained but no mitotic figures are seen.



X 110

Fig. 16.

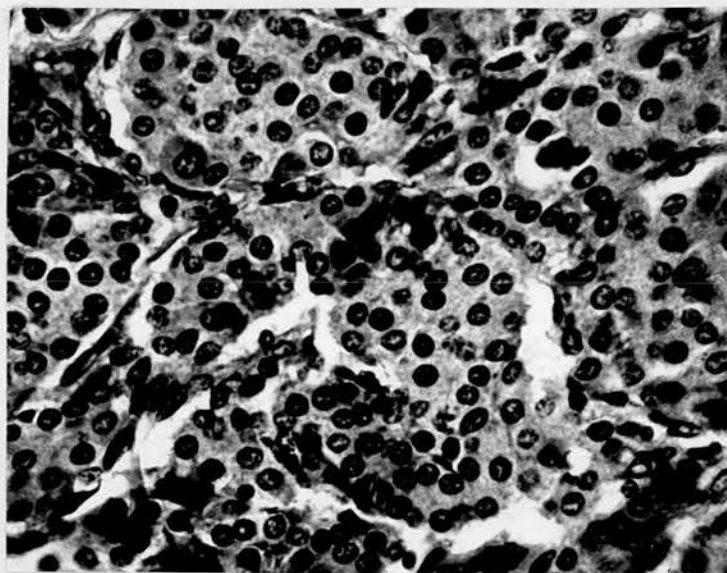


Fig 16 A

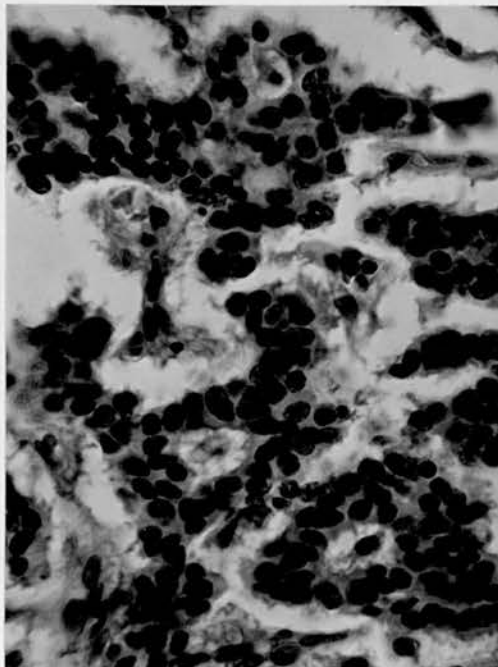
X500

Figs. 17 and 17A show a uniform trabecular structure with attempts at glandular formations.



X 55

Fig. 17.

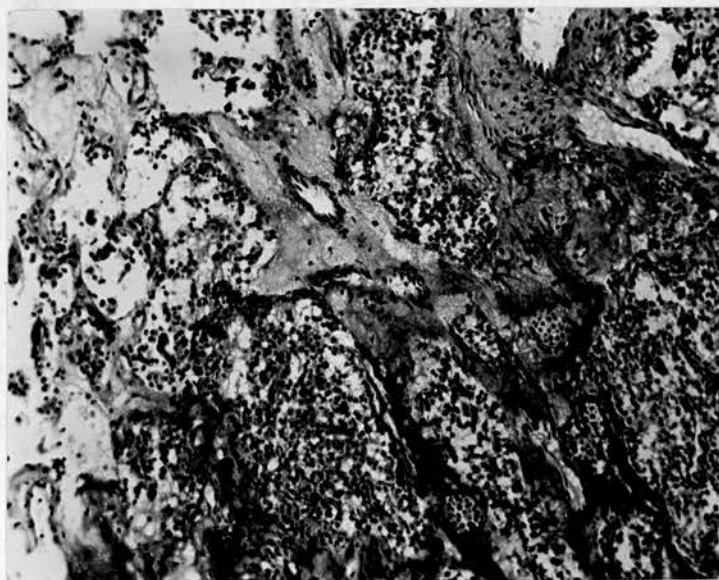


X500

Fig. 17A.

Nearer the capsule of the tumour a piece of cartilage is seen included within the tumour tissue but it is clear that it is a fully developed hyaline cartilage and is most probably the remains of the original cartilage in the bronchial wall. The stroma is more abundant and highly vascular in some areas.

The histological pattern may sometimes simulate that of a renal carcinoma (hypernephroma) and even be mistaken for it. This was the experience of Engelbreth-Holm (1944-45), Holley (1946) and others. In one of the cases I studied (Figs. 18 and 18A) such a picture was recognised. The cells contain an abundant clear cytoplasm, the nuclei are darkly stained and the stroma is highly vascular.



X 110

Fig. 18.



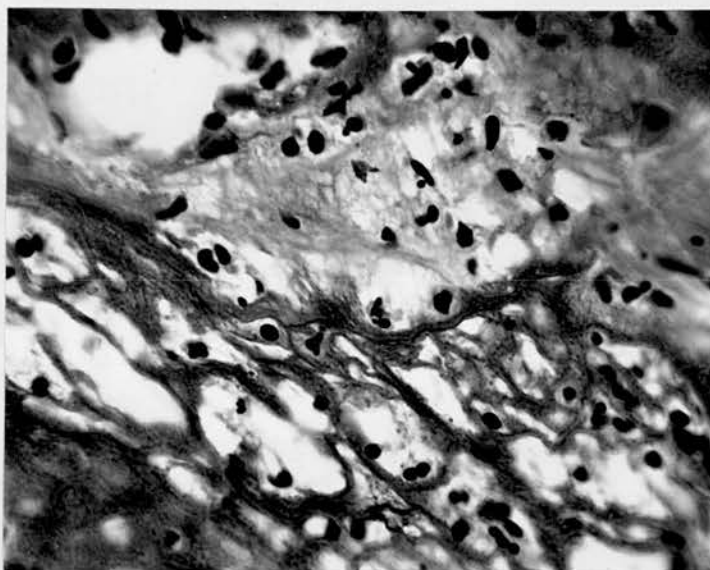


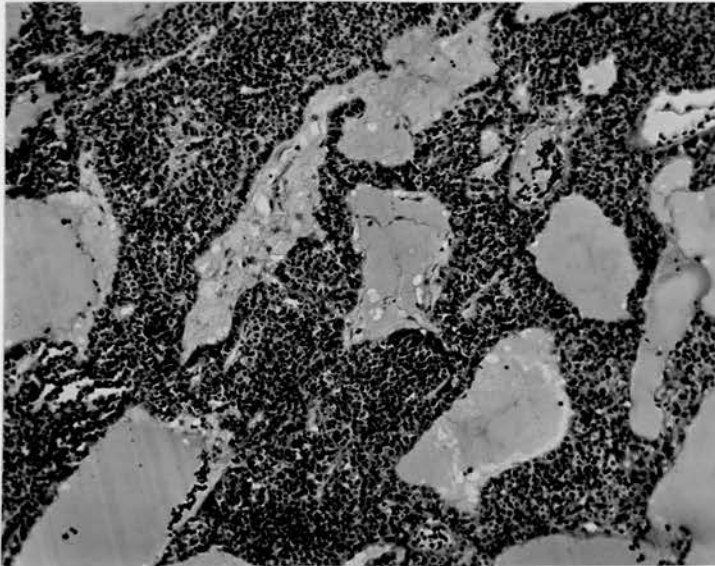
Fig 18 A                      X500

In the same section there are areas where the cells are small, uniform, cubical or columnar in shape and resemble the cells more commonly encountered in bronchial adenoma.

Occasionally the tumour shows large spaces filled with homogeneously stained material and separated by columns and cords of small, uniform, darkly staining cells. The histological appearances are similar to that variety of basal cell carcinoma of the skin known as epithelioma adenoides cysticum. (Figs. 19 and 19A).

Though these histological appearances are variable enough to allow the description of various patterns, in many cases one can trace the

transition from one type to the other - from a solid glandular structure to acinar formation and then to acini showing mucoid or watery secretion in their cells. Occasionally too, the same tumour displays more than one of these histological pictures.



X 110



X 500

Figs. 19 &amp; 19A.

Therefore there seems to be no justification for the separation of these tumours into "adenomas" and "cylindromas" or into "secretory" and "non-secretory" adenomas, etc.

These varying pictures are better regarded as different manifestations of the same tumour.

Origin of Bronchial Adenomas:

That there is no universal agreement upon the origin and nature of these tumours may be seen from the following titles given by various authors to what is in all probability the same type of tumour (Table 15.)

| Author            | Date | Title                      |
|-------------------|------|----------------------------|
| Geipel            | 1931 | Basal cell cancer          |
| Wessler & Rabin   | 1932 | Benign bronchial adenoma.  |
| Kernan            | 1935 | Carcinoid                  |
| Moersch & Bowing  | 1935 | Adenocarcinoma             |
| Clerf & Crawford  | 1936 | Benign glandular tumours.  |
| Zamora & Schuster | 1937 | Vascular adenoma           |
| Welt & Weinstein  | 1937 | Cylindroma & Carcinoid     |
| Womack & Graham   | 1938 | Mixed tumours of the lung  |
| Ochsner           | 1940 | Reserve cell tumour        |
| Goldman           | 1940 | Polypoid bronchial tumours |
| Adams et al       | 1942 | Malignant adenoma of lung  |



If these tumours are primarily epithelial tumours as they are believed to be, they should arise from the bronchial surface, from the bronchial ducts or from the mucous and serous glands. Fried (1948) in his monograph on bronchogenic carcinoma and adenoma states that there are two possible sources for the origin of the bronchial adenomas: (1) The bronchial mucous glands (2) The basal cells of the bronchial mucous membrane. When the mucous glands are involved the tumour cells resemble the secreting cells of the gland. However, a more frequent source for the genesis of these tumours is the basal cells of the bronchial mucosa. These cells, found in clusters interspersed between the columnar and goblet cells, represent a dynamic unit playing a role in regenerative and fibrogenic processes taking place in the lung. This cell, is also the mother cell for bronchogenic carcinoma.

However, most workers agree that origin from the surface epithelium is unlikely because the tumours are separated from it by a connective tissue layer. The most frequent suggestion is that they arise from the bronchial glands or ducts.

Thus Clerf and Crawford (1936) consider that the structure of many of these growths suggests a mucous gland origin. Sano-Meade (1947) state that the cells which one sees in bronchial adenoma resemble the different component cells of the bronchial glands and are found in the same anatomical locations. Brunn and Goldman (1941) believe that these tumours arise from the bronchial glands and their ducts which, being mixed glands, are apt to have varying patterns and which in general follow the behaviour of adenomatous tumours arising from these glands elsewhere in the body. Wessler & Rabin (1932) also believe that these tumours arise from the bronchial mucous glands or their ducts. Adams and his associates (1942) believe that bronchial adenomas arise from the mucous glands and their ducts but they also remark that the high incidence in women and the occurrence of pulmonary haemorrhage with the menstrual bleeding suggests that circulating hormones may bear some relation to the pathogenesis of these tumours.

Womack and Graham (1938) believe that they are mixed tumours composed of one or two germinal layers (mesoderm and entoderm) and that they are somewhat like the mixed tumours of the salivary

glands.

Stout (1943) expresses the idea that bronchial adenomas may arise from the "peculiar cells with acidophilic granules called onkocytes" which he demonstrated among the mucous and serous glands of adult human bronchi and their ducts.

Finally, Willis (1948) in discussing the origin of these tumours states that there is little room for doubt that the tumours arise from the mucous glands of the bronchial wall. He adds: "I see nothing to favour the view suggested by Hamperl and supported by Stout that the bronchial adenomas arise from onkocytes. Nor is there any substantial evidence to sustain Womack and Graham's opinion that they are mixed tumours of developmental origin."

It can be concluded that the origin of bronchial adenomas although often discussed is still undetermined, but that the majority of observers favour an origin from the mucous and mixed glands of the bronchial walls or their ducts.

Is Bronchial Adenoma "benign" or "malignant"?

This is one of the most controversial points in pathology. All kinds of views with regard to benignancy or malignancy of bronchial adenomas



have been advanced, from a pure denying of the said potency to an assertion of their potential malignancy and even to a classification of them as adenocarcinomas of grade I.

This problem, however, is not only of academic importance. Therapy has not been uniform because of lack of agreement on this subject.

Because of their slow growth, their supposed encapsulation, the behaviour of metastasis and most important, their clinical course, the adenomatous bronchial tumours have often been classed as benign. Fried (1947) suggests that adenoma is always a benign tumour, that metastases are extremely rare and that recurrence after operation has seldom been observed. He suggests that the tumour is not even locally malignant and that although its growth may form a "bulge" it hardly ever "breaks through". Foster-Carter (1941) regards bronchial adenomata as benign tumours and states that though slow infiltration of the bronchial wall may occur, it plays no part in the course of the disease.

On the other hand, Goldman and Conner (1950) object strongly to this view and say: "This fallacious idea cannot be too strongly

discouraged. Tumours which are often demonstrably not encapsulated, which frequently recur after bronchoscopic removal, which may infiltrate surrounding tissues and which frequently metastasize, are far from benign." Holley (1946) concluded that in the light of available information it is necessary to state that some bronchial adenomas become malignant.

There have been unequivocal reports of extension beyond the borders of the original tumour. Adams et al (1942) presented 5 cases as malignant adenomas because there was infiltration of the bronchial wall in all, invasion of the local lymphatics in one, metastases to the peribronchial lymph nodes in two and distant metastases in two: one in the liver and the other in the vertebral body. In Anderson's case (1943) with metastasis to the liver, the tumour in both the bronchus and the liver simulated cylindroma.

The following summary of the record of a case of bronchial adenoma which changes later to an adenocarcinoma illustrates one type of course which these cases may pursue.

Mrs. M.S. aged 42 was admitted to the Thoracic Unit on 3.11.1948 complaining of

haemoptysis. She always complained of a cough which was worse in winter and the sputum had been fairly profuse. In the spring of 1937 she had a small haemoptysis and since then she has occasionally had small haemoptyses - usually "only a spot of blood." During the month before her admission she had repeated frequent haemoptyses. A previous X-ray report (October 1948) read: "There is a dense sharply outlined opacity, spherical and  $6\frac{1}{2}$  cms. in diameter in the left lower lobe behind the heart and just above the diaphragm. Lung fields otherwise normal. Mediastinum central. Diaphragm at normal level." On 4.11.1948 the X-ray appearances were nearly the same as those reported previously.

Sputum contained few polymorphs and mononuclears, but no tumour cells.

Bronchoscopy on 6.11.1948: Larynx and trachea normal. There was an excess of mucus in both main bronchi. On the left side the orifice to the upper lobe and the orifice to the dorsal lobe were clearly seen and were normal. The orifices of the lower lobe bronchi could not be seen either directly or through the telescope on account of a smooth bluish grey swelling projecting into the lumen of the left stem



bronchus at the level of the lower bronchial orifice. The projecting tissue was not ulcerated. Biopsy was attempted but there was profuse bleeding before the jaws of the biopsy forceps were completely closed. After aspiration and further application of adrenaline the abnormal tissue was seen to be projecting from the posterior aspect of the left stem bronchus and probably arose from the posterior basic bronchus.

On 9.11.1948 bronchoscopy was attempted again and a polypus was seen projecting from the posterior basic bronchus. Part of the polyp was removed for microscopy.

Pathological Report (B.3583): The specimen shows a fragment of tumour tissue composed of large cells with clear cytoplasm and hyperchromatic ovoid nuclei of variable size. These cells show differentiation towards columnar ciliated epithelium disposed in acinar formation. Mitoses are very few. The histological appearance is that of a bronchial adenoma.

On 12.11.1948 Lobectomy performed - the lower lobe was removed by hilar dissection. Some enlarged glands removed too.

Pathological Report (B.3601) Gland from hilum of left lower lobe. "The gland is heavily pigmented

with carbon. There is no infiltration with malignant growth."

Other Pathological Reports:(B.3635) on -

- (1) Glands posterior to lower lobe branch of left pulmonary artery;
- (2) Section of tumour;
- (3) Section of bronchial wall with adjacent tumour.

- (1) It is not possible to identify the specimen definitely as a lymph node. Most of the tissue is occupied by groups of clear polyhedral tumour cell masses separated by thin stromal bands. The tumour cells, in relation to the stroma, are frequently columnar. Here and there the solid alveolar groups of cells show slight but definite acinar differentiation. One side of the nodule is limited by a well formed fibrous capsule which in a few places is infiltrated by tumour cells. At one end of the specimen an area of fibrosis and pigmentation commonly seen in mediastinal glands is present and between this and the capsule the appearance suggests infiltration of the peripheral sinus by tumour. At this point in the extracapsular tissue, a few groups of tumour cells are seen in lymphatics.

- (2) This specimen shows a circumscribed tumour mass in normal lung. The mass is poorly encapsulated and early infiltration of the capsule is seen. The central portion is autolysed and it is difficult to identify the pattern which appears similar to specimen I.
- (3) Includes bronchial mucous glands but no bronchial epithelium. The bronchial wall is infiltrated by groups of cells similar to those in I, but here a more trabeculate arrangement with more frequent columnar cells is seen, though only traces of acinar differentiation are seen.

The pattern of the growth is similar to that reported in B.3583 and is that seen in bronchial adenoma. In view of the long history there can be no doubt that the growth has remained simple for a long time. Now, however, as happens with these tumours, local invasion and unfortunately invasion of lymphatics has occurred. Thus the growth must be regarded as malignant.

= Poorly differentiated adenocarcinoma arising from a bronchial adenoma.

From the subsequent history of the case: she remained relatively well till April, 1950



when O/E she had hepatomegaly, subcutaneous nodules and glandular enlargement - which no doubt denote metastases from her pulmonary neoplasm.

... ..

Comment:

Twelve years history of haemoptysis starting when she was about 30 years old; and the malignant nature of the condition was only detected after resection. Even then, apart from the evidence of invasion the histological pattern was similar to that of bronchial adenoma and to the bronchoscopic biopsy. In this case it cannot be argued, as is sometimes done, that this case might have been malignant from the beginning because the long history of 12 years is very much against a malignant neoplasm. Though there is no absolute proof as to the sequence of events in this case, yet it is reasonable to think that the disease started as a benign tumour twelve years previously and after remaining benign for many years it started to be invasive. At that time it was resected when the early malignant transformation was evident. Two years after operation distant metastases in lymph glands, liver, etc. took place.

... ..

The truth about the nature of this tumour is that here, as with other similar kinds of tumours, "benign" and "malignant" are only relative terms and all gradations of behaviour are to be seen: between highly differentiated, more slowly growing adenomas and poorly differentiated, infiltrating and metastasizing carcinomas. Most of these tumours, however, seem to occupy an intermediate or borderline position in the scale of behaviour, often designated as potentially or semi malignant.

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CONCLUSIONS(1) Incidence of Carcinoma of the Lung:-

Evidence is presented that during the last two decades especially, primary carcinoma of the lung has shown a real and obvious increase in its incidence. The various suggestions that this increase is only apparent have been critically discussed and were shown to have no real foundation. The increase in the incidence of the disease is far too much to be accounted for by better methods of diagnosis, ageing of the population, etc. etc. The factor or factors responsible for this increase, at the present state of our knowledge, are not known.

The disease continues to be more encountered in the male sex with an average ratio of 4 males to 1 female.

(2) Histopathology:-

Various authors give different percentages as regards the incidence of the histological types of lung cancer. Some maintain that the undifferentiated types are commoner while others believe that the squamous type is in excess. In our post mortem material there is a preponderance of the undifferentiated types. In the bronchoscopic biopsies they still prevail but the percentage of



the squamous cell variety is more than double that which is found among autopsy material.

Most observers, however, remark that in most cases there is more than one histological type in the same tumour and that this is seen clearly if different parts of the tumour are examined microscopically.

At present, there is no unanimous opinion regarding the value of the histologic classification of primary cancer of the lung in estimating the prognosis and it seems that early diagnosis is much more important from the prognostic point of view than histological typing.

(3) Bronchoscopy:-

This is the most valuable method of diagnosis of carcinoma of the lung. About three quarters of cases can be correctly diagnosed by this method. Bronchoscopy too, is of value to the surgeon in assessing the operability or otherwise of the tumour, its exact location, etc. In experienced hands it is a safe and relatively minor procedure.

(4) The Value of Cytologic examination of Sputum in the Diagnosis of Lung Cancer:-

This method has an undoubted but very much limited value in diagnosis. It is of value because it is

easy, quick and can be repeated without any trouble to the patient in cases of doubt. In few cases, too, especially in peripherally located cancers, it may give a positive result while a bronchoscopic biopsy may be negative.

This method of diagnosis, however, requires careful preparation of the smears, an experienced pathologist and time. The time factor in particular has been stressed.

There is no absolute morphologic criterion to distinguish a cancer cell from a normal cell. One must rely on groups of cells and not on single, isolated cells in diagnosis. It is believed that it is better to err on the negative side than to give a false positive report.

Sputum examination can be regarded as having some value as an adjunct to more established methods of diagnosis and not intended to replace them.

(5) Bronchial Adenoma:-

is a distinct and well recognised clinical and pathological entity. As contrasted with bronchial carcinoma, it occurs in younger age groups and affects more women than men. The histological picture is very variable but the characteristic thing about it is the uniformity of the individual cells, the

regularity of their nuclei and the rarity of mitotic figures or any evidence of rapid growth.

There is still some controversy as regards their origin and behaviour; but the consensus of opinion seems to favour an origin from the mucous glands or their ducts in the bronchial walls and to regard the tumour as occupying an intermediate or borderline position in the scale of malignancy similar to that of gastro intestinal "carcinoids", mixed parotid tumours, etc.

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#### ACKNOWLEDGEMENT

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