

A SURVEY OF 501 CASES OF BRONCHOGENIC CARCINOMA

BY

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This survey was undertaken as part of a general programme for the investigation of the possibility of an association between susceptibility to disease and eye and hair colour. No evidence of such an association in the case of bronchogenic carcinoma was found, but evidence on various other aspects of this disease was obtained, more especially statistical confirmation of views already put forward by other observers.

These data have been obtained from 501 cases of bronchogenic carcinoma which occurred in members of the armed Forces during the period 1939-50. The series is not a random one, as selection on certain lines has occurred: (1) All cases were males. (2) The age incidence was necessarily limited to the Service ages. It ranged from 18 to 62 years. (3) None of the patients is still living. (4) Only "proved" cases have been used, "proof" being here defined as (a) histological evidence, either from biopsy or post-mortem examination, or (b) post-mortem evidence of a pulmonary growth with secondary deposits in the adrenal glands. This second criterion has been adopted because of the remarkable rarity with which neoplasms other than bronchogenic carcinoma produce adrenal secondaries, and the frequency with which histologically proved bronchogenic carcinomas do produce such metastases. Fifty-two cases of this second group have been included.

These grounds of selection necessarily influence the interpretation of the data and are further considered in relation to the particular results they affect.

Many of the findings were in every way similar to those described in previously published series; for example, previous history, clinical findings, cerebral presentation, abdominal presentation, distribution of secondaries. Only those subjects on which new data of a numerical nature have been found have been dealt with here.

ASSOCIATION WITH EYE AND HAIR COLOUR

Eye and hair colours have been considered separately, and also the combination of these two

TABLE I
DATA

	Ana- plastic	Squam- ous	Adeno- car- cinoma	Not Stated	Totals
<i>Age at Onset of Symptoms Known</i>					
Radiotherapy	76	29	4	20	129
Pneumonectomy	9	7	1	4	21
Other forms of treatment	1	0	0	0	1
Total treated	86	36	5	24	151
Not known if treatment was given	19	4	1	6	30
No specific treatment for carcinoma	134	31	25	62	252
Totals for "age at onset known"	239	71	31	92	433
<i>Age at Onset of Symptoms not Known</i>					
Radiotherapy	3	6	0	1	10
Pneumonectomy	2	2	0	1	5
Other forms of treatment	1	1	0	0	2
Total treated	6	9	0	2	17
Not known if treatment was given	0	2	0	1	3
No specific treatment for carcinoma	22	9	5	12	48
Totals for "age at onset not known"	28	20	5	15	68
Totals for treated cases	92	45	5	26	168
Totals for treated not known cases	19	6	1	7	33
Totals for untreated cases	156	40	30	74	270
GRAND TOTALS	267	91	36	107	501

factors using the classification proposed by MacConaill (1941), namely, blondes, brunettes, glaucopes, and cyanopes. A control series of 5,000 cases of injuries drawn from the same age groups and geographical areas was made and compared with those of bronchogenic carcinoma. The series of bronchogenic carcinoma has also been investigated for the possibility of an association between eye and hair colour and histological type of carcinoma, presence of adrenal secondaries, length of survival in untreated cases, and length of survival in treated cases. A small excess of brunettes was found in the incidence of the disease, presence of adrenal secondaries, shorter survival, both in treated and untreated cases, but none of these differences approached a significant figure.

ANATOMICAL SITE

In 222 cases (47.7%) the left lung was considered to be the site of the primary growth; in 243 cases (52.3%) the right lung; in 36 cases the side of origin could not be determined because of advanced disease. Examination of these figures gave $\chi^2=0.47$, for $n=1$, with P between 0.3 and 0.5. The difference is not significant.

AGE AT ONSET OF SYMPTOMS

Here it must be remembered that the age range of the series was only 18 to 62 years, and that therefore comparison with other unselected series could not be made. In 68 cases there was a continuous history of chest symptoms extending over many years, which made it impossible to assign a date to the onset of symptoms referable to the carcinoma. However, it is of interest to note that out of 433 cases in which a date could be given to the onset of symptoms, 67 of the patients were aged 30 or under, and 20 were aged 25 or under. The youngest was 18. This confirms the statement made by Willis (1948) that "the disease is not very uncommon in young people".

AGE INCIDENCE OF THE DIFFERENT HISTOLOGICAL TYPES

Geschickter and Denison (1934) and Frissell and Knox (1937) discussed the association of squamous-celled carcinoma of the bronchus with the older age groups.

TABLE II
AGE AT FIRST SYMPTOMS RELATED TO HISTOLOGICAL TYPE

	Anaplastic	Squamous-celled	Adeno-carcinoma
Number of cases	239	71	31
Mean age at onset (years)	37.8	41.2	38.0

Comparison of the data for squamous-celled and adenocarcinoma showed no significant difference, possibly because of insufficient material. Comparison of the data for squamous-celled and anaplastic types gave the difference between the mean ages at onset as 3.40 ± 0.59 years, 5.8 times the standard error. This provides statistical confirmation of the view that squamous-celled carcinoma of the bronchus has a later date of onset than the anaplastic type. The age limits of the series are of importance in this respect, as the older age groups are not as well represented in the Services as are the younger. It is very probable that the age difference shown is an underestimate.

RESULTS OF RADIOLOGY

Radiological examination of the chest was made in 462 cases (92.4%). In 148 cases (32% of those radiographed) a diagnosis was given by the radiologist, subsequently shown to be correct in 75 (50.7%) of them (Table III).

TABLE III
RADIOLOGICAL DIAGNOSES OF 148 CASES*

Diagnosis	Number of Cases	Percentage
Neoplasm, pulmonary	75	50.7
Tuberculosis	17	11.5
Bronchiectasis	7	4.7
Pneumonia	32	21.6
Lung abscess	3	2.0
Inflammatory, type unknown	6	4.1
Neoplasm, secondary	6	4.1
Chronic bronchitis	2	1.4

* In the remaining 314 cases a description of the radiological findings was given but without diagnosis.

Simpson (1929) described 52 cases of this disease in which a diagnosis was made as a result of radiological examination. Twenty-nine of these (56%) were diagnosed as neoplasm. Bryson and Spencer (1951) stated that the initial radiological diagnosis was incorrect in 60.4% of their series of 804 cases. It appears that there has not been any change in the reliability of radiological diagnosis of the disease since 1929.

RESULTS OF BRONCHOSCOPY AND BIOPSY

Bronchoscopy was carried out in 288 cases. 267 of these (92.7%) evidence of some form of bronchial abnormality was found, though this was not always recognized as neoplastic until the results of biopsy were known. In 21 cases (7.3%) bronchoscopy failed to reveal any abnormality. Biopsy was performed in 343 cases, either by bronchoscopy specimens or glands, and only 11 times (3.2%) failed to provide evidence of malignancy.

ACCURACY OF DIAGNOSIS

Fifteen cases (3%) were not diagnosed correctly until post-mortem examination. This compares very favourably with previously published series, for example, Simpson's (1929), in which only 73 of 139 cases were correctly diagnosed during life (an error of 43%). This supports the view that at least part of the apparent increase in the incidence of this disease is due to improvement in diagnosis.

TREATMENT

One hundred and thirty-nine cases (27.7%) were treated by radiotherapy or radon. Pneumectomy was performed in 26 cases (5.2%).

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lobectomy in one (0.2%). Exploratory thoracotomy was performed in 53 cases (10.6%), which were found to be inoperable because of mediastinal involvement. Bryson and Spencer (1951) stated that out of 752 cases, drawn from 26 hospitals formerly under the control of the London County Council, only 48 (6.4%) were considered suitable for radiotherapy and six (0.8%) for surgery. Brooks, Davidson, Price Thomas, Robson, and Smithers (1951) have estimated that fewer than 200 of the 9,000 persons dying each year in England and Wales from this disease undergo pneumonectomy (2.2%). These figures suggest that cases of bronchogenic carcinoma in the Services came under observation and treatment at an earlier stage than those occurring in the civilian population.

EFFECTS OF TREATMENT

PROLONGATION OF LIFE.—The greatest difficulty in dealing with this question was to decide from what date in the course of the disease the observations should begin. Stocks (1951) has pointed out that the only legitimate statistical treatment is on an actuarial basis unless it can be shown that all the patients eventually died from the disease under consideration. In the present series this obligation is fulfilled. The obvious method was to consider the duration of life from the date of the start of treatment, but this introduced two major difficulties; (1) no account was taken of how far the carcinoma had advanced before treatment began, and (2) it made comparison with a control series of untreated cases impossible. The alternative method was to consider the duration of life from the date of first symptoms. This method also took no account of the stage of the carcinoma before treatment, but it was possible to make a comparison with a control series. It is fully appreciated that the first symptoms do not coincide with the onset of malignancy, and it must therefore be emphasized that the figures presented are based on an arbitrary date of onset. On the other hand, these figures are, for two reasons, heavily biased *against* prolongation of life; (1) they take no account of patients who are still living as a result of treatment, and (2) in the recent paper of Brooks and others (1951) a distinction was drawn between cases receiving radical radiotherapy and those receiving only palliative treatment. This distinction has not been found possible in this series, so that an unknown number of advanced cases is included as having been treated, whereas in all probability they might justifiably have been excluded. As an example, 22 of the 53 cases which were found at thoracotomy to be inoperable were

given palliative radiotherapy. Such cases have all been included as "treated."

In 151 treated cases the evidence allowed a date to be given to the onset of symptoms. The mean duration of life in these cases was 14.0 months (extremes one to 105 months). Two hundred and fifty-two patients who received no specific treatment for carcinoma had a mean duration of life from the date of onset of symptoms of 6.5 months (extremes one to 59 months). Comparison of these figures gives the difference of the means as 7.5 ± 1.2 months, the difference being 6.25 times its standard error.

Comparison was made between 129 cases treated by radiotherapy and 21 in which pneumonectomy was performed, using Student's "t" test (Fisher, 1950). The mean duration of life in the cases treated by radiotherapy was 13.3 months (extremes one to 94 months), in the cases treated by pneumonectomy 18.8 months (extremes two to 105 months). Thus "t" was found to be 1.82, which, with $n=148$, gave a value for P between 0.05 and 0.1, which is not significant.

Finally, cases treated by radiotherapy were compared with the untreated series. The difference of the means was found to be 6.8 ± 1.2 months, 5.7 times its standard error.

From these results it is evident that treatment both by pneumonectomy and radiotherapy produced a significant prolongation of life.

The possibility of an association between age at onset and duration of life, in both treated and untreated cases, was investigated. No significant differences were found.

ANAPLASTIC AND SQUAMOUS-CELLED BRONCHIAL CARCINOMA.—The effect of treatment on the different histological types was also considered.

TABLE IV
EFFECT OF TREATMENT ON DURATION OF LIFE IN DIFFERENT HISTOLOGICAL TYPES

	Mean Duration in Months		
	Untreated	Radiotherapy	Pneumonectomy
Anaplastic ..	5.2 (134)*	11.0 (76)	11.1 (9)
Squamous-celled ..	10.8 (31)	17.8 (29)	30.1 (7)
Adenocarcinoma ..	7.9 (25)	31.8 (4)	7.0 (1)

* No. of cases in brackets.

It will be seen that there is a marked difference between the mean durations of untreated cases of anaplastic and squamous-celled carcinoma. These data have been subjected to the "t" test with the result that "t" = 4.86, $n=163$, and P is less than 0.001. Adenocarcinomas were too few for statistical treatment to be justified.

The difference in the duration of life between anaplastic and squamous-celled carcinomas treated by radiotherapy was also considered. Calculation gave " t "=3.05, n =103, and P less than 0.01. The number of cases treated by pneumonectomy was too small for statistical treatment.

The difference in age at onset between these two types of bronchogenic carcinoma has already been discussed. The evidence that cases of squamous-celled carcinoma have a later date of onset and a longer survival period, in both treated and untreated cases (all three differences being statistically significant), than have cases of the anaplastic type suggests that there are real grounds for regarding these histological types as separate entities. It is of interest to note that it was not possible to give a date of onset in 20 cases of squamous-celled carcinoma out of a total of 91 (22%) because of a long history of pulmonary symptoms. In cases of anaplastic carcinoma the unknown onset group was only 28 out of 267 (10.3%). This suggests the possibility of the squamous-celled type having its origin in chronic pulmonary irritation.

ATHEROSCLEROSIS

Wanscher, Clemmesen, and Nielsen (1951) have produced evidence of a negative correlation between carcinomas of all types and atherosclerosis. The present material has been graded for 115 cases in which the state of the arteries was discussed in detail, as far as possible in the manner laid down by these authors. Cases in which the descriptions were limited to such statements as "heart and vessels NAD" have not been included.

TABLE V
DEGREE OF ATHEROSCLEROSIS AS DEFINED BY
WANSCHER AND OTHERS (1951) IN CASES OF
BRONCHOGENIC CARCINOMA

Group	I	II	III	IV
Number of cases ..	89	20	6	0

Comparison of these data with those of Wanscher and others for non-cancerous cases of the same age groups gave $\chi^2=48.1$, $n=3$, P less than 0.001. Further statistical treatment was not considered to be justified, as the degree of atherosclerosis in the present series was based on the opinions of many different pathologists. Nevertheless, the evidence does provide confirmation of the findings of Wanscher and others and suggests that further investigation of this curious repulsion between carcinoma and atherosclerosis would be of considerable interest.

PERIPHERAL NEURITIS

Unexplained peripheral neuritis in association with bronchogenic carcinoma has been described by Lennox and Prichard (1950). Eleven such cases were found in the present series, an incidence of 2.2%, which agrees very well with 1.7% found by Lennox and Prichard. As these cases were very similar to those already published by the above observers details have not been given. Points of interest were that in eight of the cases the neuritis was the first symptom, in none of them was any evidence found of metastases in brain or cord, in none of them was there any evidence of enlarged glands or other causes of pressure on nerve trunks, four of the cases showed improvement of the peripheral neuritis while the carcinoma worsened. Unfortunately there were no histological investigations of the affected nerves.

A control series was made of 553 cases of proved neoplasm arising in tissues other than the bronchus. Cases of cerebral and spinal tumour were excluded because of the obvious difficulties in the diagnosis of peripheral neuritis had it been present. Similarly cases with metastases in the central nervous system were not used. Apart from these exclusions the cases were selected only for histological proof of neoplasia. Of this series of 553 cases none showed any signs or symptoms which could be interpreted as peripheral neuritis.

Comparison of this control series was made with the 501 cases of bronchial carcinoma using Yates's correction for continuity. With $n=1$, the value found for χ^2 was 11.38, from which P is less than 0.001. This provides further confirmation for the view that the association between bronchogenic carcinoma and peripheral neuritis is not merely coincidental, though it throws no fresh light on the cause.

PEPTIC ULCER

In 27 cases, 12.1% of those in which a necropsy was recorded, there was evidence of peptic ulceration. Ivy, Grossman, and Bachrach (1950) have estimated that the necropsy incidence of this condition in western Europe ranges from 5 to 10%. In view of the recent statements on the association between cigarette smoking and bronchogenic carcinoma (Daff, Doll, and Kennaway, 1951) and the long-recognized association between the same habit and peptic ulcer, a higher incidence of peptic ulcer in cases of bronchogenic carcinoma than in the general population would not be surprising. As at the majority of the necropsies it seems that no special search was made for peptic ulcer, stomach and duodenum being frequently described

as "NAD" or "no growth seen," it is very probable that these 27 cases are an under-estimate and do not represent the true incidence. In one case, very fully described, there were three active ulcers, two gastric and one duodenal. In another there were four active ulcers, three gastric and one duodenal. In neither of these cases could any histological evidence of malignancy of the ulcers be found.

SUMMARY

A series of 501 proved cases of bronchogenic carcinoma occurring in Service personnel has been described. Evidence has been presented on (1) prolongation of life by treatment, (2) differences between anaplastic and squamous-celled carcinomas, (3) the negative correlation with atherosclerosis, (4) the association with peripheral neuritis. The association with peptic ulcer has been discussed, and also the results of radiological and bronchoscopic investigations. No evidence of an association with eye and hair colour was found.

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