TABLE II.—*Viscometer Readings of Sputum from Patients in Group 2 Receiving Tablet B*

Patient No.	Viscometer Readings after Taking Tablet B				
	Initial Specimen	1st Week	2nd Week	3rd Week	4th Week
1	20	26	16	8	5
2	27	22	12	11	10
3	23	24	9	16	14
4	29	25	15	12	0
5	14	17	11	10	7
6	24	7	2	4	7
7	26	27	17	18	15
8	23	20	13	12	10
9	27	9	7	8	7
10	24	20	19	12	10
11	20	20	14	12	4
12	26	8	0	4	3
13	26	16	12	15	4
14	18	13	12	10	6
15	30	22	19	12	4
16	21	20	17	15	10
17	18	20	15	16	10
18	17	20	17	10	5
19	27	23	20	19	12
20	30	30	22	9	10
21	35	29	26	6	7

TABLE III.—*Mean Viscosity Readings During Trial Period, with Percentage Change in Parentheses (Negative Sign Indicates Reduction in Viscosity)*

Group	Viscosity Readings				
	Initial Specimen	1st Week	2nd Week	3rd Week	4th Week
1	23.6	21.9	22.8	20.3	22.1
	(0)	(-7.2%)	(-3.4%)	(-13.9%)	(-6.3%)
2	24.0	19.9	14.5	12.0	7.6
	(0)	(-17%)	(-39.5%)	(-50%)	(-68.3%)

Discussion

The results of this investigation show that a marked reduction in viscosity or liquefaction occurred in patients receiving oral alpha-chymotrypsin. Recognizing that purulent sputum is less viscous than mucoid sputum, a record was made of the incidence of purulent specimens in each group. The number of purulent samples in group 2 differed only slightly from that in group 1: 57 mucopurulent specimens in group 1 (60%), and 70 in group 2 (67%). From this observation one may deduce that the reduced viscosity in group 2 patients is due to the direct mucolytic effect of the enzyme. No side-effects were observed and most of the patients in both groups described improvement in their symptoms and felt the tablets assisted them in expectorating sputum.

Summary

A small-scale double-blind trial using oral alpha-chymotrypsin is described.

The results indicate that oral alpha-chymotrypsin causes liquefaction of sputum as denoted by a reduction in its viscosity.

The Armour Pharmaceutical Company Ltd. supplied the tablets of alpha-chymotrypsin (chymoral).

REFERENCES

- Billow, B. W. (1960). *Southw. med.*, **41**, 286.
 Limber, C. R., Reiser, H. G., Roettig, L. C., and Curtis, G. M. (1952). *J. Amer. med. Ass.*, **149**, 816.
 Parsons, D. J. (1958). *Clin. Med.*, **5**, 1491.
 Peck, M. E., and Levin, S. (1952). *J. thorac. Surg.*, **24**, 619.
 Roettig, L. C., Reiser, H. G., Habeeb, W., and Mark, L. (1952). *Dis. Chest*, **21**, 245.
 Taub, S. J. (1960). *Clin. Med.*, **7**, 2575.
 Teitel, L. H., Seigel, S. J., Tendler, J., Reiser, P., and Harris, S. B. (1960). *Industr. Med. Surg.*, **29**, 150.
 Unger, L., and Unger, A. H. (1953a). *J. Amer. med. Ass.*, **152**, 1109.
 — (1953b). *Ann. Allergy*, **11**, 494.
 Wilson, A. B. K., and Stevenson, F. H. (1957). *Lancet*, **2**, 820.
 Yates, J. L., and Goodrich, B. E. (1953). *Dis. Chest*, **24**, 320.

CONSERVATISM IN SURGICAL TREATMENT OF BRONCHIAL CARCINOMA

A REVIEW OF 826 PERSONAL OPERATIONS*

BY

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Every year we spend large sums on cancer research, and devoted workers labour to elucidate its problems. The object of this is presumably to prevent cancer; yet, within the limits of human fallibility, we know the cause of the commonest cancer afflicting the human body, and we do almost nothing about it. Why?

In 1950 cancer of the lung took second place to cancer of the breast. Now it exceeds it. In Great Britain it accounts for a quarter of all male deaths from cancer. It has increased 40 times in the past 30 years. It kills five times as many people as are killed annually on the roads, and we are beset by propaganda and punitive measures to enforce road safety, but hear little about the much greater menace of the two. Deaths from it increase by a steady 1,000 a year in the United Kingdom.

In the U.S.A. cancer of the lung caused 2,500 deaths in 1930, 18,000 in 1950, and over 30,000 in 1959. In New York State—where the statistics are particularly reliable—its incidence increased by 385% between 1930 and 1950, whereas that of other cancers fell.

A Major Health Problem

This pattern is confirmed in 16 other countries. The relationship between this appalling and increasing epidemic—which is surely one of the major international public health problems of the day—and cigarette smoking is not doubted by anyone who has troubled to read the formidable statistical, chemical, experimental, and pathological evidence now accumulated. It is surely by now familiar to everyone; but I will very briefly refer to some of the facts.

Seven years ago the American Cancer Society interviewed 200,000 men aged between 50 and 70. Since then 12,000 have died. Among the non-smokers there were 3.4 deaths per 100,000 from bronchial carcinoma; among cigarette smokers 78.6 deaths, with 28.9 deaths for pipe smokers and 11.4 among cigar smokers. These rates were directly related to the amount smoked: fewer than 10 a day, 51.4 per 100,000; 20 to 40, 143.9; and over 40, 217 per 100,000. The overall death-rate was 105% higher among smokers than among non-smokers, deaths from heart disease 115% higher and deaths from cancer of the lung 800% higher. A similar study of 200,000 subjects by the Veterans Administration yielded parallel results. In 1880 Americans smoked 16 cigarettes per head per annum; in 1959 the number was 3,700.

Doll and Hill's (1954, 1956) pioneer work—which among other things demonstrated that of every 11 men who smoke 20 cigarettes a day one will die of lung cancer—will certainly be familiar. In their survey of the smoking habits of British doctors they found a death

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rate of 7 per 100,000 among non-smokers and 125 per 100,000 in cigarette smokers, also directly related to the number smoked.

It has been objected that although Americans smoke more than the English their cancer rate is not so high. It is, however, only in the last decade that cigarette consumption in the U.S.A. has outstripped that in England. It is what happened 20 years ago that matters. We know that to-day in England the cancer rate is higher in industrial towns than in the country; but 20 years ago cigarette consumption in such towns was vastly greater than among the rural population. Social behaviour is also important. Hammond (1958) showed that Americans throw away as butts 40% of their cigarettes; the English discard only 25%. Carcinogens are concentrated as the cigarette burns shorter, and a small difference in butt length (though the difference here is not small) leads to a substantial difference in the carcinogen inhaled. In Scandinavia manufacturers are obliged to print a ring round cigarettes one-third of the way from the butt. Beyond this point it is dangerous to smoke.

Some 20 carcinogens (mostly polycyclic hydrocarbons) exist in cigarette tobacco, and their carcinogenicity is much increased at the high temperature (370–700° C.) of cigarette combustion. This is why cigars and pipes are less lethal. Wynder and others have consistently proved that tobacco smoke condensate is carcinogenic in at least two species of animal and several different strains of mice.

Auerbach *et al.* (1957), by serially sectioning over 400 lungs, found squamous metaplasia in 3.8% of those belonging to non-smokers and in over 90% of those who had smoked 10 or more a day. Actual islands of cells thought to be pre-malignant were not present in any non-smokers, but were in 4.3% of those smoking 20 a day and in 11.4% of those smoking 40 or more.

As Ochsner (1960) remarks, if one-tenth as much evidence existed that Brooklyn Bridge were unsafe, it would be closed to-morrow. He also says, "Smoking heavily is just as much a form of suicide as shooting oneself."

Why then do we who give so much lip-service to preventive medicine do so little to prevent this most horrible of diseases? Is it because we are ourselves addicted to a drug hedged round by emotive and social sanctions? Or is it the economic fact that the annual tobacco tax of £700,000,000 in England neatly pays for the National Health Service?

Early Recognition of Lung Cancer

So much for prevention. What about treatment? Of every three patients with lung cancer one is rejected out of hand as inoperable, one proves to be so after bronchoscopy or thoracotomy; and it is only in one-third that the affected lung can be resected.

The reason for this must in many instances be due to failure to recognize early manifestations of bronchial carcinoma. The average time elapsing between the first definite symptoms and operation is about eight months, three of them perhaps excusable, five not. The surgeon is thus presented with highly unfavourable material. In the past 12 years I have operated upon 826 patients with cancer of the lung. In only 570 of them was it possible to resect the growth, the other 256 operations being thoracotomies—a resectability rate of 70%. It

would of course be possible to reduce this proportion (and incidentally to improve both the survival and the mortality figures) by carefully selecting patients for surgery; but it has been my policy to explore all patients in whom no absolute contraindication to surgery was present; for surgery presents the only hope of cure, and even when cure is out of the question it is often of great palliative value. This should be remembered when one considers those many patients who lived less than two years: a great many of them lived more comfortably than they would have done without surgery.

Site and Age Affected

Of the 570 growths resected no less than 65% had already spread to visceral pleura, to regional glands, to blood-vessels, or to the chest wall. Indeed, it is remarkable that in no less than a quarter even of those patients surviving five years and more the growth was not originally confined to the lung, and in 8% of them the chest wall or mediastinum had been invaded.

Among my patients only one woman was affected to every 11 men—a smaller proportion than in most other series, and possibly accounted for by the nature of some of the hospitals in which I work.

The upper lobe of the left lung was the commonest site affected and 31% of growths were in this situation. Next were right upper and right lower lobes, with equal frequency (23%); left lower lobe, 18%; middle lobe 5%.

Of the men, 40% were aged between 51 and 60; 28% were 61 to 70 and 21% were 41 to 50. Thus about 90% lay in the decades from 41 to 70, the rest being distributed in roughly equal proportions from 21 to 30 and from 71 to 80. This spread above and below the norm was greater in the short-lived patients and almost absent among the longer survivors, obviously reflecting the greater malignancy of growths in young subjects and the naturally short expectation of life in the old.

It must also be observed that many long survivors are not to be expected after any operation (be it pneumonectomy or herniorrhaphy) performed on a group of subjects one-third of whom are already over 60 years of age. Furthermore, such patients in this country have an extremely high incidence of emphysema and chronic bronchitis.

Symptoms

In a man over 45, especially if he smokes cigarettes, alteration in the character of a cough, pain or discomfort in the chest, febrile chest illness—often diagnosed as "a touch of the 'flu'" or "a patch of bronchopneumonia"—haemoptysis, or sudden breathlessness are (in that order) the commonest early symptoms of lung cancer and demand a chest x-ray examination. Any abnormal shadow in such a film not resolving within a week or 10 days of antibiotic therapy must be assumed to be a cancer until disproved. Bronchoscopy is then mandatory. Not long ago a chest physician wrote to the medical press saying that of course everyone knew pain in the chest was a sign of inoperability in lung cancer and he never sent such cases to the surgeon. Pain (the consequence of pleural reaction to collapse) is in fact the second commonest early symptom. Less common but important symptoms are: (1) The onset of stiffness and pain in wrists, elbows, ankles, and knees, sometimes followed by effusions and clubbing of fingers and toes. This is hypertrophic pulmonary osteoarthropathy

and was a feature (usually the presenting one) in 13% of my patients and in 18% of those surviving three years or more. It is always completely relieved by removal of the growth or by vagotomy in inoperable cases. Bilateral peripheral joint pains of sudden onset in men of cancer age demand a chest x-ray examination. (2) Peripheral polyneuritis, usually of motor type (but sometimes of sensory or mixed types), like osteoarthropathy is always bilateral, but unlike it does not remit after pulmonary resection. It is particularly dangerous for the anaesthetist to employ curare in such patients, and mild myopathies easily go undiagnosed. The incidence of myopathy among my patients was 2.5%. (3) Emphysematous patients may present with spontaneous pneumothorax or ballooning lung cysts when a growth causes partial obstruction of a bronchus; and a persistent rhonchus—i.e., one unchanged by coughing—signifies organic bronchial narrowing.

It is not well recognized that by far the commonest variety of lung abscess is the malignant abscess. Most of these are breaking-down squamous carcinomas, and because they are well differentiated the operative prospects are good; but less often an abscess appears distal to an obstructing growth, or it is caused by aspiration of septic material from a growth into some other part of the lung. In each instance failure to carry out bronchoscopy means failure to diagnose the malignant genesis of the abscess.

Where bronchoscopy is negative but an abnormal x-ray opacity persists, exploratory thoracotomy is essential. No good doctor would sit and watch a lump in the belly, but it is surprising how many are prepared to sit and watch a "lump" in the chest x-ray film.

Apart from bronchoscopic findings or dissemination, the clinical signs of inoperability are hoarseness, dysphagia, distension of neck veins, Horner's syndrome (with or without brachial plexus pain), phrenic paralysis, and recurrent massive pleural effusion. Except where there is evidence of vertebral or rib-neck erosion, patients ought not to be rejected for surgery on radiological grounds alone.

In the absence of such contraindications I have operated upon all patients judged able to tolerate pulmonary resection, being prepared in many to perform palliative operations without hope of cure, in some excising the involved chest wall, in others removing pus-filled lobes or excising empyemas. The chief limiting factor in elderly heavy smokers is often respiratory insufficiency, but one's operative range has been greatly increased in recent years by the use of tracheostomy, which enables resection to be carried out in patients one would formerly have had to reject. Right pneumonectomy carries a much higher risk than left and is seldom possible or desirable in elderly subjects. In such people sleeve resections often permit the removal of otherwise inoperable growths.

Type of Operation

The operation performed has depended on the character of the growth and the respiratory capacity of the patient. It is futile to carry out extensive extirpations and kill the patient or render his life intolerable for want of breath. My own operations have ranged from intrapericardial pneumonectomies with clearance of the lymphatic bed (in as radical a manner as is

possible in the chest) through lobectomies and sleeve resections (when I judged lung preservation to be essential) to an occasional segmental removal of tiny peripheral growths. Of the 570 resections, 299 were pneumonectomies, 266 lobectomies, and 5 segmentectomies. This proportion of lobectomies to pneumonectomies is very much higher than in any other series known to me; but it would not appear from the three-year and five-year survival rates that this policy has in any way prejudiced my patients' prospects, and I am sure it has enabled them to live their allotted spans in much greater comfort and usefulness than would have been the case if they had all been subjected to doctrinaire radical pneumonectomies.

Authors	No. Explored	Resected	Mortality	Pneumonectomies	Lobes	5-Year Survival
C. Price Thomas (1952) (personal series)	—	214	—	—	—	21-15%
Holmes Sellors (1955) (personal series)	689	446	18%	364	82	21%
Gifford and Waddington (1957) (Liverpool)	714	464	—	—	—	28%
Burford <i>et al.</i> (1958) (St. Louis)	603	356	11%	280	74	22%
Churchill <i>et al.</i> (1958) (Massachusetts)	330	220	10%	127	93	28%
A. B. Taylor (1960) (United Birmingham Hospitals)	—	678	13.7%	—	—	21.7%
Jones <i>et al.</i> (1960) (Los Angeles)	513	284	5%	197	87	19.1%
Ochsner (1960) (New Orleans)	759	477	20%	—	—	10%
Flavell (1961) (personal series)	826	570	5.6%	299	266	32.6%

The youngest patient was a girl of 19; the oldest a clergyman of 82. There were 32 deaths among those resected while still in hospital (an operative mortality of 5.6%) and two cardiac deaths among the thoracotomies. The overall operative mortality was thus in the region of 4%; and almost all these deaths were of a cardio-pulmonary character. As might be expected the pneumonectomy death-rate was double that for lobectomy. There were eight cases of bronchopleural fistula—a fistula rate of 1.4%. Adenocarcinomas comprised almost exactly 10% of the whole, the proportion being about twice this among female patients. Only five alveolar-celled carcinomas were found. All the rest were classified in varying degrees as squamous or anaplastic. This is the 90% of bronchial cancers we believe attributable to carcinogens in cigarette smoke and therefore preventable.

Prognosis

A little under half the patients undergoing resections live for two years or more—that is, their lives are prolonged by surgery. Only 6% of thoracotomy patients live more than a year.

Of 273 patients who had undergone resections five years and more ago and on whom a complete follow-up is available, 107 lived less than one year, 44 for one year, 10 for two years, 13 for three years, 10 for four years, and 89 for five years or more. Of the last-mentioned group 23 have lived over seven years, 14 over eight years, 9 over nine years, and 10 over 10 years. All but 15 had squamous growths, and the degree of differentiation of these is, I think, the most important single factor in determining long survival.

Of patients undergoing resection for bronchial carcinoma, 41% may thus expect to survive for more than three years; and the five-year survival rate was 32.6%. Most patients doomed to a recurrence develop it within 12 months, and the great majority within two years. Patients who are well two years after operation are more likely to die of other natural causes than of metastasis. Of the five-year survivors five originally had adenocarcinomas, seven were anaplastic, and all the rest squamous.

Palliative Measures

Deep x-ray therapy is indicated as a palliative measure for (1) inoperable anaplastic growths, especially in patients under 45; (2) mediastinal obstruction; (3) Pancoast syndrome; (4) dysphagia; and (5) bone involvement by either primary or secondary growths. It is also of value in diminishing an exhausting cough or reducing unusually brisk or frequent haemoptyses. It is absolutely contraindicated if the growth has already disseminated, if the neoplasm is an adenocarcinoma, if sepsis is present in the lung, or if the patient is already short of breath because of emphysema.

A full course of therapeutic deep x-irradiation taxes a patient at least as much as does a pneumonectomy.

Intractable chest-wall pain is sometimes completely relieved by intercostal neurectomy; but when growth erodes the vertebral column or involves the brachial plexus cordotomy may be necessary. Infection is controlled by antibiotics, and pus in the pleural cavity is removed by aspiration. Only if a bronchopleural fistula is present should pus be drained surgically. Recurrent effusions are treated by aspiration, but occasionally are prevented by parietal pleurectomy.

My experience with chemotherapy has not been happy. Treatment with nitrogen mustard compounds is sometimes accompanied by diminution of the x-ray opacity and an improvement in general well-being and appetite. The former is generally due, I think, to the effect of penicillin and the latter to hydrocortisones both given with the cytotoxic drugs. On the other hand, damage to bone-marrow is always severe and sometimes uncontrollable.

Finally, may I make a plea for adequate drug palliation of the inoperable in the terminal stages of the disease? So much can be done for them and so little often is. The nausea associated with hepatic secondaries is mitigated by adequate dosage with promethazine theoclate ("avomine"), amiphenazole ("daptazole"), or pyridoxine; appetite and a sense of general well-being is often at least partially restored by cortisone derivatives (such as 20 mg. of prednisolone) daily; agitation and anxiety are quieted by chlorpromazine; codeine and aspirin are often as effective drugs as any for pain, but pethidine, methadone, or heroin should never unnecessarily be withheld. Above all, dosage must be adequate to achieve relief, and there should be no hesitation in administering heroin even in doses up to 2 gr. (0.13 g.) where distress is great.

As you have seen from the results given here, it is not often given to doctors to cure; but we should not forget that it is always possible to relieve.

Summary

A plea is made for the application of effective preventive measures against bronchial carcinoma, now a major problem in public health.

The symptoms and treatment of bronchial carcinoma are described.

A series of 826 operations for lung cancer, performed by one surgeon, is reviewed. Of these, 570 involved pulmonary resection.

The importance of lung preservation in reducing both immediate and long-term mortality after pulmonary resection is stressed. A total of 299 pneumonectomies and 266 lobectomies were performed, with a hospital mortality of 5.6% and a five-year survival rate of 32.6%.

REFERENCES

- Auerbach, O., Gere, J. B., Forman, J. B., Petrick, T. G., Smolin, H. T., Muehsam, G. E., Kassouny, D. Y., and Stout, A. P. (1957). *New Engl. J. Med.*, **256**, 97.
 Burford, T. H., Ferguson, T. B., and Spjut, H. J. (1958). *J. thorac. Surg.*, **36**, 316.
 Churchill, E. D., Sweet, R. H., Scannell, J. G., and Wilkins, E. W. (1958). *Ibid.*, **36**, 301.
 Doll, R., and Hill, A. B. (1954). *Brit. med. J.*, **1**, 1451.
 ——— (1956). *Ibid.*, **2**, 1071.
 Eastcott, D. F. (1956). *Lancet*, **1**, 37.
 Flavell, G. (1953). *Brit. J. Tuberc.*, **47**, 135.
 ——— (1956). *Lancet*, **1**, 260.
 Gifford, J. H., and Waddington, J. K. B. (1957). *Brit. med. J.*, **1**, 723.
 Hammond, E. C. (1958). *Ibid.*, **2**, 649.
 Jones, J. C., Robinson, J. L., Meyer, B. W., and Motley, H. L. (1960). *J. thorac. Surg.*, **39**, 144.
 Ochsner, A. (1960). *J. Amer. Geriat. Soc.*, **8**, 159.
 Price Thomas, C. (1952). *Ann. roy. Coll. Surg. Engl.*, **11**, 205.
 Sellors, T. H. (1955). *Brit. med. J.*, **1**, 445.
 Taylor, A. B. (1960). *Thorax*, **15**, 3.

UNEXPLAINED STEATORRHOEA IN THE SYNDROME OF HYPONATRAEMIA AND CARCINOMA OF BRONCHUS

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The occurrence of hyponatraemia in patients with bronchial carcinoma was first reported by Winkler and Crankshaw (1938). Two further cases were described by Schwartz *et al.* (1957); who also noted that the low serum sodium level was associated with a high urinary sodium excretion. They found that the only effective way of raising the serum sodium to normal was to restrict the fluid intake, and postulated that the hyponatraemia was due to a sustained inappropriate secretion of antidiuretic hormone (A.D.H.). Roberts (1959) described a similar case, and Schwartz *et al.* (1960) studied another patient with this syndrome who was treated with nitrogen mustard with partial correction of the electrolyte disturbance. Rees *et al.* (1960) described the case of a patient with bronchial carcinoma and a low serum sodium level in whom amino-aciduria and increased phosphate excretion was found although the kidneys were histologically normal at necropsy. They suggested that an acquired renal tubular defect was responsible both for these changes and for the hyponatraemia, rather than excess A.D.H. activity.

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