OHE Early Diagnosis Paper 6

The Early Diagnosis of Some Diseases of the Lung

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In July, 1965, the Office of Health Economics held a colloquium on Surveillance and Early Diagnosis in General Practice at Magdalen College, Oxford. It was apparent from the discussion at this meeting that General Practitioners believed that if they were to act effectively in this field, they had to have clear cut information on current screening methods and the impact of early diagnosis of disease on the long term health of the patient. As a result of this view the Advisory Committee set up by the Office of Health Economics came to the conclusion that the best method of furthering this issue was to ask experts in a number of relevant clinical fields to write short papers specifically for General Practitioners.
The Early Diagnosis of Some Diseases of the Lung is the sixth of these papers in the ensuing series. Other papers in the series are:

1. *The Early Diagnosis of Raised Arterial Blood Pressure*
2. *The Early Diagnosis of Visual Defects*
3. *The Early Diagnosis of Cancer of the Cervix*
4. *The Early Diagnosis of Depression*
5. *The Early Diagnosis of Ischaemic Heart Disease*

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CHRONIC bronchitis and emphysema account for 7 per cent of all deaths in men and 3 per cent in women between the ages of 45–64. Simple bronchitis can be diagnosed by asking about persistent expectoration, or more specifically by measuring the volume of sputum a specimen of which, if purulent, will also permit the diagnosis of mucopurulent bronchitis. Obstructive bronchitis can be diagnosed by spirometry or by measuring peak flow and forced expiry time. These cheap, accurate and simple tests can be carried out by the General Practitioner. After diagnosis the only method likely to arrest development of disability is to persuade subjects with early evidence of airways obstruction to stop smoking.

Bronchial carcinoma, which accounts for a steadily rising number of deaths, can be diagnosed by two methods—chest X-ray and sputum cytology. The former is more acceptable, quicker and cheaper. Treatment cannot be successful unless diagnosis precedes metastasis of the tumour. The fact that approximately 80 per cent of patients whose tumours are removed by surgery die with metastasis shows that this usually precedes development of radiologically diagnosable disease. The small proportion without metastases should be greater the earlier diagnosis is made but in a large scale controlled study six monthly X-rays did not reduce mortality. Periodic examinations might, however, be used to persuade cigarette smokers to stop and this would reduce mortality.

There has been a marked reduction in the prevalence of active pulmonary tuberculosis during the twentieth century. Chest radiography and sputum examination are again methods of diagnosis. Drugs now almost guarantee successful treatment at all stages of the disease providing organisms are sensitive and the patients co-operative. However, early diagnosis still reduces the probability of 'resistance' developing, residual lung damage, and the implementation of types of treatment causing social upheaval. Routine chest radiography should now be confined to those referred by General Practitioners who should pay particular attention to those who if infectious are particularly dangerous, and to immigrants.

1. CHRONIC BRONCHITIS AND EMPHYSEMA

IN the United Kingdom chronic bronchitis and emphysema are responsible for 7 per cent of all deaths in men and 3 per cent in women between the ages of 45–64. Mortality has recently been declining slowly in women but increasing in men, especially over the age of 50. During the past twenty years epidemiological, clinical and pathological studies have done much to clarify the confusion of terminology which formerly bedevilled understanding of these conditions. Three manifestations of chronic bronchitis are now recognised[1]: simple chronic bronchitis characterised by mucoid expectoration; mucopurulent chronic bronchitis in which the sputum is intermittently or continually mucopurulent owing to active bronchial infection; and obstructive chronic bronchitis in which, in addition to expectoration, there is narrowing of the airways causing increased resistance to airflow. Simple bronchitis does not cause disability and is usually discounted as a smoker's cough, though it increases liability to recurrent bronchial infection. Mucopurulent bronchitis is an important cause of lost working time but it is obstructive bronchitis which eventually causes persistent disabling breathlessness and which may end in death from respiratory or cardiac failure. Pulmonary emphysema is now defined in morbid anatomical terms as abnormal enlargement of respiratory air spaces in the lung with destructive changes in their walls[2]. Pathological studies have shown that although emphysema and chronic bronchitis are commonly associated[3] either emphysema or obstructive chronic bronchitis can cause fatal disability in the absence of the other[4].

Diagnostic Methods

Simple bronchitis can be diagnosed by asking about regular expectoration. This can be done in a standardised manner by using the six questions on cough and phlegm proposed by the MRC in their standardised questionnaire on respiratory symptoms*[5] which permits a rough grading of severity according to whether phlegm is produced only on rising or throughout the day. Quantitative diagnosis is best made by asking for a specimen of sputum and measuring the volume brought up either during the first hour or throughout the day[6 7]. Such a specimen will also permit a diagnosis of mucopurulent bronchitis when the sputum is discoloured by pus. Recurrent mucopurulent bronchitis in the interval between attacks of infection may be diagnosed by asking about 'chest illnesses' (question 21 in MRC questionnaire). Questions about the colour of phlegm in past illnesses have not been found reliable[8].

Airflow obstruction can be diagnosed with considerable accuracy and ease by means of a spirometer which records both the forced expiratory volume in one second (FEV 1·0) and the total expired volume or vital capacity (VC) either on a graph or a

* Obtainable with instructions from W. Homan & Sons, Dawlish, Devonshire.

dial.* If expectoration is delayed by airways narrowing the proportion of air expired in the first second (FEV/VC) will be less than 65 per cent. A simple and cheaper instrument is the Wright Peak Flow Meter† which measures the degree of impairment of ventilatory capacity. To show whether any such impairment is due to air flow obstruction rather than restriction of lung expansion (by such things as skeletal disease, pulmonary fibrosis or loss of functioning lung) the simple test of timing the duration of a forced expiration may be used[9]. In normal subjects forced expiration is completed in less than six seconds: prolongation beyond this is evidence of airflow obstruction. Both these methods are capable of detecting reduction of ventilatory capacity due to airway narrowing long before it is severe enough to cause disability.

The functional consequences of emphysema cannot be distinguished from those of obstructive chronic bronchitis until the condition is severe. A minor degree of airways obstruction may thus be due to either emphysema or obstructive bronchitis; in advanced cases, however, chest X-ray and detailed test of lung function may enable the distinction to be made[4]. Conventional examination of the chest has little to contribute. The unreliability of physical signs of emphysema even at the most advanced stage has been reported by Fletcher[10]. In early bronchitis there are usually no abnormal signs, occasional rhonchi or sibili may be heard in acute bronchitis and asthma and are quite non-specific.

The Value of Early Diagnosis

To establish the value of early diagnosis of chronic bronchitis or emphysema it is necessary to understand the sequence of events by which disability develops. Prevalence surveys have shown a close association between sputum volume (simple chronic bronchitis), recurrent chest illnesses (mucopurulent bronchitis) and impairment of ventilatory capacity (obstructive chronic bronchitis) and this has suggested that mucous hypersecretion in the bronchi encourages infection which damages the bronchi and lungs causing bronchial narrowing and emphysema[11]. This hypothesis has in turn led to the suggestion that preventive and therapeutic measures applied to cases of simple or mucopurulent bronchitis without severe impairment of ventilatory capacity might delay or prevent the progression of airways obstruction and thus prevent disability. Recent studies have, however, thrown doubt on the hypothesis and thus on the value of measures based on it.

Between 1959 and 1963 a double blind trial of chemotherapy and chemoprophylaxis was carried out on 373 men with recurrent mucopurulent bronchitis but with FEV levels above 1·5 litres[5]. The effect on the number and duration of bronchitic exacer-

* Convenient spirometers are the Vitalograph (Garthur Ltd., Maids Morton House, Old Buckington, Bucks) which records on a graph or the McDermott Dry Spirometer (Graw Electronic Industries Ltd., Pontyrhyl, Bridgend, Glamorgan) which records on a dial.

† Airmed Ltd., 16 Wigmore Street, London W1

bations was indefinite. On the other hand there was no difference in the rate of decline of FEV or on the volume or purulence of sputum specimens between the treated and control patients. More recently, sputum volume, frequency of chest illnesses and rate of change of FEV, have been studied in some 900 working men over a five-year period[12]. FEV declined no faster in those with than in those without simple bronchitis, nor in those with more than in those with fewer chest illnesses. The most significant factors affecting rate of decline were a reduction in the ratio FEV/VC (the lower the level the faster the rate of decline) and cigarette smoking (faster decline in heavier smokers). This suggests that cigarette smokers who already have evidence of even mild airways obstruction are at special risk of developing disabling chronic bronchitis.

But if future casualties from chronic bronchitis or emphysema could be detected in this way it would be valueless unless the progression of the disease can be arrested at an early stage. Chemotherapy is of undoubted benefit in established cases but there is no evidence that it delays progression in the early stages[5]. Bronchodilator drugs, although often of considerable value in alleviating disability in clinical cases of obstructive bronchitis, are unlikely to have prophylactic value. The obvious measure would be avoidance of cigarette smoking. In the later stages of disease, it has been found that those who are most willing to stop smoking tend to be those who are progressing most unfavourably and thus there is no apparent benefit from stopping smoking[13]. In the study of working men the rate of change of FEV in the small number of men who stopped smoking was not on average significantly different from that of those who continued to smoke, but there was a wide variety of patterns and some men showed some increase of FEV after stopping. This occasional benefit has also been demonstrated by Gregg[14] and most clinicians have witnessed similar benefit in individual cases. This method of prophylaxis has the drawback of being difficult to apply. Even after vigorous explanation of the dangers of the habit all too few smokers of cigarettes are able or willing to dispense with them.

Conclusions

Detection of early cases of chronic bronchitis is easy and cheap and can be done by acceptable means. The general practitioner is in a favourable position to carry out this detection and to attempt to dissuade those affected from continuing to injure their lungs by cigarette smoking. Demonstration that lung function is already adversely affected provides evidence that deterioration is likely to occur and this information may be sufficient to persuade men to stop smoking. If further follow-up confirms that there has been a deterioration, the advice may be given with even greater emphasis. Even if the progression of bronchitis were unaffected the subsequent mortality in these men from lung cancer would almost certainly be reduced.

There is a wide field open for further study especially in relation to the effects of changing to smoking forms of tobacco other than those used in modern cigarettes.

2. BRONCHIAL CARCINOMA

The two most striking features of the epidemiology of bronchial carcinoma are the steadily rising death rate and the low survival rate after diagnosis. In this situation some improvement by means of earlier diagnosis is most desirable.

Diagnostic Methods

There are two possible methods of diagnosis—chest X-ray and sputum cytology. The chest X-ray, as in the case of tuberculosis, is acceptable, quick, reasonably reproducible and relatively cheap: the number of false negatives can be reduced by multiple readings; false positives in those with definite shadows due to innocent lesions may lead to unnecessary thoracotomy. The sputum cytology is less acceptable, slower and more expensive. The two methods have never been compared on randomised unselected groups. The best study is that of Lilienfeld et al[15] whose results suggest that the two techniques are similar from the point of view of sensitivity, specificity and the number of false positives. At present the X-ray seems the only practical possibility for large numbers.

Value of Early Diagnosis

Treatment cannot be successful unless diagnosis precedes metastasis of the tumour. It is probable that many tumours start growing from five to twenty years before they become radiologically apparent[16] but it is not known how early in this long history metastasis may occur. In some cases the first symptom is due to a metastasis from a small primary growth which may not be visible in a chest X-ray. The fact that approximately 80 per cent of patients whose tumours are removed by surgery die with metastasis shows that this usually precedes development of radiologically diagnosable disease. Nevertheless the small proportion without metastasis is presumably greater when the diagnosis is made earlier. Unfortunately, Dunn[17] has calculated that the average time interval from the earliest time at which the disease can be identified to the time it becomes clinically manifest is about seven months, which means that any diagnostic measure must be applied several times every year if it is to give any important advantage. A similar calculation for carcinoma of the breast gives a figure of four years.

The large literature relating the presence and duration of symptoms to prognosis[18, 19, 20, 21] is not very relevant: those with fewer symptoms tend to have better resection and survival rates, but the relationship is not as close as one would expect since metastasis are not the chief cause of symptoms.

There are many comparisons between the outcome of such carcinomas diagnosed by mass radiography and those diagnosed by 'static' units and those diagnosed in hospital. The literature has been reviewed by Davies[22]. The findings of Brett[23], Cuthbert,[24] Nash et al[25] and Posner et al[26] are typical of many others in showing a

higher resection rate and a higher two and/or five year survival rate amongst those resected after diagnosis by mass radiography compared with those diagnosed clinically. This seems promising but is not conclusive since the cases are not derived from comparable populations. Studies of populations which have been X-rayed at regular intervals affords better, though not hard evidence. Boucot et al[27] reported a survey of 6137 men who were X-rayed every six months for four years. Twenty-six carcinomas were discovered which were not visible at the time of the first survey. Unfortunately, the outcome in these twenty-six cases did not suggest a survival rate appreciably better than those diagnosed in the usual ways. The findings of Duncan and Howell[28] reporting on the results of regular X-raying of the employees of the Atomic Energy Authority are more encouraging. 141 carcinomas were diagnosed and the five year survival rate was 18 per cent which is at least three times better than most hospital control series but in the absence of a proper control group the validity of the comparison is uncertain. The findings of Nash et al[29] fall into the same group.

The only investigation in the literature designed to produce hard evidence about the value of repeating chest X-rays is that of Brett[30]. 119 factories were randomly divided into two groups. The men in one group (25 311) were offered a chest X-ray initially and again in three years' time. The men in the other group (29 723) were offered six monthly chest X-rays during the three year period. Just over 60 per cent of the men in each group were X-rayed at the end of three years. Mortality rates from bronchial carcinoma were originally calculated as 0·65 per 1000 per annum in the test group and 0·6 per 1000 in the control group. A later publication by Brett[31] gave figures of 0·7 in the test and 0·8 in the control group after an extended follow-up. There is therefore no evidence that the six monthly X-rays produced a significant difference in mortality.

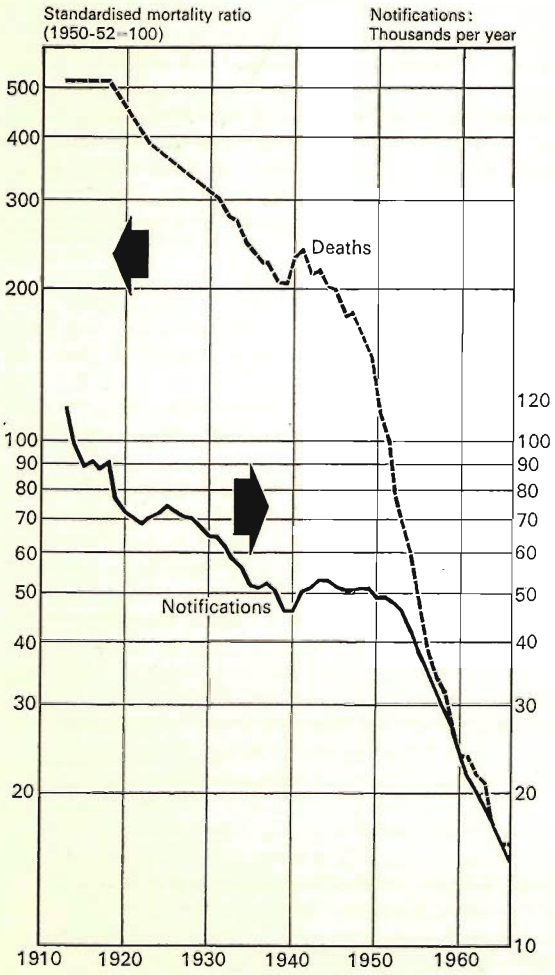
Several surveys have demonstrated a higher incidence and/or mortality from bronchial carcinoma in smokers who have a persistent cough than in those who deny it[32]. Although it seems probable that this association is often due to the cough being caused by the carcinoma rather than by some premalignant condition, it is desirable to see whether regular sputum examination of smokers who have a productive cough may reveal abnormalities which could either be reversed by cessation of smoking or could be due to carcinoma which has not yet metastasised and whose presence might be confirmed by further sputum studies, bronchoscopy or radiography. But this is a matter for future study not for present policy.

Conclusion

Until there has been a marked improvement in the results of treatment of bronchial carcinoma there is no case to be made out for regular routine chest X-rays or sputum examination in the prevention or control of the disease. If, however, routine chest surveys were carried out on cigarette smokers they might be used to remind these

Figure 1

Notification (1913 to 1966) and Standardised Mortality Ratio (1911 to 1966), Tuberculosis, England and Wales.



Source:
'On the State of the Public Health', Ministry of Health, various years, 2nd Registrar General's Statistical Review, England and Wales, 1966.

people of the risks that they continue to run, and of the rapidly declining risk that follows stopping smoking[33].

3. PULMONARY TUBERCULOSIS

The most important feature of the epidemiology of pulmonary tuberculosis—in respect of early diagnosis—is the speed with which it has changed and still is changing in the United Kingdom and elsewhere. The magnitude of the change can be expressed in many ways. In England and Wales the mortality rate fell at an average rate of 3 per cent per annum from 1900 until 1948 since when the rate of fall has been about 15 per cent. The number of new cases was 50 000 in 1952—but only 20 000 in 1962. Such changes have been associated with a marked reduction in the prevalence of active tuberculosis (*Fig. 1*).

Diagnostic Methods

Chest radiography has been for many years, and still remains, the main method of achieving early diagnosis of pulmonary tuberculosis. Little use was made of it on a mass scale until the photo fluorographic technique was introduced by d'Abreu in 1939. This was followed by rapid technical development and detailed studies of the effect on diagnosis of film size and number of readers, and soon a cheap reproducible method, with which skilled observers had acceptably low false negative and false positive rates, was available for early diagnosis.

Sputum examination (microscopy and/or culture) has become popular in developing countries since it gives fewer false positive than chest radiography, requires less expensive equipment, is more transportable, and the technique of microscopy is easier to teach to the uneducated than that of reading X-rays. In 'developed' countries these advantages are less important and since sputum collection might be less acceptable than a chest X-ray and since microscopy alone would certainly miss many early cases it has not been widely used.

Tuberculin testing has been little used for screening purposes. It is a test for infection rather than disease and is inconvenient as a screening test since the test has to be read two days after its application. The readings are not very reproducible and interpretation is made difficult by non-specific sensitive or BCG inoculation.

Value of Early Diagnosis

At first chemotherapy was of limited potency and its value was enhanced by early diagnosis. It was during this period that mass radiography had its greatest value. Later the situation changed. A long series of chemotherapeutic trials have evolved drug combinations which almost guarantee successful treatment for all stages of the disease, if the organisms are sensitive and the patients co-operative. This has markedly reduced the value of earlier diagnosis although it still leads to a decreased probability

Table A

Year	Active Tb. Cases		Cost per active case
	No.	% of those examined	
1944	262	5·7	—
1950	362	2·9	—
1960	284	1·5	£195
1966	108	0·6	£608

Figures based on the Welsh Mass Radiography Series, supplied by Dr T. Frances Jarman.

of 'resistance' developing, of residual lung damage and of the treatment causing social upheaval.

At the same time the improvement in chemotherapy was associated with a marked fall in the yield of cases from MMR surveys. Table A summarises the yield and cost per case in the Welsh Region since 1944.

The populations now required to measure the effect of mass X-rays on tuberculosis mortality in this country would be impossibly large. Attempts have been made to demonstrate the effects of mass X-ray campaigns on notification rates[34] [35]. The small or negligible effects obtained were interpreted as showing that most new notifications were due to the breakdown of old disease rather than to new infections.

In this changing situation there are two possibilities for mass radiography. First, that mass radiography should be stopped when it costs more to diagnose and treat a case with the help of MMR than without it. The latter cost could only be measured accurately by unethical experiments, comparing the slight differences in cost of treating cases diagnosed early and at clinically manifest stages, adding to the latter the cost of treatment and loss of working efficiency of secondary cases due to leaving infectious cases unisolated though these would rarely occur. Allowance would also have to be made for early cases which would have healed without treatment. No accurate balance sheet can be drawn up but the average cost of treating a case (including three months in hospital) is about £350 and loss of productivity at £20 for twenty-six weeks would be £520. This is not much more than the cost of diagnosing (but not treating) a case a little earlier by MMR (£600). An additional point against mass radiography is that in fact only a relatively small proportion of all notified cases have been diagnosed in this way. In the Welsh Region this has rarely reached 20 per cent.

Second, that in order to increase the yield of positives and thus decrease the cost per case diagnosed, mass radiography should be confined to groups with high prevalence rates of pulmonary tuberculosis—elderly males, alcoholics, vagrants, etc—but

none of these are easy to drive into the MMR fold. The only really successful attempts at selection of high risk subjects are referrals by general practitioners to 'static' units. The practitioner does his selection on any basis he desires but the results is a yield of about 1 per cent and a lower cost—about £70—per case diagnosed. This cost will of course rise quickly over the next few years, and the same question will rise again.

Two groups need special attention. In some occupations infectious cases are particularly likely to infect other people. These include medicine, dentistry, schoolteaching, food handling and serving, hairdressing and possibly prostitution. Such people require regular examinations. The other group are the Asian immigrants who have a significantly higher tuberculous notification rate than United Kingdom residents. The highest rate is among Pakistanis. It would seem logical to make the diagnosis by X-raying them before they leave their country.

Sputum examination is not a method of early diagnosis except perhaps in diseases like progressive massive fibrosis, where the X-rays are already abnormal before tuberculosis develops. The presence of tubercle bacilli in the sputum is an indication for anti-tuberculous therapy.

Tuberculin testing in spite of its disadvantages as a screening procedure may be of real value if a policy of eradication rather than control is adopted as is suggested by the nine-year trial of prophylactic isoniazid in school children in San Francisco[36]. Isoniazid was given to 2910 children with a reaction of 5 mm. or more to five units of PPD and whose parents agreed, and the results compared with 1192 children reacting similarly whose parents did not give permission. The rate of developing tuberculous lesions was 0·34 per 1000 in the treated group with 20·9 per 1000 in the untreated. Although the trial was not randomised, the method is clearly worth further study.

Conclusions

A chest X-ray still appears to be the best method of early diagnosis but its value is decreasing to a point where its general use may cost more than it saves. Routine chest radiography should now be confined to those referred from general practitioners, who could pay more attention to those, who, if infectious, are particularly dangerous and to immigrants. Tuberculin testing to make an early diagnosis of infection in childhood combined with isoniazid chemoprophylaxis might be considered if a policy of eradication is adopted.

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