TABLE IV.—Correlation Between Serum Albumin, Ascites, and Xylose Excretion in Cirrhosis

Case No.	Albumin (g.)	Ascites	Xylose (g.)
1	2.6	+	3.25
2	2.4	+	3.8
3	3.9	—	9.0
4	3.4	—	9.6
5	1.7	—	6.3
6	2.2	+	4.6
7	3.4	—	7.5
8	3.3	+	6.4
9	1.7	+	5.5
10	2.0	+	3.5
11	2.3	+	4.3
12	4.1	—	5.7
13	2.4	+	2.4
14	4.1	—	3.4

tion of D-xylose in cirrhosis, but the above data may suggest that oedema of the small intestine secondary to chronic liver disease may be an important factor. This speculation has prompted us to initiate a study of other oedema states, such as are found in congestive heart failure, and their effects on the function of the small intestine.

The group of seven patients with malabsorptive syndrome support what has already been emphasized in previous publications. They demonstrate the utility of this test and its pronounced alteration in disease of the small intestine. D-Xylose, being a pentose normally absent in the human and relatively unaffected by various metabolic processes, is a better absorptive test of carbohydrates than is a ubiquitous and metabolically active substance such as glucose.

Summary

The D-xylose excretion test has been widely used in the study of the absorption of carbohydrates by the small intestine. This pentose is normally absent from the human and is relatively unaffected by the various metabolic processes of the body. A decrease in D-xylose absorption was noted in most of the diseases of the small intestine reported in the literature. These include sprue, intestinal diverticulosis and fistulae, tumours of the small intestine, and ischaemia that follows embolism of the superior mesenteric artery. The present study deals with the state and mechanism of absorption of carbohydrates in two unrelated conditions, enteric fever and cirrhosis of the liver, utilizing the D-xylose excretion test.

Enteric fevers may be regarded as diseases of the small intestine because of the particular involvement of that organ with inflammation, lymphatic swelling, and hyperplasia.

Thirteen cases with proved enteric fever were studied. There was a significant reduction of absorption of D-xylose in this group. Nine out of the 13 (69%) had urinary levels lower than the lowest recorded in our control group.

Fourteen patients with cirrhosis of the liver were studied. There was also a marked reduction of D-xylose absorption in this group. Nine out of 14 (64%) had D-xylose excretion less than the lowest recorded in the normals. Furthermore, there was a correlation between the serum albumin levels and the degree of absorption of D-xylose which suggested to us that, among other factors, oedema of the small intestine secondary to chronic liver diseases may influence intestinal absorption.

A third group of seven patients with malabsorptive syndrome was studied. The marked decrease in absorption of D-xylose in this group supports what has already been emphasized in previous publications.

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THE FUNCTIONAL EFFECT OF PULMONARY IRRADIATION*

BY

MAURICE SUTTON, F.R.C.Sed., F.F.R., D.M.R.T.

Medical Research Council, Radiotherapeutic Research Unit, Hammersmith Hospital, London

When the lungs are irradiated by x rays to any degree an inflammatory reaction results which may lead to fibrosis (Whitfield, *et al.*, 1954). A number of workers have studied the effect of post-radiation pulmonary fibrosis on lung function (Leach, 1943; Baldwin, *et al.*, 1949). Little is known, however, about pulmonary function during the actual irradiation and in the period prior to the development of pulmonary fibrosis. It was decided to perform serial lung-function studies on patients receiving pulmonary irradiation. Accordingly a number of radiotherapy patients who were having their lungs irradiated either directly because of carcinoma of the bronchus or indirectly in cases of carcinoma of the breast were subjected to lung-function studies before, during, and after treatment.

The patients under study received either x-irradiation from the conventional 240-kV deep x-ray machines or supervoltage radiation from the 8-MeV linear accelerator. An attempt was made to show the difference in functional effect between the two forms of radiation.

Groups of Patients Studied

Carcinoma of bronchus treated radically on the 8-MeV linear accelerator.—These cases all had histologically proved tumours. The squamous-celled tumours were treated by a technique employing two non-opposed fields with wedges, and a tumour dose of 4,500 rads was given in one month. The anaplastic tumours were treated with two opposed fields without wedges, and a tumour dose of 4,000 rads was given in one month. The size of the fields and thus the volume of the lung irradiated depended upon the size of the tumour,

*This investigation was carried out during the tenure of a British Medical Association Research Scholarship.

but in both techniques the integral dose was of the order of 17 megagram rads (equivalent to 20 megagram roentgens).

2. *Carcinoma of bronchus treated radically on the conventional 240-kV deep x-ray machines.*—In these cases the diagnosis had been made on radiological and bronchoscopic appearances, though it had not been established by biopsy. A nine-field technique was employed to cover the tumour adequately. A tumour dose of 4,500 roentgens (r) was given in one month. The integral dose was of the order of 35 megagram roentgens.

3. *Carcinoma of breast treated by radical mastectomy and post-operative radiotherapy to the supraclavicular and internal mammary glands of the same side.*—This was done by a three-field technique using two opposed fields to the supraclavicular area and a straight-on field covering the internal mammary chain. A skin dose of 3,600 r in four weeks was given.

4. *Carcinoma of breast treated by simple mastectomy and post-operative radiotherapy to the breast area and adjoining lymph drainage areas.*—For this a six-field technique was employed. The breast area was treated by two tangential and two oblique fields. The supraclavicular and axillary glands were treated by two opposed fields. A skin dose of 3,600 r in four weeks was given.

In both of the techniques for treating carcinoma of breast the apex of the lungs receives about 4,000 r. By the use of the tangential technique only a small part of lung directly beneath the breast area is irradiated directly. A larger part of the underlying lung receives some scattered radiation. Conventional 240-kV deep x-ray machines were used for this treatment.

Only those patients who were capable of performing the lung-function tests satisfactorily were accepted for the experiment. A number with carcinoma of the bronchus were unable to perform the exercise test because of their functional disability and these were excluded. A small number of patients in each group were unable to co-operate in the performance of the tests and were also excluded.

Method of Study

Three measurements were made at each attendance.

1. Vital capacity (V.C.).

2. *Indirect maximum breathing capacity (Ind. M.B.C.).*—This was measured by multiplying the forced expiratory volume over 0.75 second (F.E.V._{0.75}) by 40 (see Gandevia and Hugh-Jones (1957) for terminology). A simple spirometer of the type described by Bernstein *et al.* (1952) was employed. The mean of three measurements was accepted and the volume corrected to B.T.P.S. and expressed in litres.

3. *Standardized ventilation (S.V.).*—This was determined from a standard exercise-tolerance test of the type described by Hugh-Jones (1952). Each patient was asked to perform a standard amount of exercise (350 kg. m. per minute for five minutes). The volume, in litres, was corrected to B.T.P.S.

The S.V. was chosen as a measure of the ventilatory cost of the exercise, as it is valid even when the subjects could not complete the five minutes of exercise. Occasionally it was necessary to accept only two minutes of exercise. With very short periods of exercise (under two minutes), however, it is not always satisfactory, and this was a cause of rejection of some of the patients suffering from carcinoma of bronchus.

These lung-function studies were carried out twice before radiotherapy had begun and the mean of these results was noted. They were performed weekly during treatment and at monthly intervals thereafter. In the breast cases the first lung-function test was carried out after the mastectomy wound had healed.

Results

There were 146 patients with histologically proved carcinoma of the bronchus who had a radical course of supervoltage radiotherapy on the 8-MeV linear accelerator and who were subjected to serial lung-function studies. Of these, 42 were alive at the end of 12 months—28 had had serial lung-function studies at monthly intervals; the physical condition of the other 14 rendered them incapable of performing satisfactory lung-function tests.

Fig. 1 shows the mean results of all the 28 patients, expressed as a percentage of the pretreatment result. It is true to say that these are the results of a highly

FIG. 1.—Lung-function studies in patients suffering from carcinoma of bronchus treated on 8-MeV linear accelerator. All values expressed as percentages of initial readings.

selected group—namely, those patients who not only survived one year but were capable of carrying out relatively strenuous lung-function tests at the end of this period. However, a study of the performance of these patients gives some idea of the effect of pulmonary irradiation on lung function. One cannot completely exclude the effect that the carcinoma is having on lung function, but it is probably less than the effect it would have in a patient who dies within a few months of the treatment. In such a patient the tumour has probably hardly responded at all to treatment and the change in lung function is probably attributable directly to the growth of the tumour. In a patient who survives for over a year the growth of the tumour has probably been retarded by treatment and the lung-function studies may represent to a large extent the direct results of pulmonary irradiation. This is supported by the fact that all 28 patients referred to in Fig. 1 showed some radiological evidence of pulmonary fibrosis, such as

FIG. 2.—Lung-function studies in patients suffering from carcinoma of bronchus treated at 240-kV. All values expressed as percentages of initial readings.

mediastinal shift, elevation or peaking of the diaphragm, retraction of the ribs, or bands of fibrosis.

There were 10 patients with carcinoma of the bronchus who received a radical course of radiotherapy on the conventional 240-kV deep x-ray machines and who were subjected to serial lung-function studies. All but two died between the fifth and twelfth months after treatment.

Fig. 2 shows the results of the lung-function studies on these patients up to the fifth month, expressed as a mean percentage of the pretreatment results. It was decided not to graph the results for a longer period as it would be difficult to interpret. Thus a patient in poor physical condition would depress the mean results of the lung-function test and when he died the mean would be artificially improved, whereas the lung-function tests of the other patients might have been quite constant during this entire period.

From a study of Figs. 1 and 2 certain general trends emerge. In patients having their lungs irradiated for carcinoma of the bronchus there is usually an improvement in lung function during treatment. This might be due to familiarity with the procedure or it might be due to relief of bronchial obstruction with increase in the volume of functioning airway. As Ind. M.B.C. tends to improve to a slightly greater extent than V.C. it is probable that the latter explanation is correct. All of these patients had centrally situated lesions, and relief of bronchial obstruction due to these would be expected to have greater effect than shrinkage of peripherally situated tumours.

FIG. 3.—Lung-function studies in patients suffering from carcinoma of breast treated by post-operative radiotherapy to gland areas only. All values expressed as percentages of initial readings.

FIG. 4.—Lung-function studies in patients suffering from carcinoma of breast treated by post-operative radiotherapy to chest wall and gland areas. All values expressed as percentages of initial readings.

At about the third week of treatment on the 240-kV deep x-ray machines the patients tend to show a falling-off in lung function. This coincides with the skin reaction and general malaise that they may suffer. With a fairly severe skin reaction it may be painful to take a deep breath. Those treated on the 8-MeV linear accelerator do not develop a skin reaction, they have less general discomfort, and as a reflection of this they continue to improve from the functional point of view. In both these groups there tends to be continued improvement for a variable time after treatment, followed by a period in which lung function remains stationary. The death of the patient is preceded by a sudden deterioration in lung function beginning about two months before the actual decease. Lung function closely reflects clinical impression in all these patients.

At the end of one year in those patients treated on the 8-MeV linear accelerator the mean V.C. and Ind. M.B.C. had decreased respectively to 76% and 96% of the pretreatment readings. This does not represent a severe functional disability, which is especially significant in view of the fact that all these patients showed some evidence of post-irradiation pulmonary fibrosis.

Fig. 3 demonstrates the results of serial lung-function studies in eight cases of carcinoma of the breast treated by post-operative irradiation of the supraclavicular and internal mammary lymph node areas.

Fig. 4 shows the results of the serial lung-function tests in eight cases of carcinoma of the breast treated by post-operative irradiation of the breast area as well as the internal mammary and supraclavicular lymph node areas.

From a study of Figs. 3 and 4 there appears to be little difference in functional effect between the two groups. There was no severe deterioration in lung function as described by Leach (1943) and Baldwin *et al.* (1949). This is almost certainly due to changed techniques in radiotherapy. In both groups there is a slight improvement in lung function during the first half of treatment. This is probably due to familiarity with the procedure. In the second half of treatment there tends to be a slight falling off due probably to the fairly severe reaction and general discomfort that they often have. Lung function remains fairly constant after treatment.

Discussion

Groover *et al.* (1922) first drew attention to the syndrome of lung damage as a result of exposure to ionizing radiation. The anatomical and histological appearances of lung damaged by radiation have been recorded both in the laboratory animal (Lüdin and Werthemann, 1930; Engelstad, 1934; Warren and Gates, 1940; Tullis, 1949) and in man (Hines, 1922; Groover, *et al.*, 1922; Evans and Leucutia, 1925; McIntosh, 1934; McIntosh and Spitz, 1939; Schairer and Krombach, 1939).

The early changes are congestion and oedema of the alveolar walls and an increased production of bronchial mucus. Whitfield *et al.* (1954) describe the necropsy findings in a patient suffering from Hodgkin's disease, who died three months after irradiation of the lungs. The dominant change was reduction in the total alveolar space, associated with thickening and fibrosis of the alveolar walls, thickening of the capillary walls, and swelling of the alveolar lining cells. Within the alveoli and alveolar ducts hyaline membrane had formed.

The early changes are often followed, after a variable period, by the development of pulmonary fibrosis which may be clinically and radiologically obvious. Ross (1956) believes that 96% of patients treated by conventional deep x-ray therapy for carcinoma of the breast develop some degree of post-radiation fibrosis. In his series the first radiographic abnormality was observed in almost all cases between two and six months after the end of treatment. The process then continued for about 18 to 24 months, but occasionally fresh scarring appeared after a longer period.

A number of workers have carried out lung-function studies on patients suffering from severe post-radiation pulmonary fibrosis. Leach (1943) found the V.C. was lowered to as much as 60% of the predicted value. These results referred to cases of carcinoma of the breast treated by techniques which caused severe lung damage due to direct irradiation of the underlying lung. Modern radiotherapy employs glancing fields which do not irradiate the lungs to the same extent. Another factor that probably contributed to the reduction in functioning pulmonary capacity was the fact that the skin and subcutaneous tissues of the chest undergo fibrotic changes after irradiation. The normally pliable skin becomes stiff and inelastic. A radical mastectomy, in itself, probably produces a diminution in V.C. by removing some of the respiratory musculature and rendering the skin of the chest tight. Baldwin *et al.* (1949) found the V.C. to be reduced to 75% of its predicted value in radiation fibrosis. With a moderate degree of fibrosis the remaining pulmonary tissue may undergo compensatory emphysema which would also reduce the V.C.

The M.B.C. has been shown to be affected in radiation fibrosis. Baldwin *et al.* (1949) found it decreased to 80%. Leach (1943) also found it reduced. The ability of a patient to breathe out at a high velocity depends on many factors: the muscular force available, the compliance of the lungs and thorax, and airway and tissue resistance (Comroe, *et al.*, 1955). It is reduced out of proportion to the decrease in V.C. in patients with obstruction of their airways. On the other hand, the M.B.C. may be fairly well maintained in some patients with pulmonary fibrosis, even though there is marked reduction in V.C., their only defect is a limitation to expansion of the thorax. Since the greatest possible rate of expiration is often obtained with a degree of effort well below the maximum of which the patient is capable, it is a satisfactory test to perform on patients suffering from carcinoma of the bronchus. Also, Franklin *et al.* (1955) believe that the expiogram is more sensitive than the x-ray film revealing small changes in lung structure.

It has been noted that hyperventilation on exercise is often associated with pulmonary fibrosis (Baldwin *et al.*, 1949). The ventilatory cost of exercise is adequately measured by the standardized ventilation. The cause of this hyperventilation is not clear. It has been shown that arterial oxygen saturation at rest and during exercise is normal in patients with radiation damage (Bergmann and Graham, 1951). Similarly, alterations in plasma carbon dioxide content have not been observed. Bronchspirometric studies have shown that this is due, primarily, to continued satisfactory function by the uninvolved lung. It therefore seems unlikely that patients with irradiation damage of one lung hyperventilate in order to restore an abnormal blood chemistry to physiological equilibrium. In fact, they appear to hyperventilate despite the absence of

any known physiological need for such activity. Leach *et al.* (1942) believe that this is due to abnormal reflexes originating in the altered lung.

It is important to remember that familiarity with the procedure and the co-operation of the patient affect the results of lung-function studies, and may lead to variations that do not necessarily reflect the patient's pulmonary function.

Summary

Serial lung-function studies have been performed on patients having their lungs irradiated for carcinoma of the bronchus or carcinoma of the breast.

Lung function tends to be depressed towards the end of the course of radiotherapy at 240 kV. Such a depression is not seen with supervoltage radiotherapy. This is probably attributable to the difference in radiation reaction.

Moderate functional disability results from direct pulmonary irradiation by supervoltage x rays as measured at the end of one year.

No real functional disability results from radiotherapy for carcinoma of the breast when modern radiotherapeutic techniques are employed.

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"This has been a year of intense activity undoubtedly owing to the considerable rise in the number of cases as reported last year. The trend which is brought continually to our notice, and causes us grave concern, is the extreme youth of many of the unmarried mothers. The reasons underlying this inescapable fact go far beyond the limits of our walls, and we ponder on the causes which strike at the general well-being of society as a whole and on what is being done to arrest those untimely events." (Committee of Management, Chairman's Report, National Council for the Unmarried Mother and Her Child (Inc.), Fortieth Report, May, 1959–March, 1960.)