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Effects of mediastinal irradiation upon respiratory function following mastectomy for carcinoma of breast[1]

A five-year follow-up study

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A five-year follow-up study of respiratory function in patients with mediastinal irradiation following mastectomy for carcinoma of the breast revealed the following:

Physiological dead space diminishes progressively, reaching a maximum decline at 12 months following irradiation. Partial recovery occurs thereafter with a levelling out at about 62% of the pre-radiation level.

Pulmonary diffusing capacity also declines rapidly but recovery begins after 18 months and improves to within normal limits by the fifth year of the follow-up.

The residual volume immediately increases at the end of irradiation therapy but rapidly and permanently returns to normal.

Some increase in alveolar ventilation is apparent throughout and continues for at least four years, presumably as a result of the permanently reduced dead space.

Whitfield, Bond, and Arnott (1956) stressed that 'the margin of a dose of *x*-rays that is therapeutically effective and one that produces undesirable damage to adjacent healthy tissue is always small'. Structures particularly vulnerable to the effects of mediastinal irradiation are probably those which derive their arterial blood supply from the thoracic aorta or harbour lymphatic channels terminating in the hilar lymph nodes. The alveolar epithelium of the lungs (Warren, 1942), the bronchial tree (Jacobsen, 1940), and the oesophagus (Engelstad, 1934), in particular, represent such potentially susceptible targets. Direct irradiation damage to the lungs was first emphasized by Groover, Christie, and Merritt (1922) and subsequently by many observers (Garcia-Calderon, Sarasin, and Marquis, 1948; Whitfield, Lannigan, and Bond, 1954; Baldwin, Cournand, and Richards, 1949; Sutton, 1960). Radiological evidence of lung damage resulting from prophylactic radiotherapy to the thorax of patients following mastectomy for carcinoma of the breast is less common, with a reported incidence which varies from 5·6% (Engelstad, 1940) to 60% (McIntosh and Spitz, 1939).

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Long-term systematic studies concerning respiratory function, including pulmonary diffusing capacity (DLco), over intervals of at least five years following mediastinal irradiation are not available. A relatively early radiation pneumonitis needs to be distinguished from the more subtle and long-term effects leading occasionally to pulmonary radiation fibrosis and a permanent alveolar-capillary block syndrome.

Particularly desirable are comparable and objective methods of assessment of lung function in relation to the dosage of prophylactic irradiation. Patients with carcinoma of the breast have a fairly good prognosis following surgery, and a follow-up of these patients over some years is calculated to yield information concerning both immediate and long-term effects of prophylactic irradiation of the mediastinum.

The current report provides a systematic analysis of the changes in lung function observed over five years.

MATERIALS AND METHODS

Thirty-six patients of an average age of 54 years were involved in this investigation. All had biopsy-proved carcinoma of the breast and underwent either simple or radical mastectomy at the Victoria General Hos-

pital, Halifax, Nova Scotia (Table I). After an interval following operation of usually 10–14 days, radiotherapy was started.

TABLE I

DIAGNOSIS AND SURGICAL TREATMENT

Type of Carcinoma	No. of Patients	Mastectomy	
		Simple	Radical
Undifferentiated	3	1	2
Scirrhous	12	3	9
Adenocarcinoma	11	3	8
Intraduct	3	—	3
Medullary	1	—	1
Infiltrating	1	—	1
Papillary	1	—	1
Anaplastic	1	—	1
Paget's disease	1	1	—
Metastatic	1	—	1
Squamous	1	—	1
Total	36	8	28

In all patients treatment was given to the axillary and supraclavicular areas in one block with two opposed fields measuring 10×20 cm.; a cobalt-60 unit with an average range of $\frac{4,200}{3} - \frac{5,280}{4}$ r was used at 80 cm. skin surface distance (S.S.D.). In addition, all patients received radiotherapy to the internal mammary nodes from the suprasternal notch to the sixth costal cartilage within a field of 5×15 cm. with a curie cobalt-60 unit at 50 cm. S.S.D., with a surface dosage range of $\frac{4,202}{3} - \frac{6,000}{4}$ r. Seventeen of these patients also received chest wall irradiation with 100 kV x rays at 30 cm. S.S.D. with a dose ranging from $\frac{3,250}{3} - \frac{5,000}{4}$ r. These included all patients who had simple mastectomies (Fig. 1).

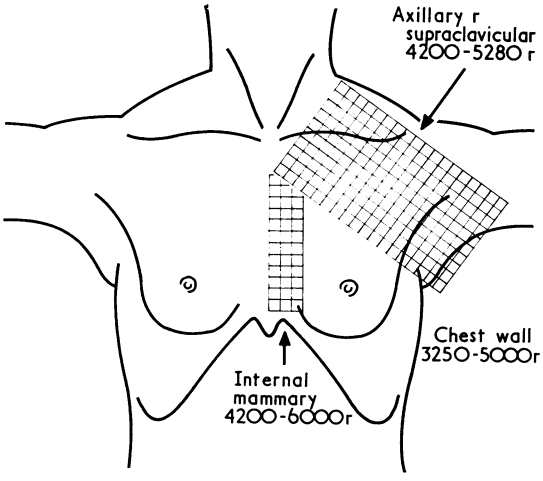


FIG. 1. *Radiation dosage.*

Just prior to the course of radiotherapy patients were referred for base-line pulmonary function tests. Subsequently these were repeated in the following order:

(*a*) after 9 treatments
(*b*) at completion of irradiation
(*c*) 3 months after completion
(*d*) after 6 months
(*e*) after 12 months
(*f*) after 18 months
(*g*) after 2 years
(*h*) after 3 years
(*i*) after 4 years
(*j*) after 5 years

For the purpose of statistical analysis this investigation was compared with that of 12 female patients not suffering from lung disease whose average age was 50 years.

The means of their lung functions will be used for comparison throughout the patients' follow-up.

The routine pulmonary function studies consisted of the following:

1. Static lung volumes: tidal volume (T.V.), vital capacity (V.C.), expiratory reserve volume (E.R.V.), functional residual capacity (F.R.C.), minute ventilation (V_E), and alveolar ventilation (V_A);
2. Residual volumes (R.V.) and indices of intrapulmonary mixing (I.I.P.M.);
3. Dynamic ventilatory measurements, namely timed vital capacity (T.V.C.), maximum voluntary ventilation (M.B.C.), and the maximum expiratory flow rates (M.E.F.R.);
4. Ear oximetry;
5. Expired end-tidal gas analysis for dead space (V_D) calculations (using the Bohr equation);
6. Arterial P_{CO_2} and arterial *p*H determinations;
7. Arterial oxygen content, capacity, and saturation;
8. Pulmonary diffusing capacity by the steady state technique (D_{LCO}) (expressed in ml. CO/min./mm. Hg);
9. Oxygen consumption ($\dot{V}_{O_2}$) and resting ventilatory equivalent for oxygen (R.V.E.);
10. Air velocity index (A.V.I.).

The original number of 36 patients has become reduced to 21 because of 10 deaths and the elimination of an additional five patients for reasons of old age, geographical distance from Halifax, re-irradiation on account of metastases, and lack of co-operation in one patient.

RESULTS

In a comparison between the controls of a similar age group and the patients prior to radiation but post-mastectomy, differences emerged in that the V.C., the 3-sec. timed V.C., and M.E.F.R. were lower in the patient group. Also there were significant differences in reductions in the means of

alveolar P_{CO_2}, alveolar ventilation, and diffusing capacity. The means of physiological dead space (V_D) showed a significant increase. A probable explanation for these differences stems from the recent surgery to the chest wall and possibly the anaesthesia. In 32 patients a comparison was made with the pre-radiation studies and those obtained after completion of nine treatments. These reveal a significant decrease in physiological dead space from the pre-radiation mean of 152 to 133 ml. (Fig. 2).

The next observations concern 26 patients whose results, after completion of radiotherapy, are compared with those prior to radiation. This reveals a further decrease in physiological dead space to a mean of 122 ml. and a persistent reduction in E.R.V. and D_{LCO} (Fig. 3a).

Twelve sets of observations three months after completion of radiotherapy are paired once again with the pre-radiation control studies. A significant increase in resting alveolar ventilation (V_A) is apparent as well as progressive reductions in physiological dead space (mean 97 ml.) and D_{LCO} (Fig. 3b).

The six months' comparison shows a significant rise in resting mean arterial oxygen saturation as

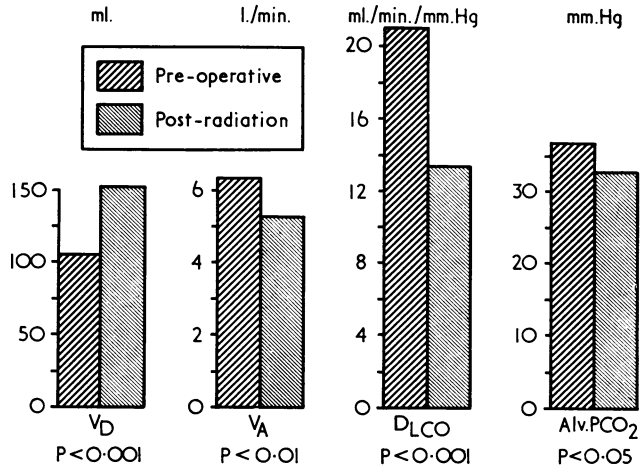


FIG. 2. *Comparison of patients with pre-operative controls before radiation shows main difference in lung function before surgrey and immediately after radiation. The key to this figure applies also to Figs* 3 *to* 8.

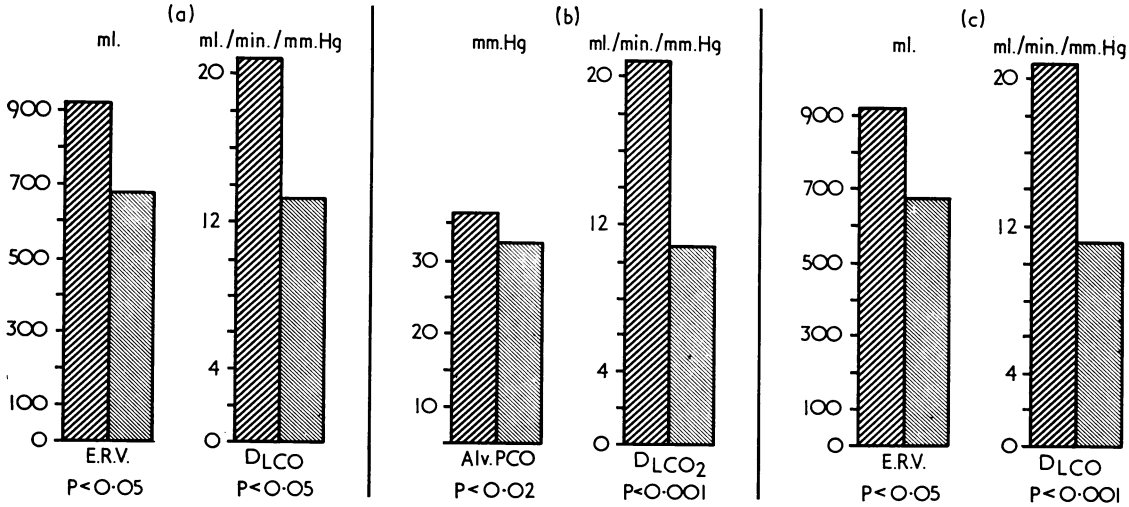


FIG. 3. *Post-radiation:* (*a*) *immediate;* (*b*) *at* 3 *months;* (*c*) *at* 6 *months.*

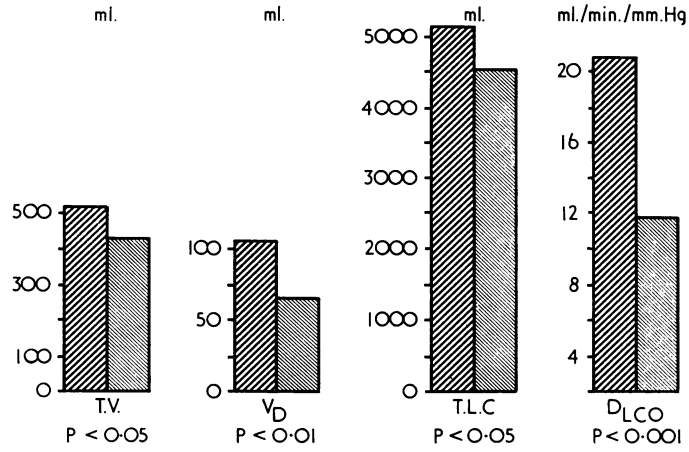


FIG. 4. *Post-radiation one year.*

a result of hyperventilation ($\dot{V}E$) at rest, a persistence in the increase in alveolar ventilation ($\dot{V}A$), and a further decline in physiological dead space (mean 88 ml.) (Fig. 3c). The DLco, although still reduced, has slightly improved since the three months' follow-up.

At 12 months a set of 10 comparisons indicate a significant decline in T.V. and an increase in 3-sec. timed vital capacity. The residual volume has diminished and there is a slight increase in E.R.V. The alveolar ventilation continues to be elevated and the physiological dead space has reached its maximum decline, namely 64 ml. The DLco has not changed during the six months' interval (Fig. 4).

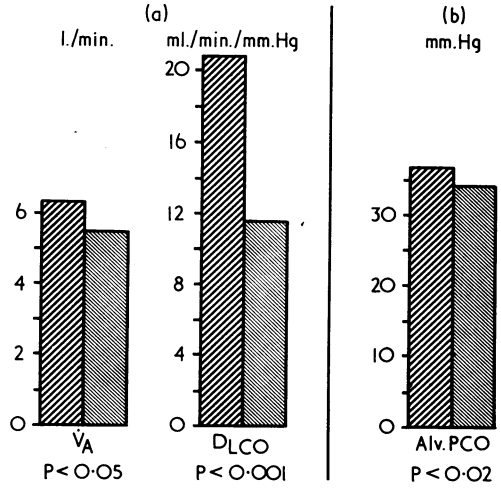


FIG. 5. *Post-radiation:* (*a*) 18 *months;* (*b*) 2 *years.*

The 18-months follow-up is provided by 11 sets of comparisons. The significant changes apply to a further decrease in residual volume and a recovery in physiological dead space which is now 111 ml., but this is still significantly lower than prior to radiation. The DLco has not changed (Fig 5a).

Six sets of comparisons at the 24-months follow-up show a significantly lower physiological dead space which at a mean of 95 ml. has increased slightly and suggests that VD changes are now levelling out (Fig. 5b).

In the 10 comparisons available at 30 months significant drops in $\dot{V}E$, R.V., and T.L.C., and a fall in I.I.P.M. are apparent. Of interest is the significant rise in DLco (mean 17·7 ml./min./mm. Hg). The VD continues to be reduced at a mean of 91 ml. (Fig. 6).

The three-year follow-up covers 10 sets of comparisons which show a further improvement in DLco (mean 18·9 ml.) and a mean VD which has slightly increased to a mean of 99 ml. The alveolar ventilation ($\dot{V}A$) is also significantly lower (Fig. 7a).

The four-year post-radiation effects are derived from a set of six studies. This reveals a significantly lower age group. The alveolar P_{CO_2} is higher than in the pre-radiation studies. The DLco and alveolar P_{CO_2} are now normal (DLco 20·1 ml./min./mm. Hg) and the VD is steady at a mean of 97 ml. (Fig. 7b).

The final set of comparisons at five years was derived from five studies. Significant are the increase in the % predicted M.B.C., the drop in $\dot{V}E$, decreases in R.V., F.R.C., and T.L.C., and a small but still significant decrease in DLco (Fig. 8).

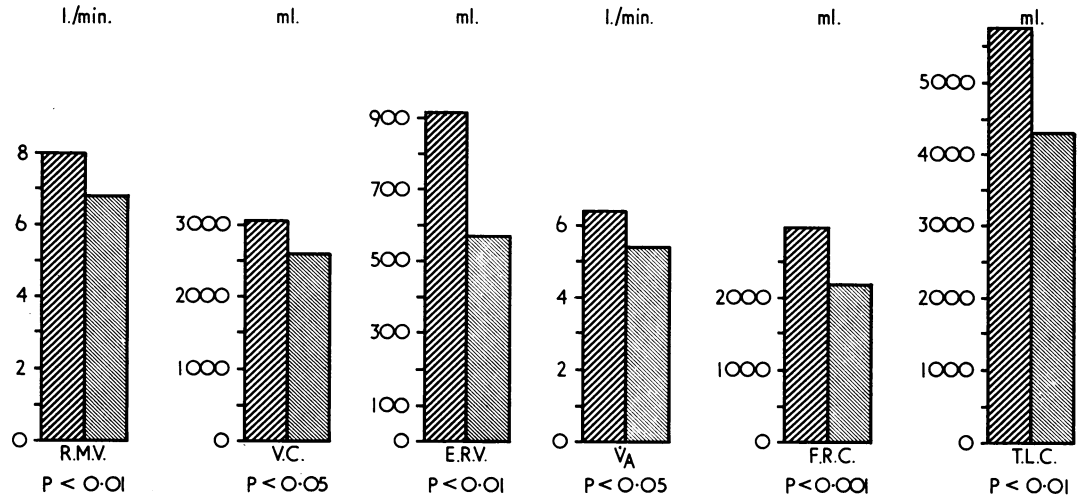


FIG. 6. *Post-radiation* 30 *months.*

An additional analysis was carried out to examine differences, if any, between the patient group who had chest wall radiation and standard radiotherapy, but no statistically significant differences in any of the lung function parameters emerged.

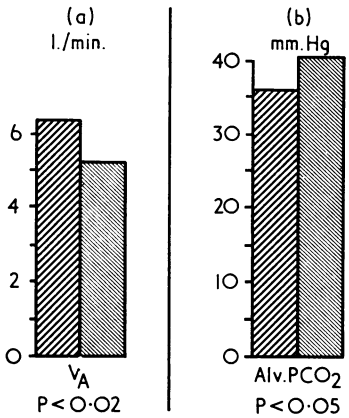


FIG. 7. *Post-radiation:* (*a*) 3 *years;* (*b*) 4 *years.*

Six out of nine patients with marked radiological evidence of radiation fibrosis received chest wall radiation as well as standard therapy; while in another six out of 13 patients who also received additional chest wall radiation no radiation reaction occurred. The overall incidence of radiation reactions in the 28 series of chest films examined was as follows:

Grade I: No reaction 13 (46·4%)
Grade II: Minimal reaction involving one intercostal space 6 (21·4%)
Grade III: Retraction of hilum with segmental or lobar changes 6 (21·4%)
Grade IV: Lobar and mediastinal shifts with elevation of the diaphragm 3 (10·8%)

The total incidence of lung irradiation reactions in this series of 28 patients with breast cancer is therefore 53·6%. This reaction rate compares with that of McIntosh and Spitz (1939), who found an incidence of 60%. The radiological pattern of the radiation effects ranges from early reversible lung shadowing without mediastinal and diaphragmatic shifts to the final grade of irreversible shadowing including mediastinal and diaphragmatic retraction. One example of each reaction grade follows in brief:

GRADE I Mrs. E. A. had a scirrhous carcinoma of the left breast. She was treated by radical mast-

TABLE II

GRADE I RADIATION REACTION: LUNG FUNCTION TESTS

	Pre-radiation	Post-radiation			
		9 Treatments	2 Years	3 Years	4 Years
R.R.	9.3	11	10	12·5	10·0
T.V.	708	455	675	437	334
% Predicted V.C.	89·9	91·2	99·5	99·8	90·9
% Predicted M.B.C.	104·1	90·8	93·7	98·1	68·6
E.R.V.	978	426	702	600	510
V_D	170	204	216	118	88
V_A	5	5·06	4·09	3·99	2·46
RV	2,687	—	1,591	1,606	2,084
DLco	10·10	—	17·72	17·77	11·96

ectomy and routine mediastinal and chest wall irradiation. Her chest films show no significant reaction. (Table II summarizes her lung function tests over a four-year follow-up.) These show declines in physiological dead space and residual volume and a remarkable recovery in diffusing capacity.

GRADE II Mrs. F. D. had a scirrhous carcinoma of the left breast treated by radical mastectomy and routine radiation. The radiograph shows a persistent shadow at the apex of the left lung. Her lung function tests (Table III) reveal a persistent increase in alveolar ventilation, a decrease in physiological dead space, and some recovery of diffusing capacity after two-and-a-half and three-and-a-half years of therapy.

TABLE III

GRADE II RADIATION REACTION: LUNG FUNCTION TESTS

	Pre-radiation	Post-radiation	
		2 Years	3 Years
R.R.	17·3	18·0	18·3
T.V.	405	366	425
% Predicted V.C.	89·0	90·5	104·7
% Predicted M.B.C.	109·9	103·6	80·6
E.R.V.	873	767	711
V_D	81	83	91
V_A	5·61	5·09	6·11
R.V.	2,363	2,483	3,577
D_{LCO}	12·28	15·16	12·07

GRADE III Mrs. G. D. had a scirrhous carcinoma of the left breast treated by radical mastectomy and routine radiation only. Her radiographs show shadowing of the left upper lobe with shifts of the mediastinum to the left. The lung function tests show a considerable reduction in D_{LCO} followed after three-and-a-half years by only slight improvement. The physiological dead space shows continuous reduction (Table IV).

TABLE IV

GRADE III RADIATION REACTION: LUNG FUNCTION TESTS

	Pre-radiation	Post-radiation			
		Immediate	1 Year	2 Years	3 Years
R.R.	13	15	12	12	13·7
T.V.	477	456	504	512	472
% Predicted V.C.	116·2	119·5	115·5	117·6	119·5
% Predicted M.B.C.	95·5	127·1	108·7	111·4	109·2
E.R.V.	927	799	943	796	518
V_D	215	79	100	98	59
V_A	3·41	5·06	4·85	4·97	5·66
R.V.	—	—	2,182	2,564	1,829
D_{LCO}	12	11·5	—	16·58	13·92

GRADE IV The grossest changes with marked opacification of the right lung, mediastinal shift, and elevation of the right diaphragm affected Mrs. E. S., who had a squamous carcinoma of the right breast

TABLE V

GRADE IV RADIATION REACTION: LUNG FUNCTION TESTS

	Pre-radiation	Post-radiation		
		Immediate	1 Year	2 Years
R.R.	13	17	18	20
T.V.	507	468	435	387
% Predicted V.C.	101	110·4	96·6	99·2
% Predicted M.B.C.	92	90·6	85·8	111·2
E.R.V.	539	602	775	583
V_D	128	106	113	118
V_A	5·04	5·97	5·79	5·38
R.V.	1,444	—	1,958	1,345
D_{LCO}	—	—	—	14·16

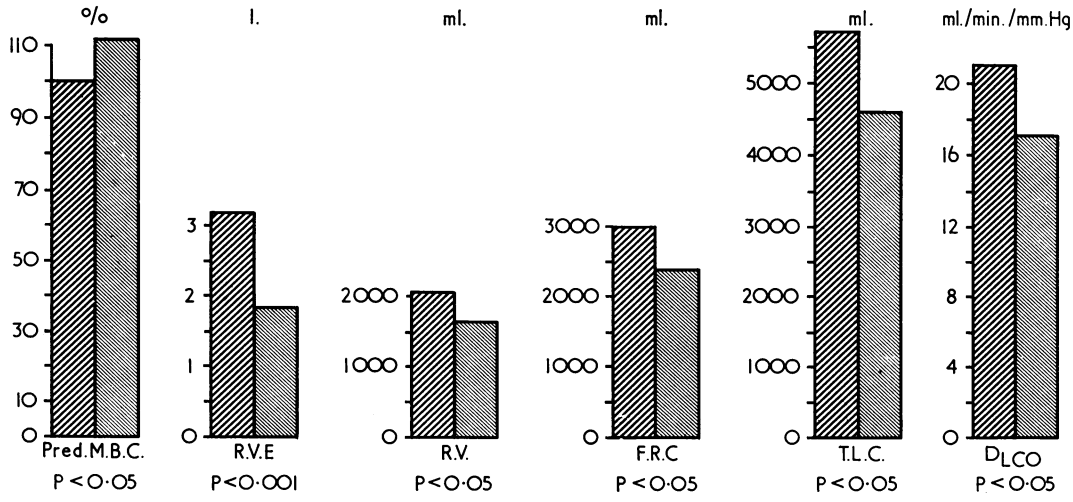


FIG. 8. *Post-radiation 5 years.*

treated by radical mastectomy and both routine and chest wall radiation. Her lung function tests show persistent reductions in DLCO and VD after two-and-a-half years (Table V).

DISCUSSION

The objective of this study had to limit itself to three main points:

1. The collection of reproducible pre-irradiation data in lung function from elderly women who had undergone radical surgery;

2. The immediate effects on lung function of irradiation of the thorax following surgery;

3. A long-term follow-up in order to correlate changes in lung radiographs with disorders in lung function.

No necropsy material is available from the 10 patients who died, and a summary of the changes in the lung in similar patients is derived from the literature.

PATHOLOGY OF IRRADIATION DAMAGE TO LUNGS Warren and Gates (1940) found that the earliest lesions in the alveolar lining cells and capillary epithelium consisted of swelling, necrosis, distortion, and fibroblastic proliferation. They also described a hyaline membrane type of reaction in the alveoli. In addition, the bronchi showed increased mucus production and degeneration of cilia, oedema, and fibrosis of the tunica, while the lymphatics were dilated. The changes in the blood vessels (presumably bronchial arteries) reveal swelling of the endothelium and a reduction in lumen which includes that of the capillaries. Arterioles and venules show oedema of the walls, fibrosis, hyalinization, and increased prominence of the endothelial cells. Larger vessels show some oedema and hyalinization, though to a lesser extent than the smaller ones.

Bergmann and Graham (1951) studied two lungs after pneumonectomy for irradiation damage following radiotherapy after radical mastectomy.

Three types of lesions were noted:

1. In the least affected parts the alveolar walls were thickened with low cuboidal epithelium and an increase in number and size of elastic fibres. The bronchi revealed moderate oedema and increased goblet cells.

2. More damaged areas showed alveolar epithelial hyperplasia with tall lining cells and thick walls containing considerable quantities of elastic tissue. The bronchial tree pattern was that of dilatation of bronchioles, degeneration of their bronchial cartilages, and oedema of the larger bronchi.

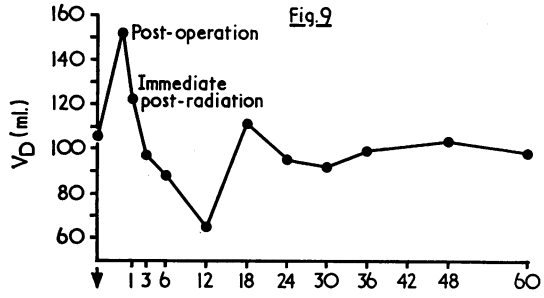
3. In severely affected areas, the normal architecture became obliterated by fibrosis with a preponderance of thick elastic fibres. The recognizable bronchi were dilated while the mucosae frequently displayed squamous metaplasia. Arteriolar walls appeared to be oedematous and the lumina were reduced by subintimal thickening. No change was noted in the pulmonary arteries, and stress was laid on the relative resistance to irradiation of the larger arteries.

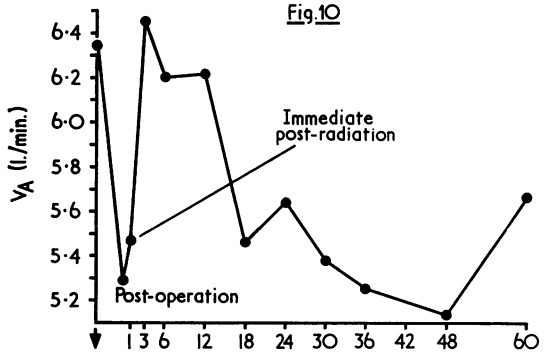
The hyaline type of membrane described by Warren and Gates (1940) was not observed by Bergmann and Graham (1951), whose emphasis centred on the great elastic tissue increase as a valuable criterion for the histological diagnosis of irradiation lung fibrosis.

It is believed that the specific effects of irradiation upon the smaller blood vessels are of importance, inasmuch as they constitute the nutritional network of the lungs (Cudkowicz and Armstrong, 1951). Mucus and surfactant production, in particular, are liable to suffer. Dilatation of larger structures with swelling of the endothelial cells, leading to thrombosis and obliterative changes in the smaller arteries, is generally accepted as a typical effect of irradiation damage. Lymphatics are similarly involved (Levitt, 1935). The end result of such changes can be sought in low lung compliances, disturbed perfusion, and decreases in diffusing capacity. Bilateral changes could lead to pulmonary hypertension and this has been documented (Freid and Goldberg, 1940). On the basis of the vascular changes described by Warren and Gates (1940), which led to thrombosis, anticoagulant therapy was recommended on a prophylactic basis immediately following irradiation therapy by Macht and Perlberg (1950). The rationale for its use was based on experimental studies by Boys and Harris (1943), who demonstrated a decrease in pulmonary vascular changes in irradiated and heparinized rabbits.

EFFECTS ON LUNG FUNCTION The chief differences between the normal female patients and those who had had a mastectomy appear in the means of the vital capacity and maximum breathing capacity, both of which are reduced in breast patients, presumably as a result of the mastectomy and loss of pectoralis muscles as well as post-operative discomfort and apprehension. Some mechanical restriction of lung movement, because of the change in chest muscle alignment, might account for the hyperventilation at rest and particularly during light exercise. The expansion of the mean residual volume associated with a normal index of intrapulmonary mixing of gases

accompanies the low mean expiratory reserve volume, the expulsion of which is physically difficult soon after mastectomy. The reduction of the mean 3-second timed vital capacity and mean maximum expiratory flow rates are the result of both mechanical chest wall restriction and an increase in airway resistance from oedema of the bronchial tree. No significant effects were noted in the means of arterial oxygen saturation at rest. The major effects involved are mean alveolar P_{CO_2}, physiological dead space, alveolar ventilation, and pulmonary diffusing capacity.





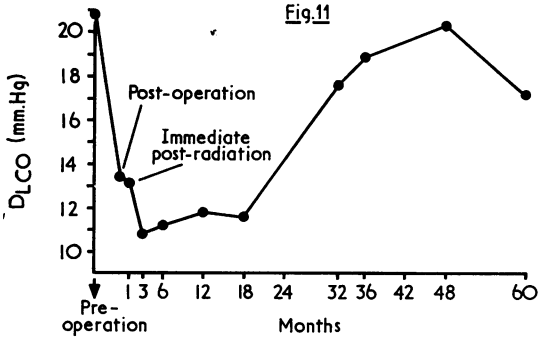


FIG. 9. *Effects of radiation on physiological dead space.*

FIG. 10. *Effects of radiation on alveolar ventilation.*

FIG. 11. *Effects of radiation on* DLco.

The direct effect of mediastinal irradiation upon the lungs is reflected in a progressive diminution of the mean physiological dead space beginning after nine irradiation treatments and persisting throughout the five years of observation (Fig. 9). Because of the anatomical proximity of the bronchial tree to the main target of irradiation, namely the mediastinum and the hilar lymph nodes, it is presumed that the changes in dead space are primarily the result of oedema of the bronchial mucosa in the early stages with a reduction in the total cross-sectional area of the bronchial tree and the volume of air contained therein. The increase in the mean alveolar ventilation (Fig. 10) is explicable in terms of dead space reduction in the presence of an unchanged mean resting minute ventilation (V_E).

The most significant changes of the current investigation are those revealed by the pulmonary diffusing capacity, which, after an initial deterioration, returns to almost normal levels after 30 months. This suggests that mediastinal irradiation does not irrevocably damage the alveolar capillary membrane, but most probably distends it as a result of interstitial lymphoedema probably secondary to the destruction of lymph channels leading to the lymph-collecting reservoirs in or near hilar lymph nodes. Presumably an alternative lymphatic pathway is ultimately formed which decompresses the alveolar lymphatics, and with this some recovery in DLco ensues (Fig. 11).

REFERENCES

Baldwin, E. de F., Cournand, A., and Richards, D. W. Jr. (1949). Pulmonary insufficiency. II. A study of 39 cases of pulmonary fibrosis. *Medicine (Baltimore)*, **28**, 1.

Bergmann, M., and Graham, E. A. (1951). Pneumonectomy for severe irradiation damage of the lung. *J. thorac. Surg.*, **22**, 549.

Boys, F., and Harris, I. D. (1943). The effect of heparinization on experimental post-irradiation tissue changes in the lung. *Amer. J. Roentgenol.*, **50**, 1.

Cudkowicz, L., and Armstrong, J. B. (1951). Observations on the normal anatomy of the bronchial arteries. *Thorax*, **6**, 343.

Engelstad, R. B. (1934). Über die Wirkungen der Röntgenstrahlen auf die Lungen. *Acta radiol. (Stockh.)*, Suppl. **19**.

—— (1940). Pulmonary lesions after roentgen and radium irradiation. *Amer. J. Roentgenol.*, **43**, 676.

Freid, J. R., and Goldberg, H. (1940). Post-irradiation changes in the lungs and thorax; a clinical, roentgenological and pathological study, with emphasis on the late and terminal stages. *Ibid.*, **43**, 877.

Garcia-Calderon, J., Sarasin, R., and Marquis, G. (1948). Quelques aspects radiologiques des pancréatites aiguës. *J. Radiol. Électrol.*, **29**, 243.

Groover, T. A., Christie, A. C., and Merritt, E. A. (1922). The use of the copper filter in the roentgen treatment of deep-seated malignancies. *Sth. med. J. (Bgham, Ala.)*, **15**, 440.

Jacobsen, V. C. (1940). The deleterious effects of deep roentgen irradiation on lung structure and function. *Amer. J. Roentgenol.*, **44**, 235.

Levitt, W. M. (1935). Deep X-ray therapy in malignant disease. *Practitioner*, **135**, 48.

Macht, S. H., and Perlberg, H. Jr. (1950). Use of anticoagulant (dicumarol) in preventing post-irradiation tissue changes in the human lung; preliminary report. *Amer. J. Roentgenol.*, **63**, 335.

McIntosh, H. C., and Spitz, S. (1939). A study of radiation pneumonitis. *Ibid.*, **41**, 605.

Sutton, M. (1960). The functional effect of pulmonary irradiation. *Brit. med. J.*, **2**, 838.

Warren, S. (1942). Effects of radiation on normal tissues 5. Effects on the respiratory system. *Arch. Path.* **34**, 917.

—— and Gates, O. (1940). Radiation pneumonitis; experimental and pathologic observations. *Ibid.*, **30**, 440.

Whitfield, A. G. W., Bond, W. H., and Arnott, W. M. (1956). Radiation reactions in the lung. *Quart. J. Med.*, **25**, 67.

—— Lannigan, R., and Bond, W. H. (1954). Fatal post-radiation pneumonitis. *Lancet*, **2**, 117.