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Research Article

THE EFFECTS OF CHEST IRRADIATION ON PULMONARY FUNCTION * †

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Pathological changes in lung tissue following chest wall irradiation have been adequately documented in the past (1–5). However, pulmonary function has not been systematically studied. Published studies (6–9) are incomplete and the findings complicated by the original disease. In view of this and because of a desire to determine the amount of radiation which might safely be administered to the chest, a systematic study was undertaken in dogs. The results of this study follow.

METHODS

Pulmonary function and vascular resistance were evaluated in dogs before and after irradiation to the chest. All studies were performed under pentobarbital anesthesia. Two different irradiation schedules were utilized. Eight dogs received a calculated dose of 1,000 to 2,900 roentgens (r) to the mid-chest in a single exposure. No animal survived longer than two and one-half months. For practical reasons, it was not feasible to study resistance and function in the same animal. Therefore, resistance was evaluated in the first five animals within 24 hours of irradiation. Diffusing capacity, functional residual volume and compliance were determined in the remaining three animals at two to three week intervals. In order to effect a longer period of survival, seven animals were irradiated under a second schedule consisting of a dosage of 200 to 300 r to each side of the chest repeated at weekly intervals up to a total calculated mid-chest dose of 3,000 to 4,800 r. Three of these animals survived longer than six months. Diffusing capacity, functional residual volume and compliance were determined at two to three month intervals following onset of irradiation. Vascular studies were also conducted in four animals at the time of the final evaluation.

All irradiation was given with 260 KV. peak equipment (filter, one-half mm. Cu, 1 mm. Al, half-value layer 1 mm. Cu; target-skin distance, 50 to 70 cm.) with the animals under pentobarbital anesthesia. Field size included the chest from xiphoid to lower neck.

Compliance. Values for total thorax, lung and chest wall compliance were obtained by the static method (10) with the animals anesthetized and curarized. A cardiac catheter, with a latex condom secured to the terminal 5 inches, was introduced well into the thoracic portion of the esophagus (11, 12). The catheter was marked at the level opposite the incisors, so that it could be placed in the same position in subsequent tests. A cuffed endotracheal tube was positioned within the trachea and sealed by inflation of the cuff. Muscle paralysis was obtained by the intravenous injection of approximately 6 ml. of a 0.01 per cent solution of succinyl-choline. Respiration was maintained artificially with a mechanical respirator, except during evaluation of the pressure-volume relationships. Air was introduced into the tracheal cannula until pressure in the cannula reached a pre-selected level. In order to minimize variations due to hysteresis, inflation time for a given volume was maintained approximately equal at each study. Tracheal and esophageal pressures were recorded. The lungs were then allowed to deflate passively into a recording spirometer. After 15 to 20 seconds the procedure was repeated. Tracheal pressures of 10, 20, 30, 40 and 50 cm. of H_2O were utilized. Three determinations were made at each pressure. Compliance was calculated as follows:

$$\text{Total thorax compliance} = \frac{\text{Volume (L. ATPS)}}{\text{Tracheal pressure (cm. } H_2O)}$$

$$\text{Thoracic cage compliance} = \frac{\text{Volume (L. ATPS)}}{\text{Esophageal pressure (cm. } H_2O)}$$

$$\text{Lung compliance} = \frac{\text{Volume (L. ATPS)}}{\text{Tracheal-esophageal pressure (cm. } H_2O).}$$

In order to determine the accuracy of values for lung compliance calculated from the above formula, the chest walls of three animals were opened and retracted, and compliance of the lungs was determined directly. Values obtained with the chest open were compared with those calculated from data obtained with the chest closed.

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Functional residual capacity (FRC). Functional residual capacity was determined by the open circuit method during spontaneous breathing (13, 14). Respiration was monitored continuously during the procedure with a nitrogen-analyzer [1] to detect completeness of washout. Washout of nitrogen was complete in three minutes. Gas collection was continued for two minutes longer. The sample volume was measured in a spirometer and the per cent of nitrogen estimated by the analyzer. FRC was calculated according to the usual formula (14).

Diffusing capacity. Diffusing capacity was estimated by the steady state carbon monoxide method during spontaneous breathing (15). Equilibration and sample collection times were two minutes each instead of the three minutes suggested in the reference article. Arterial blood oxygen and carbon dioxide tensions were determined by the bubble equilibrium technique (16). Expired gas samples were analyzed for carbon monoxide and carbon dioxide with infrared analyzers.[2] The oxygen percentage was determined with an oxygen analyzer.[3] Total gas volume, including portions analyzed, was spirometrically measured and converted to STPS. Minute ventilation was obtained by dividing the total gas volume by collection time. Diffusing capacity (Dco) was calculated from the original equations (15). Duplicate determinations were made in three animals in order to determine the reproducibility of the method. The second determination was 78, 80 and 103 per cent of the first in the three animals, respectively. Single determinations were made in all subsequent examinations.

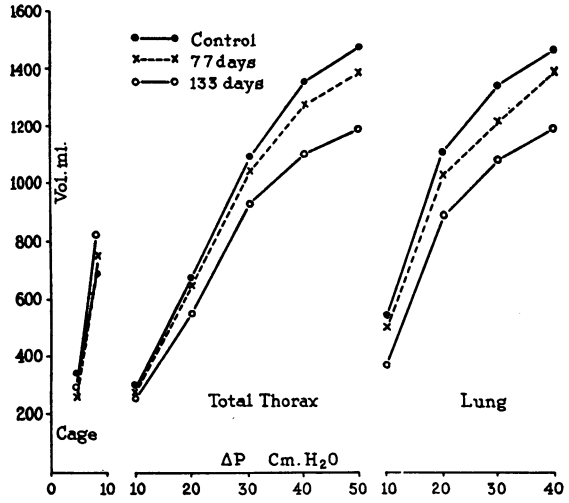

FIG. 1. AVERAGE RELATION BETWEEN PRESSURE AND VOLUME IN CAGE, LUNGS AND TOTAL THORAX BEFORE AND AFTER FRACTIONAL IRRADIATION TO THE CHEST IN SIX ANESTHETIZED CURARIZED DOGS

Three volume measurements were made at each pressure in each animal.

[1] Model A-5, Waters Conley Company, Rochester, Minn.

[2] Liston-Becker Model 16, CO_2 Analyzer, Beckman Instruments, Inc., Belmont, Cal. Model 15A, CO Analyzer, Beckman Instruments, Inc., Springdale, Conn.

[3] Model E-2, Arnold O. Beckman, Inc., 1020 Mission Street, South Pasadena, Cal.

Pulmonary vascular studies. Cardiac catheters were inserted into the pulmonary artery and left atrium via the jugular vein and carotid artery, respectively. These techniques have been described elsewhere (17). Pressures were measured with resistance wire pressure transducers. Cardiac output was calculated by the Fick principle. The per cent of oxygen in expired air was measured with the oxygen analyzer. Oxygen consumption was obtained from the product of the percentage difference in oxygen between inspired and expired air and the corrected total one minute expired volume. Pulmonary vascular resistance was calculated by dividing the difference in pressure between the pulmonary artery and left atrium by the cardiac output.

RESULTS

Compliance

The values for total thorax compliance increased progressively as the pressure was elevated to 30 cm. H_2O (Figure 1). Further pressure elevation resulted in a reduction in compliance. The same relationship was apparent for the lung. These findings are similar to those reported by others (10, 18).

Total compliance decreased following irradiation mainly as a result of a reduction in lung compliance. Three animals were studied two and four weeks following single dose irradiation. Changes were irregular at two weeks. By four weeks, however, reduction in both total and lung compliance was apparent in two of the three animals. Six dogs were studied an average of 77 and 133 days following onset of fractional irradiation (Figure 1). Control values for total thorax compliance at 20 cm. H_2O averaged 0.034 L. per cm. H_2O. By 77 days, total compliance had decreased in three of the six animals and the average value was 0.033. By 133 days, it had decreased in all six and the average value was 0.028 ($t = 2.92$, $p = 0.05$ to 0.01). The changes in lung compliance were similar. The average control value at 20 cm. H_2O was 0.056. By 77 days, lung compliance had decreased in four of the six animals and the average value was 0.052. By 133 days, it had decreased in all six and the average value was 0.045 ($t = 3.36$, $p = 0.05$ to 0.01). Cage compliance did not change greatly

in any animal. These findings indicate that the increased rigidity of the lungs-chest resulted from changes within the lung. Three of these animals were restudied 172, 228 and 273 days, respectively, following onset of irradiation. Total and lung compliance was further decreased in all three. Thoracic cage compliance was below the pre-irradiation value in only one of the three (Figure 2).

One nonirradiated and two irradiated dogs were studied immediately before and after opening the chest. The values obtained with the chest open compared favorably with those with the chest closed (Figure 2).

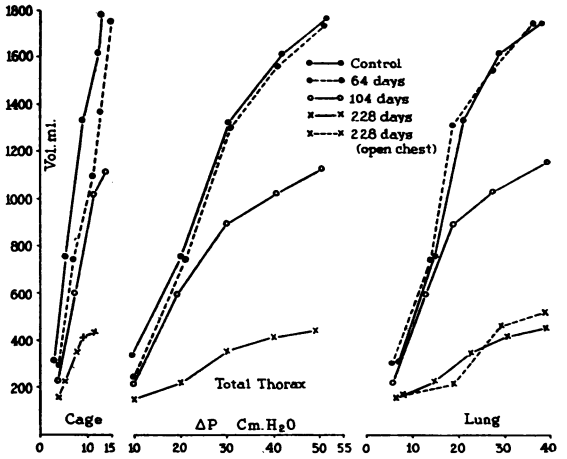

FIG. 2. RELATION BETWEEN PRESSURE AND VOLUME IN CAGE, LUNGS AND TOTAL THORAX OF DOG NO. 13 BEFORE AND AT THREE PERIODS AFTER FRACTIONAL IRRADIATION TO THE CHEST

On the two hundred twenty-eighth day, values for the lung were also obtained immediately after opening the chest. Each point represents the average of three measurements.

Diffusing capacity

Diffusing capacity did not change consistently in three animals studied two weeks and four weeks following irradiation with a single dose. It decreased progressively in those animals studied more than two months following onset of fractional irradiation (Table I, Figure 3). Control values from seven animals averaged 4.3 ml. per minute per mm. Hg. By 82 days following the onset of irradiation, diffusing capacity was below the control value in five, above it in one and the same in one. The average value was 3.2 ml.

TABLE I

Values for several measures of pulmonary function before and at various time intervals after the onset of fractional irradiation to the chest

Dog no.	Weight and sex	Time of study	FRC	Min. vent.	pCO_2	pO_2	D_{CO}
		days	*ml.*	*L./min. STPD*	*mm. Hg*	*mm. Hg*	*ml. CO min./ mm. Hg*
1	38.5 lbs. Male	C*	650	2.5	45.6	74.5	5.0
		80	609	4.2	51.9	71.1	2.3
		126	490	1.8	20.5	65.2	1.5
2	49 lbs. Male	C	678	4.7	48.7	82.9	3.7
		104	615	1.9	54.6	68.5	3.4
		161	492	2.9	48.1	47.1	1.5
7	45 lbs. Male	C	754	2.4	45.6	90.0	3.7
		97	269	2.0	38.3	84.2	3.7
		147	332	3.8	28.9	69.9	2.0
8	32 lbs. Male	C		3.4	31.6	101.1	3.5
		74		3.4	35.9	91.9	3.6
		141	465	2.2	44.4	95.0	2.8
12	48 lbs. Male	C		2.1	43.5	77.7	4.4
		87	566	3.9	30.3	86.2	3.1
		138	546	2.8	33.1	99.5	2.4
		273	344	3.9	33.5	81.7	3.6
13	46.5 lbs. Male	C		7.2	38.3	84.4	5.7
		64	545	2.3	41.6	77.7	3.1
		104	509	1.9	47.9	80.7	2.0
		228	388	9.7	50.1	33.9	1.0
14	41 lbs. Female	C	519	4.3	33.0	81.1	3.9
		70		2.3	51.3	92.4	3.0
		140	513	2.9	34.6	89.6	2.0
		172	418	3.1	53.0	80.6	4.1
Average		C		3.8	40.9	84.5	4.3
		82		2.9	43.4	78.9	3.2
		137		2.6	36.8	78.1	2.0

* C, control.

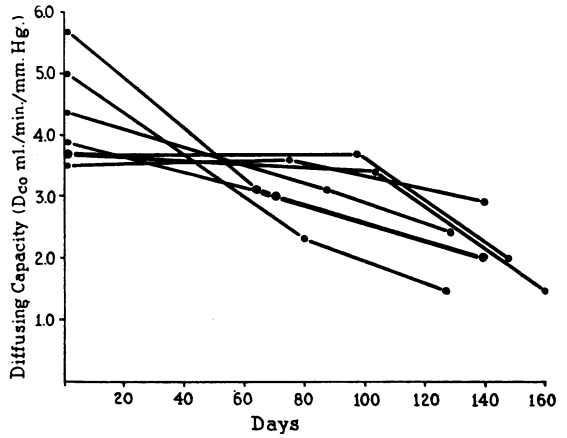

FIG. 3. CHANGE OF PULMONARY DIFFUSING CAPACITY IN SEVEN DOGS FOLLOWING FRACTIONAL IRRADIATION TO THE CHEST

Each point represents one determination.

per minute per mm. Hg ($t = 2.56$, $p = 0.05$ to 0.01). By 137 days, diffusing capacity was below the control value in all seven. The average value was 2.0 ml. per minute per mm. Hg ($t = 5.68$, $p = < 0.01$). Three of these animals were studied 172, 228 and 273 days, respectively, following onset of fractional irradiation. Diffusing capacity further decreased from the preceding value in one, but increased toward normal in two.

A low diffusing capacity was frequently associated with a low pO_2, and in occasional instances this occurred despite a decrease in pCO_2 and minute ventilation. The changes in minute ventilation, pCO_2 and pO_2 were not regular, however, and are only included for the sake of completeness (Table I).

Functional residual capacity

There was no change in the functional residual capacity in three animals studied two and four weeks following irradiation with a single dose. Functional residual capacity decreased in all animals studied more than 80 days following onset of fractional irradiation (Table I). Pre-irradiation values from four dogs averaged 650 ml. This value, on a weight basis, is similar to that reported by Simmons and Hemingway (14). Eighty-one and 137 days following irradiation, average values were 521 and 478 ml. Functional residual capacity further decreased in three animals restudied more than 172 days following onset of fractional irradiation.

Pulmonary vascular resistance

Table II shows that pulmonary arterial pressure, pulmonary venous pressure, cardiac output and pulmonary vascular resistance did not change significantly up to a period of five months following irradiation. In three animals studied after six months, pulmonary arterial pressures and resistances appeared to be elevated.

Values for resistance before and at three and 24 hours after irradiation averaged 2.1, 3.0 and 2.0 mm. Hg per L. per minute, respectively, in five animals. Re-evaluation of one animal 80 days after irradiation revealed a value of 3.2 mm. Hg per L. per minute. Two additional dogs were studied 68 and 135 days after single and fractional dose irradiation, respectively. Resistance values in these two animals were 0.8 and 1.0 mm. Hg per L. per minute. Three dogs were studied more than six months following onset of fractional irradiation. Comparison of these values (Table II) with the control values from other animals in this study and with those reported elsewhere (19) indicate that two of these values were questionably elevated and one was definitely elevated. The animal with the highest value for pulmonary vascular resistance (No. 13) also had the greatest changes in compliance and diffusing capacity as well as the most marked histological changes.

TABLE II

Pulmonary vascular variables immediately before and at various time intervals following onset of irradiation to chest

Dog no.	Time of study	Art. O_2	Ven. O_2	Cardiac output	Mean pul. art. pres.	Mean pul. ven. pres.	Pul. vas. resist.
	days	*vol. %*	*vol. %*	*L./min.*	*mm. Hg*	*mm. Hg*	*mm. Hg/ L./min.*
1A	C*	11.0	16.0	3.4	28.0	24.0	1.2
	0.1†	13.1	16.3	6.5	19.0	6.0	2.0
2A	C	14.5	17.7	5.7	17.5	10.8	1.2
	0.1‡	13.3	16.9	4.7	13.7	9.3	0.9
3A	C	18.4	20.6	5.1	16.5	3.5	2.6
	0.1‡	20.3	24.7	2.7	20.0	3.0	6.3
	0.9	17.3	20.0	6.2	15.5	2.0	2.2
5A	C	13.2	15.9	4.3	12.5	3.5	2.1
	0.1‡	12.5	15.9	3.5	14.5	2.5	3.5
	0.9	9.0	12.0	4.0	10.0	4.0	1.5
	80.0	13.8	18.2	1.8	7.0	1.5	3.2
6A	C	17.1	20.4	2.6	12.5	4.0	3.3
	0.1‡	16.6	20.3	2.4	8.5	3.5	2.1
	0.9	16.8	20.3	3.0	12.5	5.5	2.4
11	68.0§	14.7	17.7	5.8	9.0	4.5	0.8
8	135.0‖	10.5	17.6	2.5	11.0	4.5	1.0
12	273.0¶	14.1	18.7	2.8	22.0	4.5	6.2
13	228.0¶	12.1	18.5	0.8	30.8	1.9	38.0
14	172.0¶	13.4	19.5	1.4	18.2	1.4	11.6

* Control.
† Time after 2,000 r single dose.
‡ Time after 3,000 r single dose.
§ Time after 2,900 r single dose.
‖ Time after starting 4,800 r fractional dose.
¶ Time after starting 3,000 r fractional dose.

Pathology

The lungs of 11 animals were examined microscopically. The findings four days after a single

dose of irradiation revealed little abnormality except for capillary dilatation. No changes were seen in the larger vessels. Four to five months after fractional irradiation, the histological findings demonstrated focal atelectasis with some fibrosis and hyperemia of the interstitial areas. Chest roentgenograms taken regularly during the study period failed to reveal any obvious abnormalities.

In the three animals studied more than 172 days following the onset of irradiation, obvious, interstitial fibrosis with paucity of cellular elements and capillaries was apparent. The small pulmonary arteries of Dog No. 13 revealed marked narrowing due to endothelial proliferation. There was also focal necrosis of the walls, and few areas of acute hemorrhage. The lymph vessels were noticeably dilated.

DISCUSSION

The present study demonstrates that irradiation of the chest of the dog with the dosage employed is followed by progressive reduction in pulmonary diffusing capacity, lung compliance and functional residual volume.

The study failed to demonstrate significant changes in any of the physiological variables measured during the first few weeks following irradiation. Pathological studies indicate that hyperemia, edema and thick secretions occur with some regularity during the early period following irradiation (2). This discrepancy between pathological and physiological findings might result simply because measurements were made at inappropriate times or because the physiological changes were too small to be detected by the methods utilized. On the other hand, the discrepancy may also be explained on physiological grounds. For example, active constriction might produce changes in various resistance and diffusion components that would not be detected by measurements of total resistance and total diffusion. Pulmonary venular constriction is known to occur following inhalation of steam (20) or injection of endotoxin (21). As a result of increased resistance to flow through venules, hydrostatic pressures increase proximally. These elevated pressures passively distend capillaries and other small vessels, thereby reducing their resistance to flow. Caliber changes which are directionally opposite might therefore account for the absence of a significant change in total resistance. Venular constriction also increases capillary blood volume and promotes edema formation (22). Edema may result from capillary hydrostatic pressures in excess of colloid osmotic pressures, increased capillary surface area or increased permeability due to the noxious effect of irradiation on capillary walls. A normal total diffusing capacity might be expected since interstitial edema and increased blood volume have opposite and cancelling effects upon total diffusing capacity (23, 24). A differential diffusion method such as the one decribed by Forster and associates (25, 26) might detect such changes. On the other hand, the absence of measurable compliance and functional residual capacity changes during this early period argues against venular constriction of a severe degree. Elevated blood volume and edema would be expected to decrease compliance (27) and functional residual capacity.

All measured variables appeared to change significantly within six months following onset of fractional irradiation. Compliance, diffusing capacity and functional residual capacity probably decreased by 80 days and definitely decreased by 140 days. Pulmonary vascular resistance seemed to increase at about six months. These physiological changes apparently result from the interstitial fibrosis, cellular infiltration and reduced cross-sectional area of the pulmonary vessels which were observed at autopsy. Arguments for this statement follow: It is possible that focal atelectasis may in part account for the reductions in compliance and diffusion. That it is not the entire explanation is indicated by the fact that these functions were reduced in some anmials in which significant atelectasis was not observed. Variation in minute ventilation, due to different depths of anesthesia, was at first considered as a possible cause of the reduction in diffusing capacity. It soon became apparent, however, that there was little correlation between the two parameters (Table I). It is unlikely that the observed changes in diffusing capacity are related to a failure to correct for COHb in the blood. Such a correction would significantly influence absolute values but could hardly account for changes with time in a given animal. The changes in diffusing

capacity probably were not the result of changes in the level of hemoglobin. The hemoglobin levels (mean ± S. D.) before irradiation and at 2, 4 and 7 month intervals after irradiation were 14.8 ± 0.9, 12.9 ± 1.3, 12.5 ± 1.2 and 13.8 ± 1.3 Gm. per 100 ml., respectively. Hence, the change in pulmonary function was probably the result of the pathological changes observed at autopsy.

The values for diffusing capacity reported in this paper are considerably lower than those reported for four dogs by Otis and Jude (28). However, their methods differed from those in the present study. Otis and Jude maintained respiration artificially during their measurements and used a different technique to sample expired volume. These differences might tend to elevate diffusing capacity. The present study offers some evidence to support this statement. Diffusing capacity was determined in two animals, each ventilated with tidal volumes of 250 and 500 ml. Diffusing capacity with the lower volume was 4.3 and 4.0 ml. per minute per mm. Hg, respectively. With the higher volume the corresponding values were 14.0 and 10.3 ml. per minute per mm. Hg, respectively. These differences might be related to changes in diffusing area and vascular volume due to differences in airway pressures.

Total compliance decreased almost entirely because of decrease in lung compliance. Chest wall compliance decreased measurably in only one animal and its contribution to the change in total compliance was minimal. Increased rigidity of the lung may result from cellular infiltrate, fibrosis and atelectasis. All were observed in the present study and have also been reported by others. Fibrosis, cellular infiltrate, edema, atelectasis and reduction of pulmonary capillary blood volume all probably contributed to the progressive reduction in diffusing capacity. The latter most likely accounts for the tendency to a progressive decrease in arterial oxygen tension. The return of diffusion capacity toward normal in two animals may be related to clearing of cellular infiltrate or edema fluid. The most likely explanation of the progressive decrease in functional residual capacity is fibrous contracture of lungs and chest wall. However, since fibrous contracture might be expected only after the passage of some time and since residual capacity decreased even during the moderately early period following irradiation, other factors might be involved. One such factor might be pulmonary congestion.

An increase in pulmonary vascular resistance could result from passive reduction in vessel caliber by fibrosis and necrosis. Such an increase in resistance to flow would be manifested in an elevated pulmonary arterial pressure for a given rate of blood flow. Freid and Goldberg (7) have noted elevated resistance to flow and right heart failure in humans following irradiation. The present study indicates that at least six months are necessary for these changes to become apparent in the dog. Studies during exercise might have demonstrated vascular fixation earlier. The normal pulmonary vascular bed responds to exercise with a decrease in resistance due, at least in part, to passive distention as pressures increase subsequent to elevation of flow rate. In the presence of fixation, pulmonary arterial pressure would rise to higher levels than normal because resistance would remain constant. The fact that compliance decreased before six months suggests that an increase in fibrous tissue was indeed present even though it was not demonstrated by pulmonary vascular resistance studies made with the animal at rest and anesthetized. This fibrous tissue could decrease the distensibility of the vascular system. Therefore, studies during exercise might have demonstrated fixation before six months. Pulmonary hypertension during exercise in irradiated patients has been reported by Whitfield, Bond and Arnott (29).

SUMMARY

Pulmonary function has been studied in 15 dogs before and at intervals up to nine months following irradiation to the chest. Single doses of 1,000 to 2,900 r and fractional doses of 3,000 to 4,800 r were administered. Pulmonary diffusing capacity, lung compliance and functional residual volume decreased progressively as time elapsed following irradiation. Pulmonary vascular resistance remained normal for a period of five months following irradiation. These physiological changes have been discussed in relation to changes in histology.

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REFERENCES

1. Groover, T. A., Christie, A. C., and Merritt, E. A. Intrathoracic changes following roentgen treatment of breast carcinoma. Amer. J. Roentgenol. 1923, **10**, 471.
2. Engelstad, R. B. Pulmonary lesions after roentgen and radium irradiation. Amer. J. Roentgenol. 1940, **43**, 676.
3. Bergmann, M., and Graham, E. A. Pneumonectomy for severe irradiation damage of the lung. J. thorac. Surg. 1951, **22**, 549.
4. Huguenin, R., Lemoine, J. M., and Fauvet, J. Effets de la radiothérapie sur le poumon normal. J. franç. Méd. Chir. Thor. 1949, **3**, 54.
5. Warren, S., and Spencer, J. Radiation reaction in the lung. Amer. J. Roentgenol. 1940, **43**, 682.
6. Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr. Pulmonary insufficiency. Study of 39 cases of pulmonary fibrosis. Medicine 1949, **28**, 1.
7. Freid, J. R., and Goldberg, H. Post-irradiation changes in the lungs and thorax. Amer. J. Roentgenol. 1940, **43**, 877.
8. Leach, J. E. Abnormal pulmonary physiology as a result of chronic irradiation pleuropulmonitis; preliminary report. Amer. J. Roentgenol. 1943, **50**, 772.
9. Stone, D. J., Schwartz, M. J., and Green, R. A. Fatal pulmonary insufficiency due to radiation effect upon the lung. Amer. J. Med. 1956, **21**, 211.
10. Nims, R. G., Conner, E. H., and Comroe, J. H., Jr. The compliance of the human thorax in anesthetized patients. J. clin. Invest. 1955, **34**, 744.
11. Mead, J., and Whittenberger, J. L. Physical properties of human lungs measured during spontaneous respiration. J. appl. Physiol. 1953, **5**, 779.
12. Mead, J., McIlroy, M. B., Selverstone, N. J., and Kriete, B. C. Measurement of intraesophageal pressure. J. appl. Physiol. 1955, **7**, 491.
13. Darling, R. C., Cournand, A., and Richards, D. W., Jr. Studies on the intrapulmonary mixture of gases. III. An open circuit method for measuring residual air. J. clin. Invest. 1940, **19**, 609.
14. Simmons, D. H., and Hemingway, A. Functional residual capacity and respiratory nitrogen excretion of dogs. J. appl. Physiol. 1955, **8**, 95.
15. Filley, G. F., MacIntosh, D. J., and Wright, G. W. Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. J. clin. Invest. 1954, **33**, 530.
16. Brinkman, G. L., Johns, C. J., Donoso, H., and Riley, R. L. A modification of the method of Riley, Proemmel and Franke for determination of oxygen and carbon dioxide tensions in blood. J. appl. Physiol. 1954, **7**, 340.
17. Haddy, F. J., Campbell, G. S., Adams, W. L., and Visscher, M. B. A study of pulmonary venous and arterial pressures and other variables in the anesthetized dog by flexible catheter techniques. Amer. J. Physiol. 1949, **158**, 89.
18. Howell, J. B. L., and Peckett, B. W. Studies on the elastic properties of the thorax of supine anaesthetized paralysed human subjects. J. Physiol. 1957, **136**, 1.
19. Haddy, F. J., and Campbell, G. S. Pulmonary vascular resistance in anesthetised dogs. Amer. J. Physiol. 1953, **172**, 747.
20. Aviado, D. M., Jr., and Schmidt, C. F. Respiratory burns with special reference to pulmonary edema and congestion. Circulation 1952, **6**, 666.
21. Kuida, H., Hinshaw, L. B., Gilbert, R. P., and Visscher, M. B. Effect of gram-negative endotoxin on pulmonary circulation. Amer. J. Physiol. 1958, **192**, 335.
22. Visscher, M. B., Haddy, F. J., and Stephens, G. The physiology and pharmacology of lung edema. Pharmacol. Rev. 1956, **8**, 389.
23. Lewis, B. M., Lin, T., Komisaruk, R., and Noe, F. E. Diffusing capacity of pulmonary membrane and pulmonary capillary blood volume in normal subjects; the effects of exercise and body position; preliminary observations in cardiac patients. Clin. Res. Proc. 1957, **5**, 309.
24. Rankin, J., McNeill, R. S., and Forster, R. E. The influence of the pulmonary capillary blood volume, gas tensions, and hematocrit on diffusing capacity for carbon monoxide. Clin. Res. Proc. 1957, **5**, 310.
25. Forster, R. E., Roughton, F. J. W., Cander, L., Briscoe, W. A., and Kreuzer, F. Apparent pulmonary diffusing capacity for CO at varying alveolar O_2 tensions. J. appl. Physiol. 1957, **11**, 277.
26. Roughton, F. J. W., and Forster, R. E. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J. appl. Physiol. 1957, **11**, 290.
27. Bondurant, S., Hickam, J. B., and Isley, J. K. Pulmonary and circulatory effects of acute pulmonary vascular engorgement in normal subjects. J. clin. Invest. 1957, **36**, 59.
28. Otis, A. B., and Jude, J. Effect of body temperature on pulmonary gas exchange. Amer. J. Physiol. 1957, **188**, 355.
29. Whitfield, A. G. W., Bond, W. H., and Arnott, W. M. Pulmonary irradiation effects and their treatment with cortisone and ACTH. J. Fac. Radiol. (Lond.) 1954, **6**, 12.