present in 80% of the patients in whom the diagnosis was established and only 20% of the others Positive findings of splenomegaly and abdominal mass or ascites were invariably associated with diagnostic findings at laparotomy, and all but 2 of 14 patients with hepatomegaly had positive findings at operation All 3 with pleural effusion had diffuse peritoneal tuberculosis. The alkaline phosphatase level was elevated in 8 patients, 7 of whom had positive operative findings A positive genitourinary or gastrointestinal x-ray finding was invariably associated with positive findings at laparotomy After laparotomy, all but 3 patients were ambulatory and on oral intake within 48 hours; only 2 were not ready for discharge within 10 days In all, 35 patients (76%) benefited through surgery since the findings permitted therapy Four patients with gallbladder disease were cured by operation Antibiotic therapy resolved an inflammatory disease in 10. Radiotherapy and systemic antineoplastic agents gave symptomatic relief to 17 others. Cortisone therapy benefited 4 patients with various diseases.

The morbidity accompanying exploratory laparotomy should be considered with respect to the advantages of an earlier diagnosis The 2 deaths occurring in this series, although related to surgery, were in elderly patients with disseminated incurable diseases The institution of specific therapy based on a definitive diagnosis, which was achieved in over three fourths of the patients, is certainly preferable to blind therapeutic trials and tends to justify a complication rate of 15% from laparotomy.

► [I agree with the authors Diagnostic laparotomy is justified and advisable in certain cases of prolonged unexplained fever It often provides essential information required for cure or palliation of a grave illness – Ed.]

# THE CHEST

CARL MUSCHENHEIM, M.D.

# PART II
# THE CHEST

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## PULMONARY SURFACTANT

**Pulmonary Surfactant** is discussed by Douglas T. Coles and Ward S Fowler[1] A substance in the lining layer of the alveoli of the mammalian lung which represents the first layer of the alveolar-capillary membrane is referred to as surfactant Recent studies suggest that it is a lecithin-protein complex Apparently it is produced by alveolar epithelial cells The ability of the surfactant to reduce surface tension to low values when the area of the film is reduced contributes to stability of the alveolar spaces, which otherwise might collapse or overexpand If the tension in the wall of two adjacent alveoli of different diameter and radius is the same, the expanding pressure will be larger for the alveolus with the smaller radius Without other restraint, the greater pressure will cause air to flow into and expand the large alveolus while the small one collapses Eventually all the small spaces in the lung would empty into one large space. Stability appears to be derived in part from the presence of tissue elements around the air spaces and by the surface properties of the lining layer. Surface tension is low, permitting alveoli of small radius to be kept expanded by small distending pressures. Surface tension decreases as surface area decreases, which also tends to prevent small alveoli from collapsing as their radius decreases during exhalation

It seems that atelectasis will result if, for any reason, surfactant is not present. Atelectasis is associated with absence of normal surface activity of lung extracts in the respiratory distress syndrome of the newborn (hyaline membrane disease), prematurity, atelectasis after cardiopulmonary bypass procedures, and compression atelectasis. Hyaline membrane disease appears to be a result of surfactant deficiency secondary to lack of synthesis by an immature cellular lining in the lung of these infants. In the adult lung, surfactant defi-

(1) N Clin North America 48:1055-1061, July, 1964.

ciency apparently is related to pulmonary blood flow Atelectasis and loss of surface activity follows ligation of one pulmonary artery in the dog in the ipsilateral lung, but surfactant seems to be present. It has been postulated that interfering substances are present which prevent the surfactant from acting. It is possible that surfactant decomposes in the lung, yielding lysolecithin as a product to produce this interference with the remaining surfactant. In the process of lyophilization of the foam and preparation of the film, the complex may be dissociated and the surfactant recovered in vitro. These circumstances may obtain where pulmonary artery blood flow is stopped temporarily in cardiopulmonary bypass operations and in atelectasis produced by lung compression.

➤ [The relation of this surface tension lowering substance to disease has been studied extensively in the past 5–10 years. The bibliography appended to this concise review contains the key references. Ed.]

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## RADIOACTIVE TECHNICS

**Regional Lung Function in Kyphoscoliosis.** C. T. Dollery, P.M.S. Gillam, P. Hugh-Jones and P. A. Zorab[2] (London) studied lung function in 10 patients with severe kyphoscoliosis, in 2 of them before and after costectomy, using xenon-133. All patients but 3 were young, and only these 3, who also had bronchitis, had effort dyspnea. Seven patients were studied using two pairs of stationary scintillation counters repositioned over 4 or 6 areas, and 6 were studied with motor-driven counters moving vertically over the lungs.

The ratio of blood flow per unit lung volume at the level of the 2d rib to that at the level of the 5th interspace is about 0.22 in upright normal subjects; the average for the same ratio in the patients was 0.95. Of 6 patients studied in detail, 4 had a fairly even distribution of blood flow throughout both lungs, and 2 had a peak of perfusion per unit volume in the midzones with a fall-off toward both apex and base. Relatively even distribution of blood flow was not confined to the 3 patients with abnormally poorly ventilated areas in the lower zones. The average ventilation per unit lung volume at

(2) Thorax 20:175-181, March, 1965

the level of the 2d rib compared with a position 10 cm. lower was 1.46, a high value due to the 3 patients with severe reduction in ventilation at the lung bases. All 3 of these were older and had symptoms suggesting chronic bronchitis; 1 had only moderate kyphoscoliosis.

Case 1.—Girl, 16, developed idiopathic spinal curvature at age 7 years and was treated with a spinal support. Fusion was performed twice after which she could play games despite grade 3 kyphoscoliosis. The vital capacity was 2,500 ml. and the total lung capacity 4,510 ml. Wash-in and wash-out of xenon were normal at all 6 areas studied. The ratio of blood flow to lung volume was lower in the upper zones than in the lower, but there was less than the normal difference between these zones.

Case 2.—Woman, 43, had a history of cough and sputum in the winter for several years. She had developed idiopathic kyphoscoliosis at age 14, which progressed to grade 3. She now is breathless on moderately heavy exertion and has bronchitis with occasional attacks of severe wheezing. The scoliosis is in the lower thoracic spine with nearly 90 degrees of angulation. The xenon wash out was extremely slow at both lower zones. The midzone traces showed a distinct change in slope of wash out, suggesting that the alveoli consisted of widely separated populations with different ventilation characteristics.

► [Even perfusion of the lung is abnormal in the upright position. The authors explain it in these patients as due in part to the foreshortened thorax, together with an increase in pulmonary vascular pressure, which has been observed by cardiac catheterization in patients with kyphoscoliosis, with and without exertional dyspnea. They have no explanation for the reduced lower zone ventilation in the 2 older patients, who were also those who had symptoms. They leave the question open whether this finding is related to the kyphoscoliosis or to the chronic bronchitis which was noted in these 3 patients, 2 of whom had significant airway obstruction. The regional ventilation and perfusion in emphysema using the same technic was studied by Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates (see the 1964–65 YEAR BOOK, p. 164), who noted predominantly zonal abnormalities of function in patients who would, by usual criteria, be thought to have generalized emphysema. One wonders whether this may not be the explanation.—Ed.]

Pulmonary Scanning was evaluated by Henry N. Wagner, Jr.[3] (Johns Hopkins Univ.). Radioisotopic pulmonary scanning was carried out by intravenous injection, with the patient supine, of either 300 $\mu$c. of $I^{131}$ macro-aggregates of human serum albumin or 1,000 $\mu$c. of $Cr^{51}$ macro-aggregates, followed immediately afterward by scanning, using conventional technics.

The appearance of the lung scan in a normal person with the detector facing the anterior aspect of the chest is shown in Figure 12, as are the series of "profiles" obtained as the detector moves back and forth across the lung fields. The

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(3) Northwest Med. 63:857-864, December, 1964

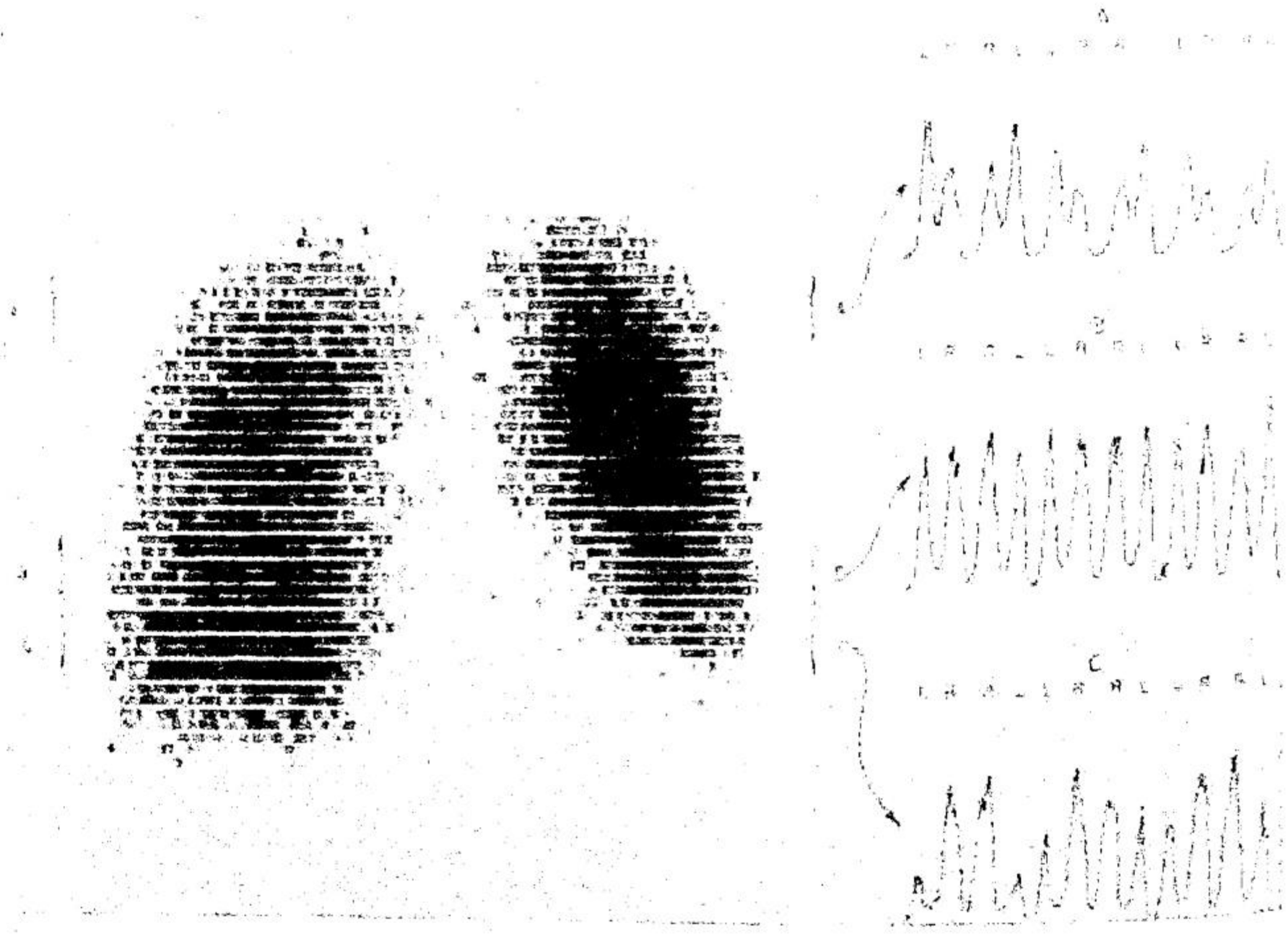


Fig 12 —Lung scan in a normal person from the anterior viewpoint and rate-meter tracings measuring the radioactivity as the detector moved across the regions indicated as *A B* and *C L* and *R* refer to left and right lungs. (Courtesy of Wagner, H N Jr Northwest Med 63 957 964, December 1964)

characteristic pattern indicates absence of radioactivity in the region of the superior mediastinum and heart The base of the right lung is usually flat, although decreased concentration can be observed normally both at the bases and apexes, presumably as a result of the excursions of the lung during respiration.

Scanning in diagnosis of massive pulmonary embolism is easy, safe and effective No toxicity or morbidity has been observed in experimental animals or in over 300 patients, some of whom had serious lung disease. The procedure can be performed regardless of the clinical status of the patient and repeatedly in the same individual Results in patients with massive pulmonary embolism proved at autopsy are shown in Figure 13. Characteristic patterns noted were frequent involvement of the right lower lobe, bilaterality, concave filling defects at the lateral lung margins and increased concentration of radioactivity in the perfused areas Particularly helpful in diagnosis is the finding of areas of decreased radioactivity corresponding to areas of normal or perhaps increased radiolucency on the chest x-ray.

Several patients with chronic pulmonary disease showed strikingly discrete areas of avascularity. Pulmonary avascu-

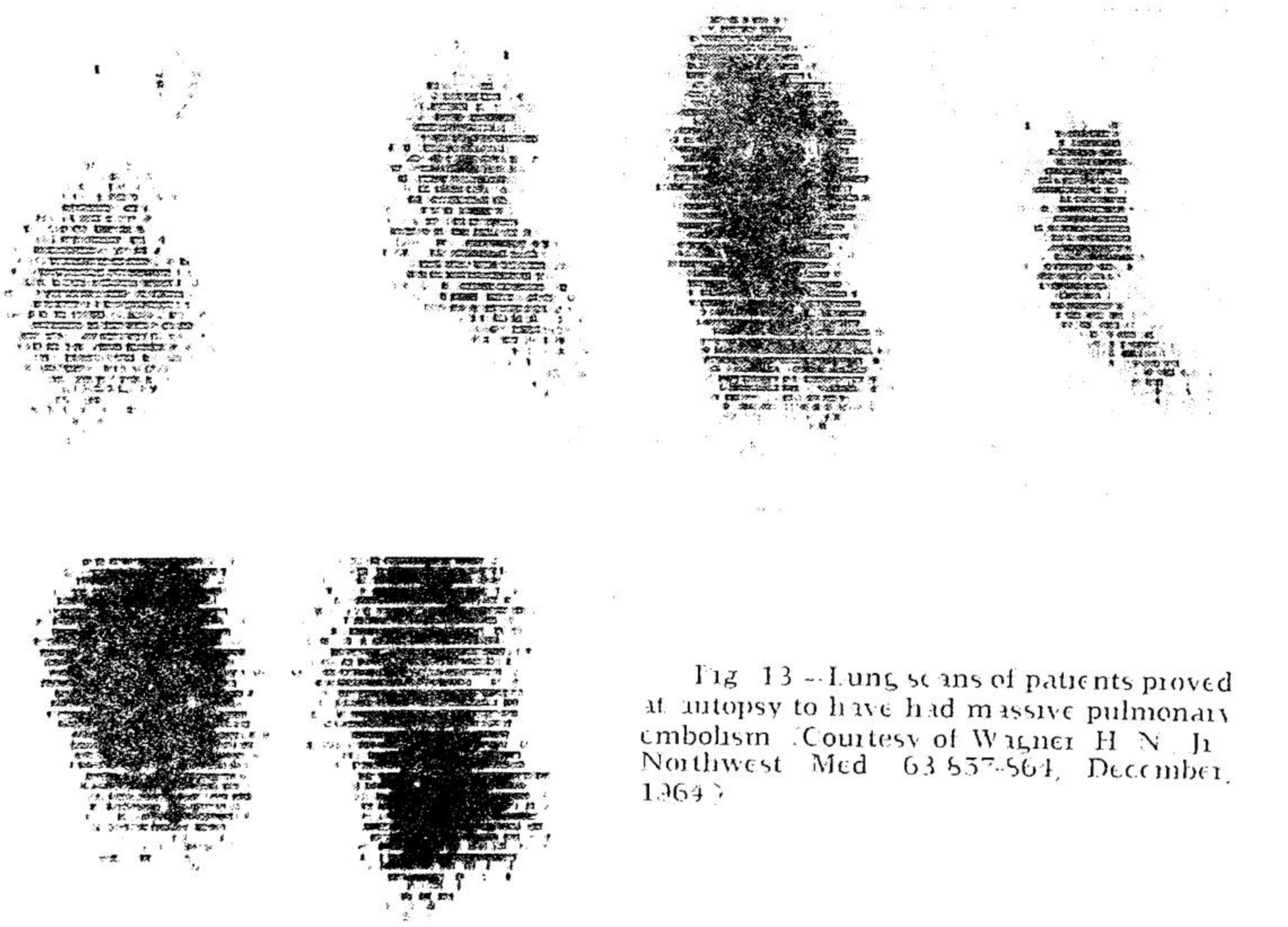


Fig 13 —Lung scans of patients proved at autopsy to have had massive pulmonary embolism (Courtesy of Wagner H N Jr Northwest Med 63 557-564, December, 1964)

larity was observed in acute diseases, such as pneumonia and atelectasis, as well as in chronic diseases, including neoplasms, abscesses and sarcoidosis Preliminary studies of patients with a variety of congenital cardiac lesions suggested that the scanning technic may provide a safe and effective means of determining degree of perfusion of the lungs and of delineating poorly perfused areas In several cases, scanning provided information about pulmonary blood flow that was helpful with regard to the patient's ability to withstand pulmonary surgery. The effect of posture on pulmonary blood flow in normal man and the abnormal distribution of blood flow in patients with mitral stenosis were confirmed Serial lung scanning in man and animals to determine the natural history of pulmonary embolism gave encouraging results

► [This new procedure of lung scanning by radioactively labeled serum albumin is an adaptation of a method originally introduced for the study of the reticuloendothelial system. It requires less complex equipment than the radioactive xenon method of determining the relative perfusion of different regions of the lung. Whether it will prove to be more or less useful than angiography in the diagnosis of pulmonary embolism is as yet unsettled. A further analysis of lung scanning by this method is presented in the next article.—Ed.]

**Lung Scanning with Radioiodinated Macroaggregates of Human Serum Albumin** was performed in 200 cases of pulmonary disease by Leonard Rosenthall[4] (Montreal Gen'l Hosp.) Two preparations with particle sizes of 10-100$\mu$ and 5-30 $\mu$, respectively, were used The radiation dose to the lung is about 0 1 rad per 100 mc $I^{131}$ -macroaggregates There have been no toxic reactions with single or multiple doses of the denatured protein Scanning was performed with the patient prone immediately after intravenous injection of 100 mc Lugol's solution or potassium iodide was given the day before, the day after and the day of study

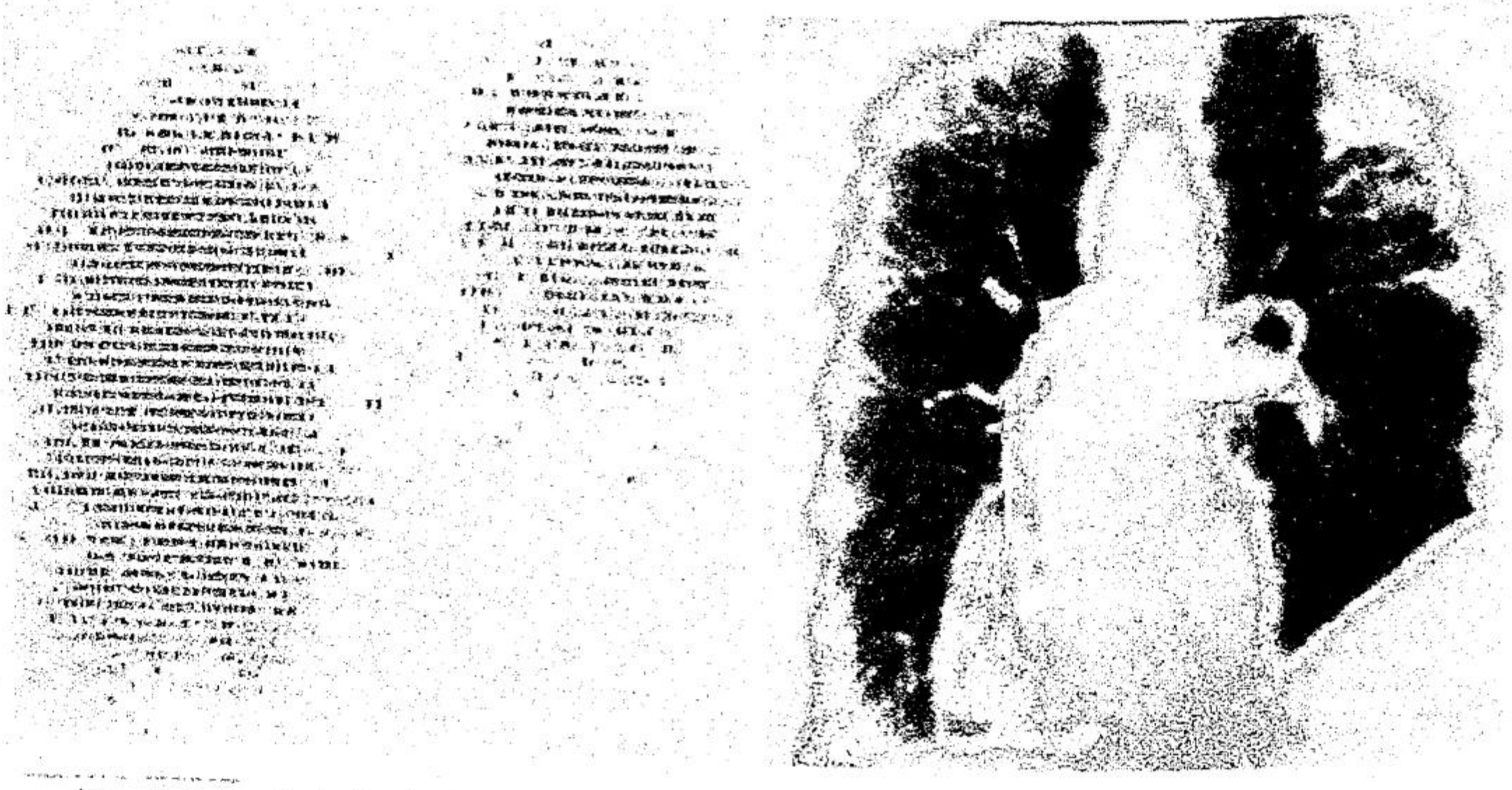
Woman, 76, was hospitalized because of pleuritic pain over the right anterior side of the chest, followed by pyrexia and hemoptysis A chest x-ray showed obliteration of the right costophrenic sulcus and an elevated right hemidiaphragm Serum lactic dehydrogenase activity was elevated, but glutamic oxalacetic transaminase activity was normal Lung scanning showed pulmonary arterial avascularity in the lower half of the right lung (Fig 14) A pulmonary arteriogram showed an embolus lodged in the main artery to the right lower lobe and reduced circulation distal to the embolus (Fig 15) Venography showed total occlusion of the left deep femoral vein

This technic detects areas of relatively reduced pulmonary arterial blood flow in pulmonary arterial obstruction with or without infarction Thus it is not specific for any one entity It is particularly useful in diagnosis of an acute pulmonary

Fig. 14 (left) -- Lung scan with the patient prone, demonstrating a pulmonary arterial vascular defect in the lower half of the right lung.

Fig. 15 (right) -- Pulmonary arteriogram showing an embolus lodged in one of the main branches to the right lower lung associated with decreased blood flow to the dependent area.

(Courtesy of Rosenthall, L. J. Canad. A. Radiologists 16: 30-34, March, 1965.)



(4) J Canad A Radiologists 16 30 34 March 1965.

embolus in the presence of a normal chest x-ray, but this may be misleading if the patient has emphysematous bullae not readily apparent on the x-ray. Diffuse fibrosis will give a normal scan. Normal scans have been obtained in pulmonary edema and in bronchopneumonia. Lesions 3 cm. in diameter apparently escape detection. Much of the confusion of lung scan interpretation might be obviated by obtaining a baseline scan in patients with known chronic chest disease and before surgery

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## BRONCHITIS AND EMPHYSEMA

**Survey of Types and Severity of Emphysema in Routine Autopsies.** K. Viner Smith[5] (Univ. of Sydney) examined the lungs of 103 unselected subjects for emphysema by a variety of methods. There were 65 males and 38 females, 80 of whom were aged 51-80 years, after exclusion of subjects below age 51 and over age 80, 49 males and 31 females remained.

Many subjects had more than one type of emphysema

TYPES AND SEVERITY OF EMPHYSEMA IN 80 SUBJECTS AGED 51-80 YEARS AT DEATH

| DEGREE OR TYPE OF EMPHYSEMA | MEN (49) | | WOMEN (31) | |
|---|---|---|---|---|
| None | 6 (12%) | | 17 (55%) | |
| Panacinar | | | | |
| Mild | 16 (33%) | | 5 (16%) | |
| Moderate | 0 | | 0 | |
| Severe | 0 | | 0 | |
| Centrilobular | | | | |
| Minimal | 11 (22%) | | 4 (13%) | |
| Mild | 20 (41%) | 73% | 3 (10%) | 23% |
| Moderate | 5 (10%) | | 0 | |
| Severe | 0 | | 0 | |
| Focal | 1 | | 0 | |
| Bullous | | | | |
| Mild | 14 (29%) | | 1 | |
| Severe | 7 (14%) | 43% | 1 | |
| Localized | | | | |
| Mild | 9 (18%) | | 4 (13%) | |
| Severe | 0 | | 0 | |
| Other | 3 | | 0 | |

(5) Australasian Ann. Med. 14:26-34, February, 1965.

(table) Emphysema was more common in men than in women, statistically significant at a level of 0.1%. This was true of the panacinar, centrilobular and bullous types. Most males with panacinar emphysema also had centrilobular emphysema, but the association was not significant at the 5% level. Of 36 men with centrilobular emphysema, 14 also had panacinar emphysema. There was no correlation between panacinar emphysema and bullous emphysema, or between presence of panacinar and other types of emphysema in the men studied. No significant association was found in males between centrilobular emphysema and bullous or other types of emphysema (all types other than panacinar, centrilobular and bullous emphysema). In no one type of emphysema was it common to find subjects with that type alone. No significant association was found between acute bronchiolitis or bronchopneumonia at death and emphysema of any type.

► This straightforward anatomic study provides new information on the prevalence of emphysema in the older age group and on the distribution of various types. The finding of emphysema in nearly three fourths of the subjects studied indicates a higher prevalence than has been reported heretofore. Doctor Smith does not, on the basis of these observations, find support for McLean's view that bronchiolitis is a principal cause of emphysema (see the 1959-60 YEAR BOOK, p. 133). As regards the concept of "focal dust emphysema" of Gough and Leopold, he found in most of the lungs with centrilobular emphysema more dust than in the surrounding lung, but he does not conclude from this that dust and soot necessarily have pathogenetic significance.—Ed.

**Urban Factor in Chronic Bronchitis.** W. W. Holland and D. D. Reid[6] (London) studied 293 men employed as mail van drivers and vehicle maintenance men in central London, and 477 men employed as mail-van drivers or engineering workers also driving vans in the areas in and around three country towns in southern England. The reported death rates in the latter areas from chronic bronchitis were low compared with those for London, whereas the rates of death, invalidism and absence through respiratory illness in these occupational groups followed the same trend. The response was satisfactory and similar in the two groups, 92.7% of the London group and 93.4% of the country group being seen.

Below age 50 years, London men have significant excesses of cough and phlegm production throughout the day and of severe breathlessness. Over that age, the London excess is clear for most symptoms and especially for the more severe forms of respiratory disturbance. There is for London men,

6) Lancet 1:443-445, Feb. 27, 1965.

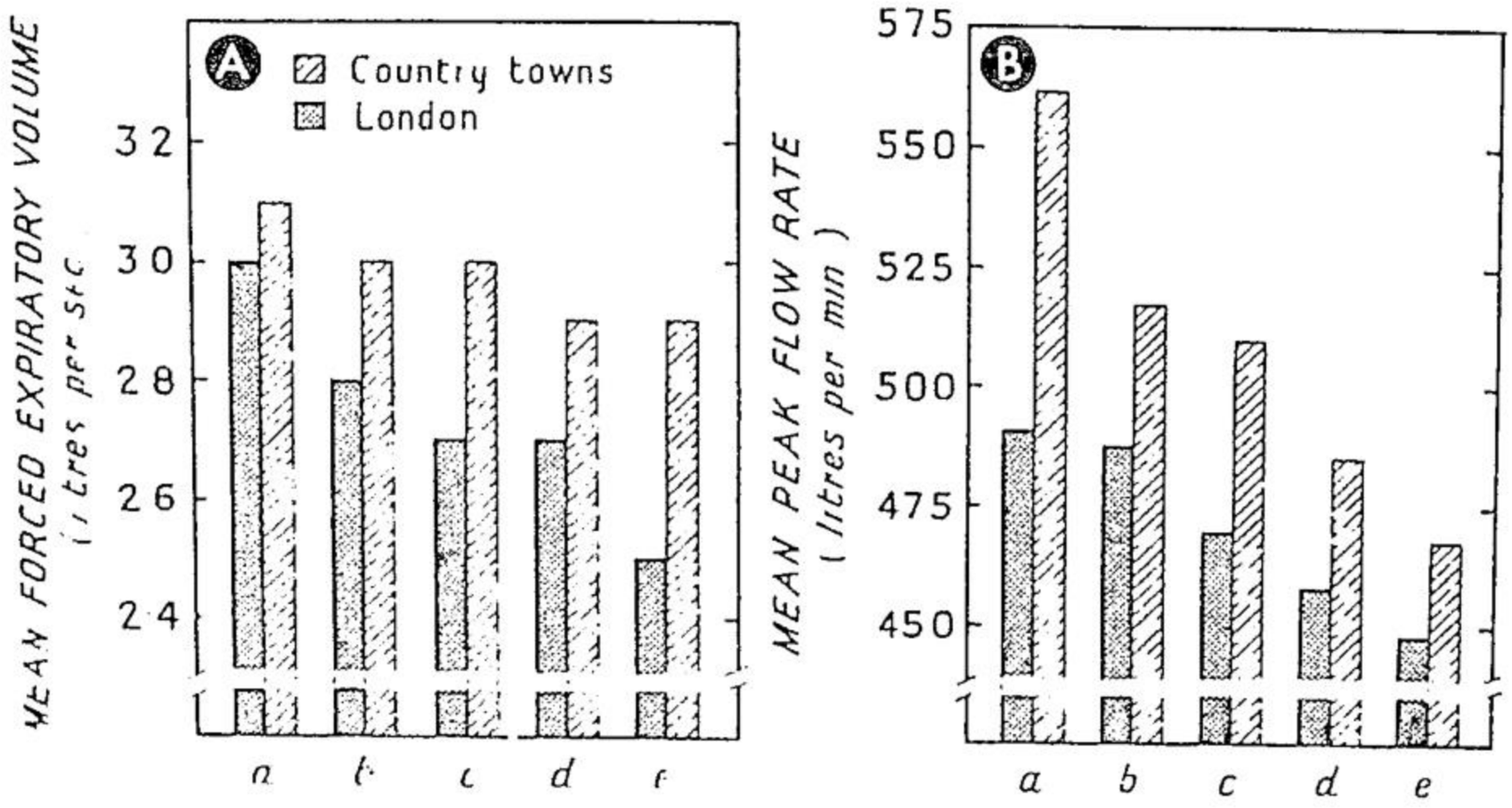


FIG. 16.—*A*, mean forced expiratory volume (1 second); *B*, mean peak flow rate (both standardized to age 40). *a*, nonsmokers; *b*, exsmokers; *c*, smokers, 1-14 Gm. per day; *d*, smokers, 15-24 Gm. per day; *e*, smokers, 25 Gm. or more per day. Mean value and number of subjects: *A*, (*a*) 3·1 (36) and 3 (13); (*b*) 3 (7) and 2·8 (56); (*c*) 3 (142) and 2·7 (74); (*d*) 2·9 (154) and 2·7 (98); (*e*) 2·8 (49) and 2·5 (38). *B*, (*a*) 502 (31) and 491 (15); (*b*) 517 (7[illegible]) and 488 (56); (*c*) 510 (142) and 470 (74); (*d*) 486 (154) and 459 (98); (*e*) 468 (41) and 448 (29). (Courtesy of Holland, W. W., and Reid, D. D., Lancet 1:445-449, Feb. [illegible], 1965.)

for most grades of disturbance, a definite age trend that is practically absent in the others. The London men had lower mean levels of lung function (peak expiratory flow rate and forced expiratory volume in 1 second). They produced more sputum, and it was more likely to be mucopurulent or purulent. Smoking was associated with increased sputum production, but differences in smoking habits could not explain the London excess in persistent cough and phlegm. Results of lung function tests supported this finding (Fig. 16). There was a downward trend in both measures of lung function with increased tobacco consumption in both groups of men. At each level of consumption, the mean for London men was below that of the men in the country towns and surrounding districts.

Of the factors studied, differences in local levels of air pollution appear to be the likeliest cause of the difference in respiratory morbidity found between men working in central London and those in the rural areas.

► [The examinations for this comparative survey were carried out in 1960 and 1961. Doctors Holland and Reid, with collaborators using standardized questionnaires and the same methods of measurement of ventilatory impairment, have made international comparisons of similar kind. The results of two such studies involving comparable groups in different countries are reported in the following 2 articles.—Ed.]

**Respiratory Disease in England and the United States: Studies of Comparative Prevalence.** W W Holland, D D Reid (London), R. Seltser and R W Stone[7] (New York) examined men in three areas. (1) post-office van drivers in London and (2) in three English country towns and the surrounding rural districts and (3) outside telephone workers in three areas of the United States who performed similar duties to the English subjects. A questionnaire for respiratory symptoms was used Lung function was determined by a McKesson Vitalor.

Analysis of results was limited to men aged 40-59 years At age 40-49, there was little difference between the three areas in proportion of individuals without persistent cough. Milder cough was more common in Americans and more severe cough in the English. The same differences were found for phlegm production. At age 50-59, the differences between the three areas were much more striking Severe symptoms were more common in London than in the other areas. There was a marked age gradient in prevalence of symptoms in the London men; this was much less marked in the other two areas. The mean one-second forced expiratory volume was lowest in both age groups in London and highest in the United States. The proportion of subjects returning over 2 ml sputum was greatest in London and least in the United States, and the same trend was apparent for type of sputum returned.

The American group contained more men who have never smoked than the English group, whereas those who smoke do so more heavily. Very few nonsmokers or ex-smokers in any area had symptoms. Symptoms were more common in heavy than in light smokers. Within each smoking category, severe symptoms were more common in the English group. The differences in pulmonary function between the areas are not accounted for by differences in smoking habits (Fig. 17). The American men were heavier and taller than either English group. Adjustment for sitting height did not eliminate the group differences. Differences in sputum volume could not be explained by differences in smoking habits.

The most striking environmental difference between the three areas of study was the level and type of air pollution. The mean levels of sulfur dioxide and suspended particulate are higher in London and the three country towns in England

(7) Arch. Environ. Health 10 338-343 February, 1965

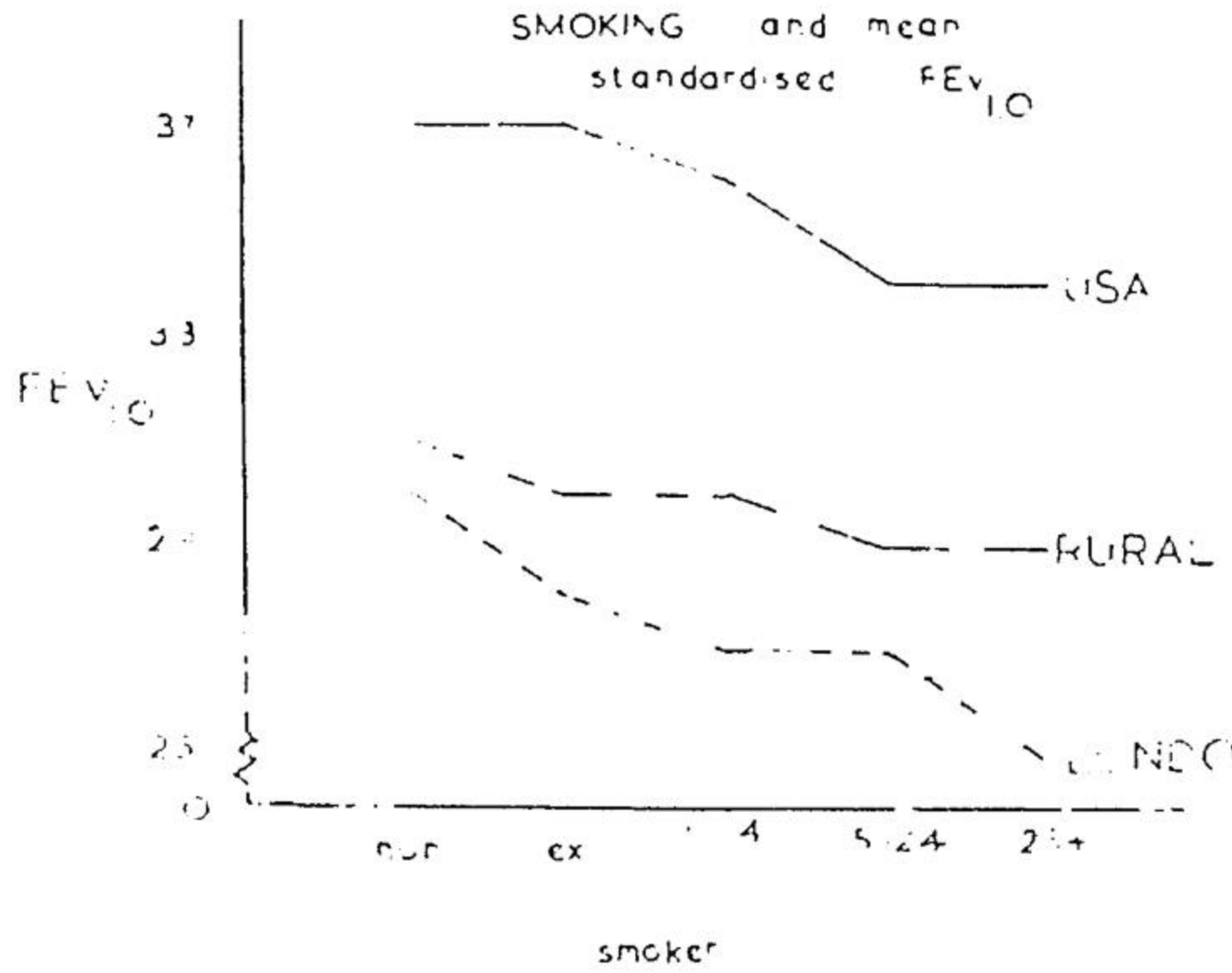


Fig. 1?—Mean one-second forced expiratory volume ($FEV_{1.0}$), in liters, standardized to age 40 in men from London, country towns (Rural), and the United States by smoking habits (Courtesy of Holland, W. W. *et al.* Arch Environ Health 10:338-343, February 1965.)

than in the three United States cities (Washington, Baltimore, and Westchester, N. Y.). The greatest difference is shown by the highest levels recorded for these pollutants. Perhaps this accounts for the differences in respiratory morbidity.

► [The American groups are compared here apparently with the same English groups reported separately by Holland and Reid in the immediately preceding article. Considering Westchester, N. Y., as a city may cause surprise to many residents of the United States, which in large part is considered a suburban area and in some sections seems quite bucolic. The authors do not state whether their observations were confined to Westchester cities, such as Yonkers, New Rochelle and White Plains. In any event, it is learned from a personal communication that the air pollution in Westchester is equal to that in Washington and Baltimore, but less than that in the three country towns in England, and much less than in London.—Ed.]

**Anglo-American Comparison of Prevalence of Bronchitis.** D. D. Reid, D. O. Anderson, B. G. Ferris and C. M. Fletcher[8] studied the reported British excess in bronchitic morbidity by comparing the results of field surveys carried out in various parts of England and in one town in the United States. Similar respiratory symptom questionnaires and a simple lung function test (the Wright peak flow meter) were used in the two locales. A random sample of men and women aged 40-64 years was drawn from the practice lists of 92 doctors working in urban and country areas of Britain. The American locale was Berlin, New Hampshire, a town in

(8) Brit. M. J. 2:1487-1491, Dec. 12, 1964.

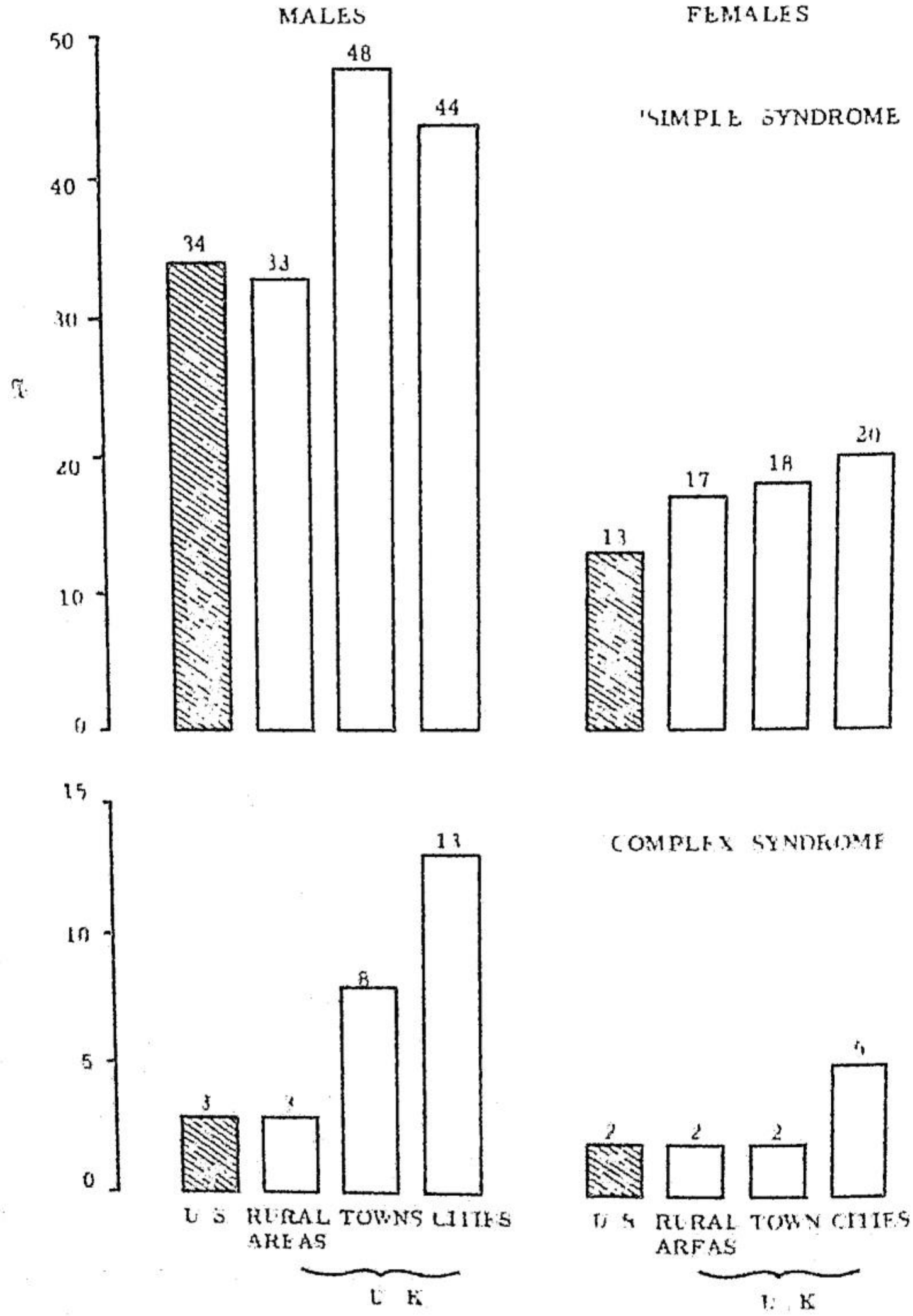


Fig. 18.—Prevalence rates in the United States (*U.S.*) and Britain (*U.K.*) for complex bronchitis, standardized for age and cigarette consumption. (Courtesy of Reid, D. D., *et al*: Brit. M. J. 2:1487-1491, Dec. 19, 1964.)

northern New England with a population in 1960 of 17,821.

The prevalence of "simple bronchitis" (chronic phlegm production) differed little between the American town and the rural and urban areas of Britain. Its relation to cigarette smoking was obvious in the results from both countries. However, "complex bronchitis," with repeated chest illnesses and breathlessness, was more common among older men in Britain. Prevalence rates standardized for age and lifetime cigarette consumption are shown in Figure 18. After differences in age distribution and smoking habits were considered, this form of bronchitis appeared to be about equally

common in the American town and the rural areas of Britain, but was much more common in the British towns and cities, especially among men. Results of function tests were consistent with the suggestion of a higher prevalence of a more severe form of bronchitis among older males living in British urban conditions.

▶ This and the preceding article indicate that the prevalence of disabling bronchitis and/or emphysema is in fact greater in Britain, specifically under British urban conditions, than it is in the United States, apart from any confusions of semantics.

In the following article, Doctor Fletcher has joined with other American collaborators in applying criteria which he and his associates used earlier in distinguishing chronic obstructive lung disease with severe emphysema from that without anatomic emphysema (see also 1963-64 YEAR BOOK, p. 106), to American as well as to British groups of patients.—Ed.

**Clinical Types of Chronic Obstructive Lung Disease in London and Chicago: Study of 100 Patients,** 50 from each city, is reported by B. Burrows, A. H. Niden, C. M. Fletcher and N. L. Jones.[9] X-rays showed definite evidence of emphysema in 18 patients, definite evidence of chronic inflammatory disease but no emphysema in 20 and no significant abnormality or minor evidence of emphysema or chronic inflammatory disease in 62.

There was little difference in complaints of cough or sputum or severity of dyspnea between the emphysema and inflammation groups. Among patients who produced sputum, evidence of infection was more frequent in the inflammatory group. According to ECGs, grade 1 right ventricular hypertrophy was more frequent in the emphysema group. Grades 2-4 right ventricular hypertrophy were found almost exclusively in the inflammatory group, as were edema, cardiomegaly and congestive heart failure. The mean forced expiratory volume was slightly lower in this group, but the patients in this group more often showed a significant improvement on inhalation of nebulized isoproterenol. All lung volumes tended to be higher in the emphysema group, and this group had a lower mean pulmonary diffusing capacity ($D_L$), especially when expressed per liter of lung volume ($D_L/VA$). Carbon dioxide retention was confined to the inflammatory group, 55% of whom showed an elevation. The characteristics of the 62 patients in the unclassified group were in most instances intermediate between those of patients in the other two groups. On the basis of characteristics, patients with

(9) Am. Rev. Resp. Dis. 90:14-27, July, 1964.

TYPICAL CHARACTERISTICS OF GROUPS A AND B

| Features | Group A | Group B |
|---|---|---|
| History | Rarely symptoms before age 50 | Early onset of cough and chronic sputum frequent |
| Sputum | Usually scanty and mucoid | Usually over 10 ml in twenty-four hours and often purulent |
| Roentgenogram | Roentgenologic evidence of emphysema frequent | Roentgenologic evidence of inflammatory disease frequent |
| Cardiovascular system | Chronic cor pulmonale rare | Chronic cor pulmonale frequent |
| Lung volumes | Vital capacity usually only slightly reduced<br>Residual volume usually markedly increased<br>Total lung capacity usually moderately increased | Vital capacity often very low<br>Residual volume usually only moderately increased<br>Total lung capacity usually within normal limits and sometimes low |
| Blood $pCO_2$ | Usually normal or slightly low, apart from acute exacerbations | Usually persistently elevated when FEV is below 1.0 liter |
| Diffusing capacity (breath-holding method) | $D_L/VA$ usually markedly reduced | $D_L/VA$ often normal or only slightly low |
| Polycythemia | Rare | Occasional |

suspected emphysema resembled those with roentgenologic emphysema, whereas those with suspected inflammatory syndrome resembled those with roentgenologic inflammatory disease.

There were 27 patients with a $D_L/VA$ under 3 and a total lung capacity over 120% of predicted (group A), 35 with a $D_L/VA$ over 4, or a $D_L/VA$ of 3.5-4 with over 10 ml of sputum in the 24-hour specimen (group B), and 38 who did not fulfill either set of criteria (group X). This arrangement resulted in a change of classification for some patients originally grouped according to x-ray criteria alone. One patient with roentgenologic emphysema was placed in group B, and 4 were placed in group X. Eight patients with roentgenologic inflammatory disease and equivocal physiologic characteristics were placed in group X and 2 in group A. Discriminating features are shown in the table.

The authors propose that chronic airways obstruction of uncertain etiology (presently called emphysema and/or chronic bronchitis) be diagnosed as chronic obstructive lung disease, and that this be further categorized as type A (emphysematous type), type B (bronchitis type) or type X (indeterminate type) on the basis of clinical, roentgenologic and physiologic findings.

**Tuberculosis as Cause of Increasing Mortality from Emphysema.** Cigarette smoking and air pollution are receiving most attention as causes of the increasing mortality from emphysema However, since these factors have been operating for a long time, it is difficult to explain why deaths from emphysema should have increased so suddenly and so considerably in recent years In the same period, there has been a marked decrease in mortality from tuberculosis, due mainly to the effect of antimicrobial drugs on patients with moderately or far-advanced disease. The question arises whether the life-prolonging effect of these drugs may be responsible for a considerable part of the increase in emphysema by enabling tuberculous patients to live long enough to develop emphysema secondary to tissue destruction caused by the tuberculous disease

Julius Katz and Solomon Kunofsky[1] (New York State Dept of Health, Albany, N.Y.) reviewed all death certificates in upstate New York for 1940-61 and found that the mortality from emphysema began to show a great increase about 1952 (table), about the time that isoniazid was introduced, and continuous and prolonged administration of two or more drugs was becoming standard Tuberculosis mortality declined more sharply during this period than in previous years, and the number of survivors from tuberculosis increased, especially among those with advanced disease

A study was then made of all death certificates for 1961

DEATHS AND DEATH RATES PER 100,000 POPULATION FROM TUBERCULOSIS AND EMPHYSEMA (UPSTATE NEW YORK, 1940-61)

| Year | Tuberculosis | | Emphysema | |
|---|---|---|---|---|
| | Number | Rate | Number | Rate |
| 1940-1941 | 3,972 | 32.7 | 25 | 0.2 |
| 1942-1943 | 4,149 | 33.3 | 20 | 0.2 |
| 1944-1945 | 4,039 | 31.7 | 27 | 0.2 |
| 1946-1947 | 3,650 | 27.8 | 44 | 0.3 |
| 1948-1949 | 3,129 | 23.0 | 83 | 0.6 |
| 1950-1951 | 2,367 | 16.7 | 141 | 1.0 |
| 1952-1953 | 1,526 | 10.2 | 353 | 2.4 |
| 1954-1955 | 1,134 | 7.3 | 449 | 2.8 |
| 1956-1957 | 964 | 5.8 | 702 | 4.2 |
| 1958-1959 | 879 | 5.0 | 875 | 5.0 |
| 1960-1961 | 725 | 4.0 | 1,060 | 5.8 |

(1) Am. Rev. Resp. Dis. 89:675-679, May, 1964.

listing tuberculosis or emphysema as primary or contributory causes of death. Of certificates listing tuberculosis as the primary cause of death, 13.5% also mentioned emphysema, compared with 4.9% for deaths from other respiratory diseases and 1.2% for all other causes of death, including lung cancer. Emphysema was mentioned in 10% of certificates giving tuberculosis as a contributing cause of death; death was due to primary emphysema in 4.9% of cases. Tuberculosis was mentioned in 3% of certificates giving emphysema as a primary cause of death; another 3.3% of patients were previously reported as having tuberculosis.

A study of deaths in 1945 revealed 1 case of emphysema as a primary cause among 941 deaths from "other causes." Emphysema was recorded as a contributing cause in 1.2% of 416 tuberculosis deaths, 1.6% of 245 deaths from other respiratory diseases and 0.2% of deaths from "other causes." Between 1951 and 1961, the proportion of deaths from respiratory diseases increased 50%, from 3.2 to 4.9% of all deaths. The proportion of deaths from emphysema in this period increased from 0.1 to 0.6% of all deaths, and the frequency of secondary tuberculosis increased from 0 to 4.9%. Emphysema has not only increased more rapidly than other respiratory diseases in its relative frequency as a cause of death in the past 10 years, but also its recognized association with tuberculosis has more than kept pace with this increase.

If the frequent association between tuberculosis and emphysema is a cause-and-effect relationship, as the evidence suggests, it is reasonable to expect that, if tuberculosis morbidity continues to decrease and the reservoir of cases from past years becomes depleted, the contribution of tuberculosis to mortality from emphysema will decrease.

► [Not only the life-prolonging effect of the antimicrobial therapy of tuberculosis, but that of other antimicrobial therapy on other pulmonary diseases must have added, in recent years, to the enlarging reservoir of patients with symptomatic (and potentially fatal) emphysema. Certainly, the survival of patients with incipient or relatively mild emphysema, who might in an earlier era have succumbed to intercurrent bronchopulmonary infections which can now be treated more effectively, must be a substantial factor. Another possibility, which is perhaps more speculative, is that patients with relatively normal lungs, when they contract an infection which is aborted by antimicrobial therapy, may nevertheless suffer damage of a kind which may progress to emphysema, especially if the insult is many times repeated. There must be a large number of persons living who are the many-time survivors of respiratory infections which without modern treatment would have progressed to fatal terminations. It seems reasonable to suppose that such infectious factors play at least as important a role as smoking and air pollution which, as the preced-

ing 4 articles attest are epidemiologically better defined but the latter are, doubtless, more amenable to epidemiologic study – Ed.]

**Chronic Obstructive Airway Disease: Bacterial and Cellular Content of Sputum.** Patrick B. Storey, W. K. C. Morgan, Alberto J. Diaz, Julian L. Klaff and William S. Spicer, Jr.[2] (Univ. of Maryland) examined 13 patients with chronic obstructive pulmonary disease on 40 consecutive days. Diplococcus pneumoniae and Hemophilus influenzae were found in 441 of 488 sputum specimens examined. There was no relation between the presence or the numbers of these organisms in the sputum and the purulence of the specimens in the group as a whole. The findings are interpreted to mean that, although D. pneumoniae and H. influenzae are often recovered from such sputa, it does not follow that they can be considered the usual cause of exacerbations. Only careful evaluation of each patient, possibly supplemented by more direct study of the bronchial secretions, will allow proper recognition of the factors (bacteriologic, viral, environmental or other) operating at any given time in the worsening or improvement of the basic disease process.

► [This report is at variance with numerous earlier studies, particularly those from Great Britain, in which these organisms were found to be apparently causally related to exacerbations of chronic bronchitis. Differences of opinion on the matter have long existed, and the present authors are not alone in their doubts about the importance of pneumococci and H. influenzae (see the article by Davis *et al.* in the 1962-63 YEAR BOOK, p. 143). – Ed.]

**Severe Arterial Hypoxemia and Liver Cell Necrosis in Patients with Pulmonary Insufficiency.** H. E. Refsum[3] (Oslo) studied liver sections taken at autopsy from 16 patients with severe pulmonary insufficiency who had combined hypercapnia and hypoxemia. In these patients, arterial oxygen was lower than 9 ml./100 ml., probably for several hours, at varying time intervals before death. The pulmonary insufficiency was due to chronic bronchitis, emphysema, tuberculosis or bronchial cancer. Right ventricular hypertrophy was found at autopsy in all cases and was of marked degree in 12; right atrial dilatation was found in 8.

Sampling of arterial blood during exacerbations of the pulmonary insufficiency before treatment showed the following mean gas values: total $CO_2$ (plasma), 38.1 mEq./L.; pH, 7.286; $Pco_2$, 79.7 mm. Hg; $HbO_2$, 39.3%; $Po_2$, 25 mm. Hg; and oxygen content, 7.08 ml./100 ml. Duration of failure at

(2) Am. Rev. Resp. Dis. 90:729-735, November, 1964.
(3) Acta med. scandinav. 178:473-478, October, 1964.

the time of blood sampling was 24 hours or more in 9 patients, 8-24 hours in 6 and less than 6 hours in 1. Treatment was begun to relieve hypoxemia and hypercapnia; it entailed bronchial suction, artificial ventilation and oxygen administration. Prolonged periods of severe hypoxemia were generally avoided from the start of treatment.

At autopsy, marked centrilobular necrosis was observed in 2 patients, small focal necroses in 4 and both conditions in 1. All showed venous congestion, and 12 showed atrophic changes, of a high degree in 4, all with focal necroses. Of the 8 patients who died within 3 days of blood sampling and observation of severe hypoxemia, 7 showed necrotic changes. Of 8 patients who survived 8 days or longer, none showed definite signs of necrosis. The duration of severe failure in patients with necrosis was about 8 and 12 hours before start of treatment in 2 instances, and 24 hours or longer in the others.

No significant difference in mean arterial oxygen content was found between patients with short survival and necrosis and those with prolonged survival and without necrosis. It did not appear that duration of severe hypoxemia or severity of clinical findings were more pronounced in the former than in the latter group. Conversely, 3 patients with the most severe necrosis, who had severe failure for about 8, 12 and 24 hours, respectively, at the time of sampling, remained conscious until soon before death, whereas 3 patients without necrosis, who had severe failure of about the same duration, were comatose during blood sampling. Terminally, there was no difference in body temperature or clinical signs of infection between those with short and prolonged survival times. Degree of venous congestion, liver weight and microscopic appearance of the liver were about the same in both groups; there was no difference in pulse or blood pressure.

The lack of definite signs of necrosis in patients with prolonged survival is assumed to be due to complete regeneration of the liver tissue. The data seem to indicate that small focal necroses may be associated with less severe liver hypoxia than is centrilobular necrosis. The high frequency of necrosis in patients with short survival confirms earlier enzymatic evidence that an arterial oxygen content below 9 ml./100 ml. blood is associated with severe cell derangement.

► [Doctor Refsum has shown previously (see the 1964-65 YEAR BOOK, page

183) that hypoxemia of this severity is associated with elevations of the serum enzymes SGO-T, SGP T and SLDH The present studies confirm his earlier conclusion that these elevated serum levels are due to released enzymes of hepatic origin Doctor Refsum pointed out in the former report that arterial hypoxemia can lead to liver cell necrosis before loss of consciousness or congestive heart failure occurs -an observation of obvious clinical importance --Ed ]

**Erythropoiesis in Subjects with Chronic Bronchitis.** Donald Massaro, Angela M. Cusick and Sol Katz[4] (Washington, D. C.) assayed erythropoietin in 10 male subjects aged 45-75 years with chronic bronchitis for over 3 years. All patients were studied when they had been free from acute episodes of infection for at least 1 month. Control subjects were 12 males aged 20 30 years.

Fifteen combined determinations of oxygen saturation and erythrocyte mass were made on 10 subjects Nine bioassays for erythropoietin were performed on plasma from 7 subjects: group A, 6 with an erythrocyte volume elevated to a degree commensurate with the degree of hypoxemia present, and

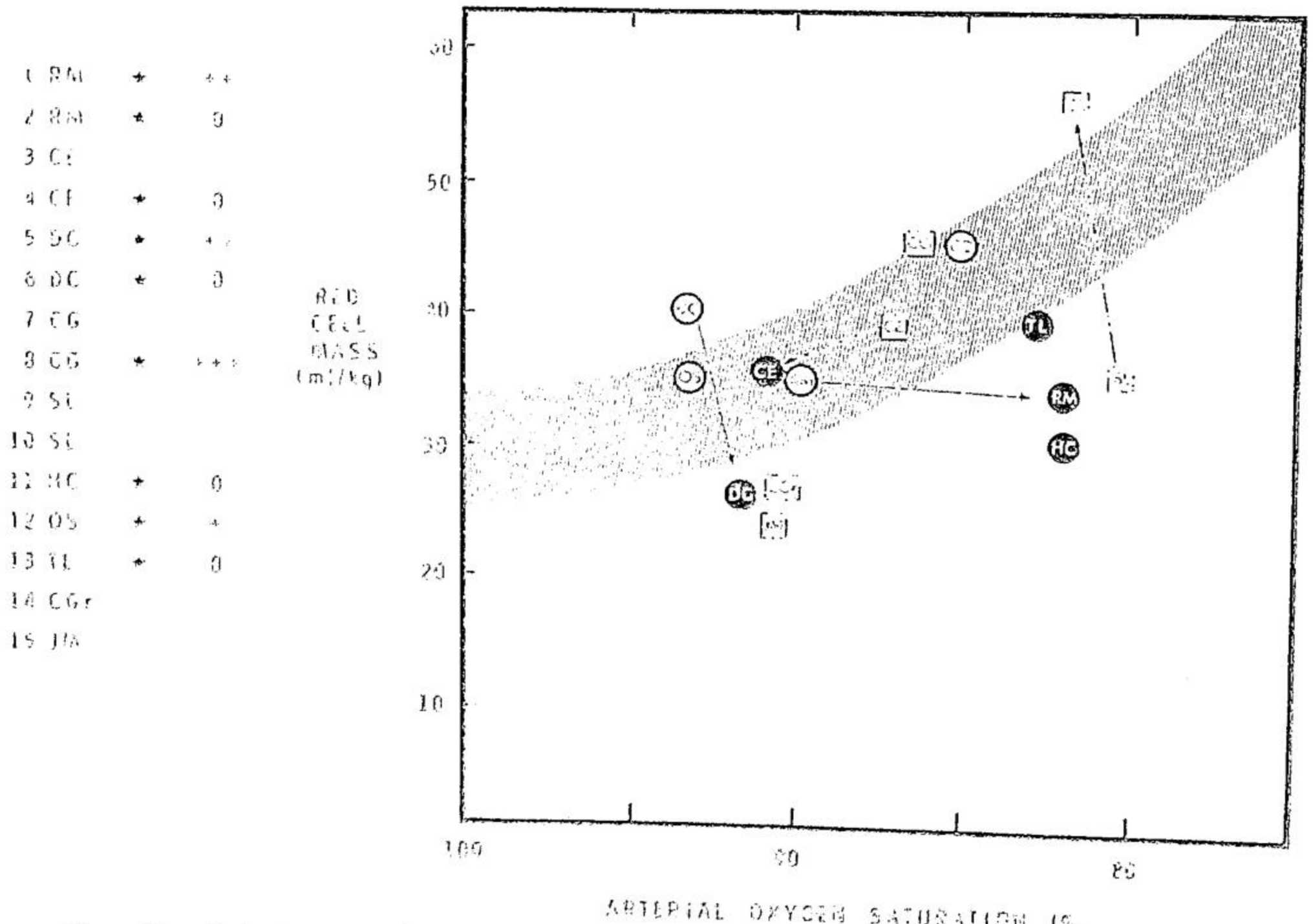


FIG 19 –Relationship between red cell mass and arterial oxygen saturation. The shaded area indicates the normal variation (7); the star, bioassay performed; plus signs, increased levels of erythropoietin; squares, no assay performed; open circles, increased levels of erythropoietin; closed circles, no increased level of erythropoietin. The arrow points from the first to the second study when the patient was studied twice. (Courtesy of Massaro, D., *et al.*: Am. Rev. Resp. Dis. 91:541-551, April, 1965.)

(4) Am. Rev. Resp. Dis. 91:541-551, April, 1965.

group B, 3 with erythrocyte masses not elevated to such a degree. Assay of erythropoietin was performed on white virgin female mice rendered polycythemic by injection of homologous erythrocytes suspended in saline.

Nine of the 15 combined measurements showed the erythrocyte mass elevation to be in the range expected for degree of hypoxemia (Fig. 19). Five subjects were studied twice several months apart. In 2, the elevation was adequate in both determinations for degree of hypoxemia present, and in 3, the elevation was adequate on one occasion but not on the other. In 4 subjects, oxygen saturation was not significantly changed; 2 of these showed large changes in erythrocyte mass despite absence of any clinical change. There was no significant change in $Paco_2$, pH or ventilatory function (table).

The erythropoietin dose-response curve showed that the reticulocytosis, induced for each unit of erythropoietin was not as great as that found by Filmanowicz and Gurney (1961), but the response was equally as linear. The degree of polycythemia produced in assay animals was not significantly different in those given control plasma and those given subjects' plasma, and erythropoiesis was depressed to the same degree in both groups of mice. The mean change in hematocrit was not significantly different. Plasma from 4 of the 6 group A subjects had increased erythropoietic activity compared with normal controls, while activity in group B sub-

PHYSICAL CHARACTERISTICS OF SUBJECTS STUDIED AND RESULTS OF PULMONARY FUNCTION AND BLOOD VOLUME DETERMINATIONS*

| Subject | Age | SA | pH | $Pa_{CO_2}$ | $Pa_{O_2}$ | MBC | $O_2$ Saturation | RQ | EM | Hct |
|---|---|---|---|---|---|---|---|---|---|---|
| | years | $m^2$ | | mm Hg | mm Hg | L/min | per cent | | ml/kg | per cent |
| 1 R M | 70 | 1 88 | 7 36 | 60 | 58 | 23 | 90 0 | 0 87 | 44 | 51 |
| 2 R M | 71 | 1 88 | 7 37 | 62 | 62 | 18 | 82 8 | 0 90 | 33 | 56 |
| 3 C F | 62 | 1 87 | 7 35 | 46 | 54 | 38 5 | 87 5 | 0 81 | 38 8 | 59 |
| 4 C E | 62 | 1 87 | 7 36 | 52 | 56 | 44 3 | 90 5 | 0 87 | 30 | 59 5 |
| 5 D C | 73 | 1 74 | 7 43 | 51 | 74 | 18 0 | 93 7 | 0 81 | 40 | 43 |
| 6 D C | 74 | 1 73 | 7 41 | 50 | 68 | 21 5 | 92 1 | 0 80 | 21 | 49 7 |
| 7 C G | 67 | 1 68 | 7 34 | 63 | 58 | 21 1 | 86 4 | 0 83 | 43 | 57 |
| 8 C G | 67 | 1 68 | 7 31 | 49 | 52 | 14 9 | 85 0 | 0 83 | 43 | 56 |
| 9 S L | 45 | 1 93 | 7 38 | 58 | 57 | 37 | 80 1 | 0 83 | 35 | 53 |
| 10 S L | 45 | 1 93 | 7 39 | 56 | 53 | 31 3 | 83 0 | 0 84 | 53 | 51 |
| 11 H C | 58 | 2 06 | 7 32 | 52 | 49 | 12 2 | 83 0 | 0 84 | 30 | 51 5 |
| 12 O S | 74 | 1 69 | 7 43 | 45 | 69 | | 93 1 | 0 83 | 34 | 46 5 |
| 13 T L | 68 | 1 72 | 7 34 | 61 | 53 | 18 7 | 83 1 | 0 82 | 39 3 | 66 0 |
| 14 C Gr | 64 | 1 58 | 7 38 | 39 | 65 | 18 9 | 90 9 | 0 88 | 26 7 | 43 5 |
| 15 J M | 45 | 1 68 | 7 40 | 45 | 67 | 15 1 | 91 4 | 0 81 | 23 | 52 5 |

*SA indicates surface area, MBC, maximal breathing capacity RQ, respiratory quotient, EM, erythrocyte mass and Hct, hematocrit

jects was not significantly different from that in control subjects

A review of the literature revealed that the erythrocyte mass was appropriate for the degree of arterial unsaturation in about 61% of cases reported. This figure falls with lower levels of arterial oxygen saturation On the basis of current data, no decision can be made as to site of the defect (humoral or end-organ) in instances in which elevation of the erythrocyte mass is not appropriate to degree of hypoxemia present

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## OXYGEN THERAPY

**Controlled Oxygen Therapy in Respiratory Failure.** During episodes of acute respiratory failure in patients with chronic generalized obstructive lung disease, hypoxia may be profound, and its relief by administration of oxygen is urgently necessary However, this often leads to further depression of ventilation Some workers favor early tracheostomy and mechanical ventilation The difficulty of this approach could be avoided if control of the inspired oxygen level could be shown to be safe in a large number of cases D. C. S. Hutchison, D. C. Flenley and K. W. Donald[5] (Univ of Edinburgh) used this method in 9 patients with chronic bronchitis and emphysema, 1 patient being studied twice Oxygen was given by Venturi mask in 1 case and by a blower system in the others; the concentration of inspired oxygen could be controlled within ±1.8% (95% confidence limits) After the initial period of air breathing, the inspired oxygen concentration was raised to 30-35% and maintained there for the next hour. If the $Pco_2$ rose by more than 6 mm. Hg, the oxygen level was reduced; if it rose by less, the level was increased. Results are shown in the table.

Case 1.—Man was comatose when breathing air. Severe hypoxemia and hypercapnia were noted. He responded rapidly to oxygen given by the Venturi mask, showing a persistent fall in $Pco_2$ irrespective of the inspired oxygen concentration.

Case 2.—Man was unconscious on admission with profound hypoxemia. The hypoxemia was partially relieved by administering 35% oxygen, but this led to a further rise in $Pco_2$ and a fall in pH.

(5) Brit. M. J. 2:1159-1166, Nov. 7, 1964.

## Data on Patients Treated by Controlled Oxygen Administration

| Case and Day of Study | Hours | Inspired $O_2$ Conc. % | Arterial Blood | | | | |
|---|---|---|---|---|---|---|---|
| | | | $P_{O_2}$ mm Hg | $P_{CO_2}$ mm. Hg | pH | $S_{O_2}$ % | Buffer Base mEq l. |
| Case 1 Day 1 (acute) | 0 | 20 9 | 36 | 72 | 7 33 | 64 | 55 |
| | | | 38 | 68 | 7 36 | 69 | 55 |
| | ½ | V = 31 | 69 | — | — | — | — |
| | | | 70 | 63 | 7 38 | 92 | 56 |
| | 1½ | V = 27 | 65 | — | — | — | — |
| | | | 65 | 57 | 7 38 | 91 | 54 |
| | 2¼ | V = 23 | 58 | — | — | — | — |
| | | | 61 | 53 | 7 40 | 90 | 54 |
| | 2¾ | 20 9 | 43 | 47 | — | — | — |
| | | | 42 | — | 7 43 | 79 | — |
| Discharge .. | | 20 9 | 59 | 47 | 7·38 | 89 | 50 |
| Case 2 .. (Study 1) Day 1 (acute) | 0 | 20 9 | 23 | 79 | 7 32 | 38 | 56 |
| | 1¼ | 36 4 | 26 | 86 | 7 28 | 42 | 54 |
| | 1½ | | 46 | 90 | 7 25 | 74 | 55 |
| | 3 | 29 2 | 56 | 93 | 7 24 | 82 | 54 |
| | 3¼ | | 48 | 77 | 7 31 | 79 | 56 |
| | 5 | 27 4 | 48 | 75 | 7 29 | 78 | 54 |
| | 5½ | | 42 | 78 | 7 30 | 72 | 55 |
| | 6 | 46 0 | 40 | 71 | 7 33 | 71 | 55 |
| | 6½ | | 92 | 78 | 7 36 | 96 | 62 |
| | | 20 9 | 97 | 78 | 7 33 | 96 | 58 |
| Day 2 .. | | 52 6 | 46 | 72 | 7·35 | 79 | 57 |
| | | | 156 | 94 | 7 25 | 99 | 58 |
| Case 2 .. (Study 2) Day 1 (acute) | 0 | 20·9 | 33 | 71 | 7 39 | 64 | 61 |
| | ½ | | 34 | 72 | 7 38 | 64 | 61 |
| | 1 | 33 8 | 31 | 73 | — | — | — |
| | | | 61 | 82 | 7 33 | 88 | 60 |
| | 1½ | | 66 | — | 7 32 | 90 | — |
| | 2 | 30 2 | 69 | 83 | 7 31 | 93 | 60 |
| | | | 46 | 75 | 7 34 | 81 | 58 |
| | 2½ | | 56 | 81 | 7 33 | 85 | 60 |
| | 3¼ | 25·0 | 60 | 81 | 7 33 | 88 | 60 |
| | | | 45 | 82 | 7 36 | 78 | 63 |
| | 4¼ | | 44 | 74 | 7 35 | 78 | 58 |
| | | | 45 | 79 | 7 35 | 78 | 60 |
| Day 2 .. | 17½ | 29·7 | 71 | 70 | — | — | — |
| | | | 71 | 70 | 7 38 | 93 | 60 |
| | | | 66 | 70 | — | — | — |
| | 18 | 40 0 | 93 | 72 | 7 38 | 97 | 61 |
| | | | 95 | 73 | 7 37 | 97 | 61 |
| | | | 90 | 74 | 7 35 | 96 | 60 |
| | 19 | 20·9 | 34 | 68 | 7·41 | 65 | 61 |
| | | | 36 | 67 | 7·39 | 69 | 59 |
| | | | 38 | 67 | 7 39 | 72 | 59 |
| Discharge.. | | 20·9 | 67 | 45 | — | 91 | — |
| Case 3 .. Day 1 (acute) | 0 | 20 9 | 39 | 100 | 7·35 | 71 | 73 |
| | | | 40 | 93 | 7 35 | 72 | 68 |
| | 1¼ | 36·0 | 67 | 115 | 7·33 | 90 | 76 |
| | 1½ | | 74 | 118 | — | — | — |
| | 2¼ | 29·9 | 54 | 122 | 7 23 | 81 | 66 |
| | 3 | | 59 | 118 | 7·25 | 84 | 67 |
| | 3½ | 24 4 | 45 | 107 | 7·25 | 73 | 61 |
| | 4½ | | 49 | 107 | 7 25 | 77 | 61 |
| | 6 | 29·5 | 52 | 103 | 7 34 | 83 | 72 |
| Discharge .. | | 20·9 | 60 | 62 | 7 34 | 88 | 54 |
| Case 4 .. Day 1 (acute) | 0 | 20·9 | 39 | 58 | 7·43 | 75 | 57 |
| | 1 | | 40 | 58 | 7·43 | 76 | 57 |
| | 2 | 34·5 | 74 | 62 | 7·39 | 94 | 57 |
| | 2½ | | 79 | 64 | 7·38 | 95 | 57 |
| | 4½ | 42·0 | 81 | 61 | 7·42 | 95 | 59 |
| | 4¾ | | 87 | 63 | 7·38 | 96 | 57 |
| Day 2 .. | | Polymask | 78 | 77 | 7·26 | 92 | 52 |
| Day 3 .. | | V = 29 | 57 | 59 | 7 42 | 89 | 58 |
| Day 4 .. | | V = 29 | 56 | 59 | 7·41 | 89 | 58 |
| Day 5 .. | | V = 29 | 60 | 57 | 7 39 | 88 | 56 |
| Case 5 .. Day 1 (acute) | 0 | Polymask | — | 86 | 7·28 | — | 58 |
| | | | 114 | 90 | 7·27 | 97 | 58 |
| | 2 | 28·9 | 47 | 86 | 7·34 | 79 | 63 |
| | 2½ | | 52 | 77 | 7·38 | 84 | 63 |
| | 4½ | 29·5 | 52 | 65 | — | — | — |
| | 6 | | 53 | 65 | 7 39 | 86 | 59 |
| | 7 | 32·2 | 62 | 65 | 7·44 | 92 | 64 |
| Day 2 .. | | 32·5 | 57 | 64 | 7 45 | 89 | 64 |
| Day 3 .. | | Polymask | 67 | 71 | 7·38 | 92 | 62 |
| Day 3 .. | | 28·7 | 53 | 57 | 7·44 | 87 | 59 |
| Day 4 .. | | | 56 | 65 | 7·40 | 87 | 60 |
| Day 6 . | | 30·1 | 63 | 63 | 7 39 | 90 | 58 |

*V = reading on Venturi gauge Hours = time after admission.

## Data on Patients Treated by Controlled Oxygen Administration (*cont*)

| Case and Day of Study | Hours | Inspired $O_2$ Conc % | Arterial Blood | | | | |
|---|---|---|---|---|---|---|---|
| | | | Pos mm Hg | Pco mm Hg | pH | $So_2$ % | Buffer Base mEq/l |
| Case 6 | 0 | 20·9 | 55 | 51 | — | — | — |
| Day 2 (acute) | | | 52 | 50 | — | — | — |
| | ½ | 35·9 | 85 | 55 | — | — | — |
| | ¾ | | 86 | 56 | — | — | — |
| | 1½ | 59·9 | 193 | 65 | — | — | — |
| | 1¾ | | 158 | 66 | — | — | — |
| Discharge | | 20·9 | 74 | 41 | 7·42 | 94 | — |
| Case 7 | 0 | 20·9 | 36 | 72 | 7·26 | 60 | 49 |
| Day 2 (acute) | | | 36 | 69 | 7·26 | 60 | 48 |
| | 2½ | | 39 | 70 | 7·26 | 65 | 45 |
| | 3½ | 31·2 | 60 | 77 | 7·24 | 85 | 50 |
| | | | 65 | 76 | 7·23 | 87 | 49 |
| | 3¾ | | 64 | 78 | 7·23 | 86 | 49 |
| | 4½ | 61·6 | 122 | 89 | 7·21 | 97 | 51 |
| | | | 116 | 93 | 7·22 | 97 | 54 |
| | 5 | | 130 | 92 | 7·22 | 98 | 54 |
| | 5½ | 30·0 | 60 | 86 | — | — | — |
| | | | 48 | 91 | 7·22 | 74 | 54 |
| | 6½ | | 45 | 91 | 7·22 | 71 | 54 |
| Day 3 | | 30·0 | 60 | 89 | 7·19 | 83 | 49 |
| | | | 58 | 90 | 7·19 | 82 | 49 |
| | | 36·5 | 68 | 92 | 7·19 | 87 | 50 |
| | | | 71 | 94 | — | — | — |
| | | | 76 | 91 | — | — | — |
| | | 30·5 | 40 | 91 | 7·19 | 63 | 48 |
| Day 4 | | 34·9 | 46 | 104 | 7·06 | 63 | 42 |
| | | 42·8 | 49 | 120 | 7·13 | 72 | 52 |
| | | 42·8 | 54 | 111 | 7·17 | 75 | 54 |
| Case 8 | 0 | 20·9 | 56 | 56 | 7·39 | 87 | 54 |
| Day 1 (acute) | | | 56 | 55 | 7·4 | 88 | 56 |
| | 1 | | 55 | 56 | 7·39 | 87 | 54 |
| | 1½ | 34·4 | 89 | 60 | 7·38 | 96 | 55 |
| | | | 91 | 61 | 7·38 | 96 | 55 |
| | | | 89 | 61 | 7·38 | 96 | 55 |
| | 2½ | 50·2 | 143 | 65 | 7·35 | 99 | 55 |
| | | | 146 | 63 | 7·36 | 99 | 55 |
| | 3 | | 133 | 66 | 7·36 | 99 | 56 |
| | 4½ | 31·6 | 77 | 66 | 7·36 | 94 | 56 |
| | | | 67 | 66 | 7·36 | 92 | 56 |
| | 4 | | 64 | 64 | — | — | — |
| Discharge | | 20·0 | 74 | 51 | 7·35 | 94 | 48 |
| Case 9 | 0 | 20·9 | 33 | 73 | — | — | — |
| Day 1 (acute) | | | 31 | 67 | — | — | — |
| | 1 | | 31 | 79 | — | — | — |
| | 1½ | 34·5 | 57 | 67 | — | — | — |
| | | | 58 | 68 | — | — | — |
| | 2½ | | 72 | 69 | — | — | — |
| | 3½ | 29·6 | 42 | 70 | — | — | — |
| | | | 46 | 74 | — | — | — |
| | 4½ | | 40 | 82 | — | — | — |
| | 4¾ | 35·6 | 47 | 78 | — | — | — |
| | | | 42 | 76 | — | — | — |
| | 5½ | | 47 | 74 | — | — | — |
| Day 2 | 20 | 29·6 | 49 | 78 | — | — | — |
| | 33 | Polymask | 100 | 91 | — | — | — |
| | | | 91 | 96 | — | — | — |
| Day 3 | | 29·0 | 46 | 77 | 7·31 | 77 | 53 |
| | | | 42 | 69 | 7·32 | 74 | 51 |
| | | | 45 | 68 | 7·32 | 74 | 55 |
| | | | 53 | 77 | 7·31 | 84 | 56 |
| | | | 52 | 78 | 7·33 | 82 | 57 |
| Day 4 | | 26·4 | 49 | 66 | 7·36 | 88 | 60 |
| Day 5 | | 35·0 | 38 | 63 | 7·38 | 86 | 57 |
| Discharge | | 20·9 | 69 | 45 | 7·42 | 93 | 51 |

ministration of penicillin did not diminish the number of leukocytes.

The results confirm previous in vitro observations that penicillin affects sensitive microorganisms only during their logarithmic phase of growth when there is rapid synthesis of cell walls. Leukocytes or their products apparently played a role in bacterial death. The results tend to negate the postulate that the continued high mortality rate in pneumococcic meningitis is due to presence of a virulent exudative response in an enclosed space adjacent to structures responsible for maintaining vital functions. Penicillin does not affect this response, and its beneficial effect is not related to its ability to suppress the inflammatory reaction. It is suggested that perhaps most patients who survive after antibiotic therapy may be those who receive drugs "early," during the period of rapid bacterial growth, perhaps even before the exudative reaction reaches its maximum. The combination of a low leukocyte count and a high bacterial count may prove to be a valuable prognostic profile of early meningitis.

► [This may help to explain our disappointing results in treatment of pneumococcic meningitis. We have tended to meet the problem by using larger and larger doses of the drug, which never seemed very rational in view of the uniform sensitivity of pneumococcus to penicillin.—Ed.]

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## GRAM-NEGATIVE BACTEREMIA

**Bacteremia Due to Gram-Negative Rods: Clinical, Bacteriologic, Serologic and Immunofluorescent Study** of 100 unselected patients seen at Boston City Hospital is reported by J. I. Maiztegui, J. Z. Biegeleisen, W. B. Cherry and E. H. Kass.[5] Patients with apparently transient bacteremia were excluded. A total of 132 isolates from the blood of the 100 patients were studied (table). Specimens from 6 patients yielded more than one gram-negative bacillus. Bacteriologic study of the isolated organisms showed that 9 different genera and at least 11 different species of gram-negative bacilli were involved. Testing in vitro of 101 isolates for sensitivity to commercial antibiotic disks was carried out (Fig. 2).

(5) New England J. Med. 272:222-229, Feb. 4, 1965

the Polymask when set at 6 L. per minute (about 60% oxygen), can cause serious exacerbations of $CO_2$ retention for at least 3 days. Controlled oxygen therapy may be required for at least 1 week, if not longer, for patients in respiratory failure. Tracheostomy and mechanical ventilation can be carried out if controlled oxygen therapy, along with administration of antibiotics, bronchodilators and respiratory stimulants, cannot maintain an arterial $Po_2$ over 50 without depressing the pH below 7.25.

[This careful study illustrates the advantages and the limitations of controlled oxygen therapy in patients with respiratory failure. The authors differ with Massaro, Katz and Luchsinger (see the 1963-64 YEAR BOOK, p. 122), who maintain that, in respiratory acidosis, oxygen should be administered only in conjunction with mechanical assistance to ventilation. In the United States, the latter has been recently the more favored method, although Barach originated the concept of controlled oxygen therapy, without respirator aid, and pioneered its use in emphysema.

Campbell, in the next article, discusses further the principles and practice of precisely controlled oxygen therapy. - Ed.]

**Oxygen Therapy in Diseases of the Chest,** according to E. J. M. Campbell[6] (Hammersmith Hosp., London), is directed to relief of hypoxic hypoxia due to inadequate alveolar ventilation, inadequate pulmonary oxygen transfer, or both. This form of hypoxia is easily relieved by modest amounts of oxygen. Failure to supervise the patient during the first hours of therapy and failure to control the oxygen concentration may allow severe carbon dioxide retention, causing narcosis, failure to cough and deterioration of the lungs, plus the risks of profound hypoxia if the oxygen supply is interrupted. Hypoxia must be distinguished from hypoxemia, a less than normal blood oxygen concentration. Moderate relief of hypoxemia is readily accomplished by increasing the inspired oxygen concentration by only 4-8%.

The necessary control of inspired oxygen concentration not provided by conventional methods can be achieved by using the principle of high air flow with oxygen enrichment (Fig. 20). Addition of 1 L. oxygen to 10 L. air produces a concentration of 28% oxygen. A total flow of at least 30 L. per minute is usually used. The high flow produces a micro-environment around the patient's face which is being flushed so thoroughly that there is no inward leakage of air and no rebreathing. The venturi principle is used, by means of which air is entrained by a jet of oxygen.

The $Pco_2$ is measured in any patient with a history of

(6) Brit. J. Dis. Chest 58:149-157, October, 1964.

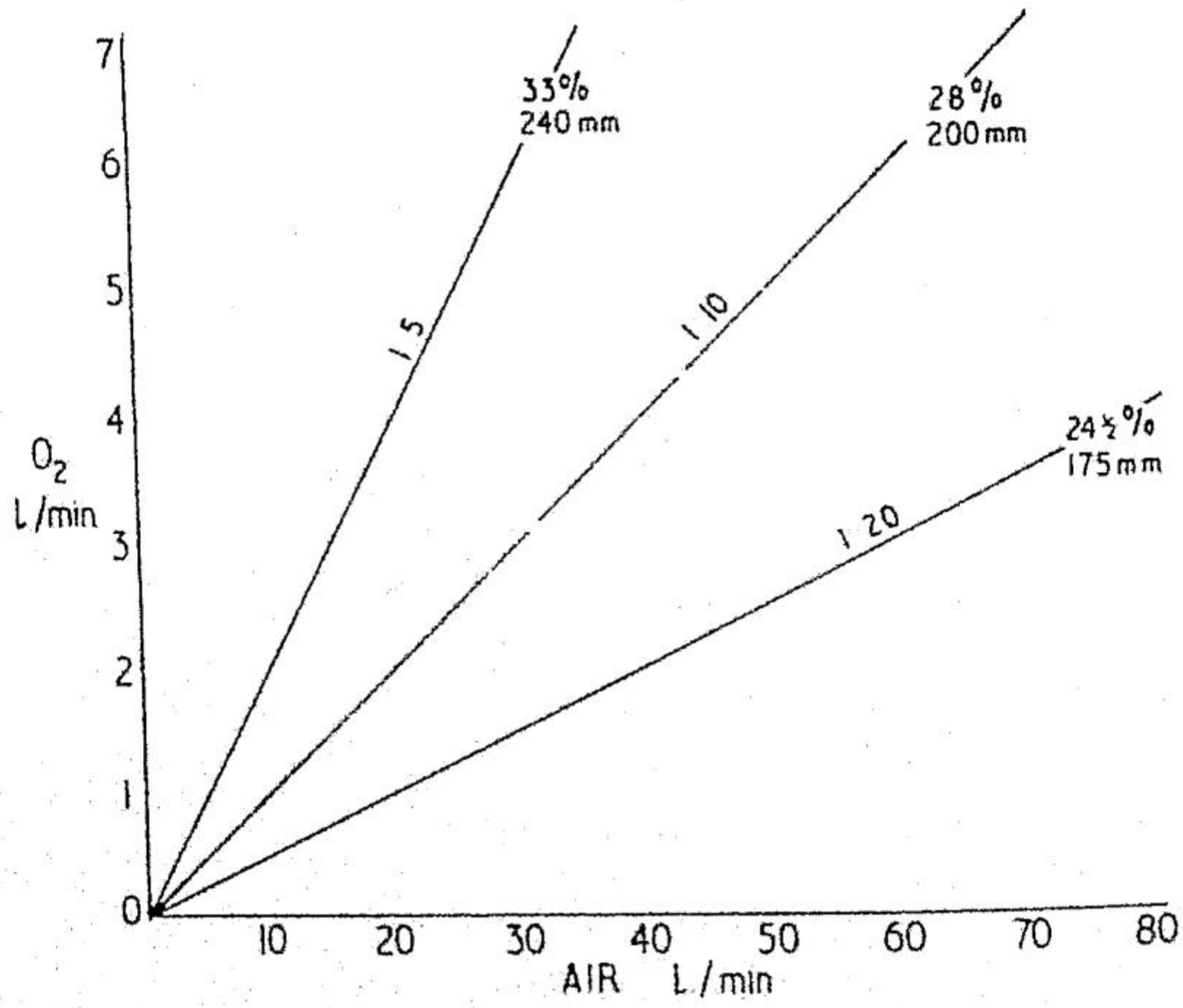



Fig 20.—Relationship between oxygen flow, air flow and oxygen concentration of resultant mixtures (Courtesy of Campbell, E. J. M. Brit. J. Dis. Chest 58: 149-157, October, 1964.)

chronic lung disease. If it is raised (e.g., an arterial level over 50 mm. Hg), the patient is given 25% oxygen, and measurements are repeated at about half-hour intervals for 2 hours. If there is no progressive under-ventilation, the oxygen concentration is increased to 28% and later may be raised to 33%. If progressive or severe under-ventilation occurs, the oxygen concentration is held at the level reached, provisional arrangements are made for tracheostomy, and intensive conservative measures (physiotherapy, aspiration and stimulants) are tried. If these fail, tracheostomy is performed. After tracheostomy, if and when assisted ventilation is not required, 28% oxygen is usually used.

► [Doctor Campbell several years ago designed an oxygen mask using the venturi principle (see the 1961-62 YEAR BOOK, page 191). In the present communication, he discusses other devices for administering oxygen according to the principle of high air flow with oxygen enrichment. One of these is a blower system designed by Flenley, Hutchison and Donald and used by them in the studies reported in the immediately preceding paper. Another is the preparation in cylinders of oxygen-nitrogen mixtures of varying concentrations within the range of 24-33% oxygen, but this he regards as expensive and inconvenient.

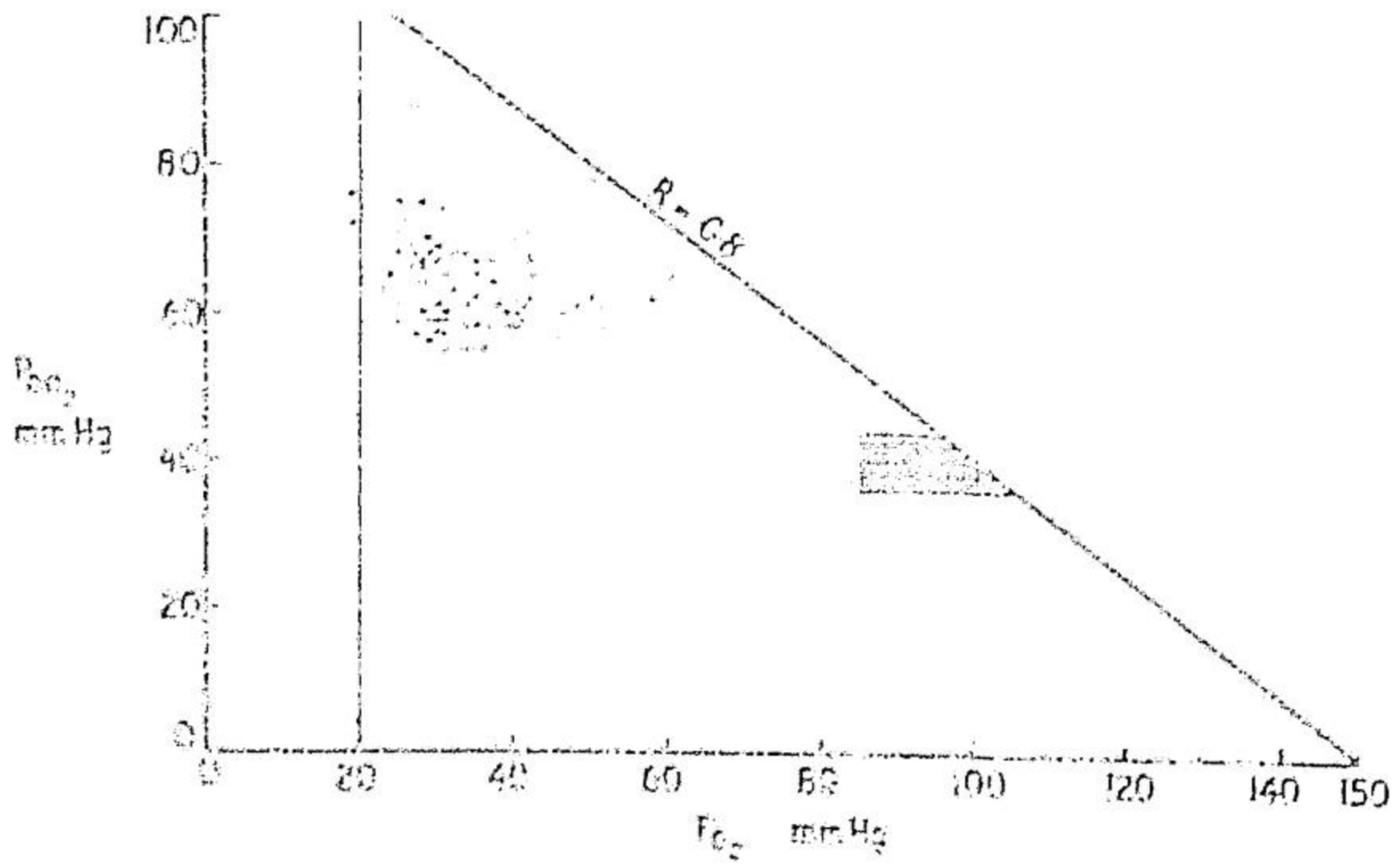
Extremely high levels of $P_{CO_2}$ (greater than 90 mm. Hg), Doctor Campbell here points out on theoretical grounds, are to be expected only in patients who have received oxygen therapy inappropriately administered. This consideration was investigated in practice by McNicol and Campbell (see following article).—Ed.]

**Severity of Respiratory Failure: Arterial Blood Gases in Untreated Patients.** M W McNicol and E. J. M Campbell[7] (London) performed calculations leading to predictions for the maximal possible severity of respiratory failure in patients breathing air and studied the arterial blood gas levels in 81 patients. It was predicted that the $P_{CO_2}$ of patients in respiratory failure could not, while they were breathing air, far exceed 80 mm Hg, nor could the hydrogen ion concentration far exceed 65 nanonormal (fall in pH below 7.19). More severe underventilation would cause death from hypoxia.

The patients studied had acute exacerbations of chronic respiratory disease. All findings were obtained before any treatment. Respiratory failure was diagnosed when the arterial $P_{CO_2}$ was 55 mm Hg or more and arterial oxygen saturation was below 90%. The results are shown in Figures 21 and 22. The lowest recorded $P_{O_2}$ was 19 mm Hg and the lowest oxygen saturation was 29%. The highest $P_{CO_2}$ was 88 mm Hg and the highest hydrogen concentration was 65 nanonormal. The lowest plasma bicarbonate value was 22 millinormal. The largest alveolar-arterial $P_{O_2}$ difference was 57 mm Hg.

Both physiologic theory and clinical observation confirm

Fig. 21.—Carbon dioxide-oxygen diagram. R=0.8 is line for respiratory exchange ratio of 0.8 calculated from alveolar air equation for inspired $P_{O_2}$ of 150 mm. Hg and $P_{CO_2}$ of 0 mm. Hg; vertical line at $P_{O_2}$ of 20 mm. Hg seems to be lowest tolerable arterial $P_{O_2}$ (Refsum, 1953). Each point represents arterial $P_{CO_2}$ and $P_{O_2}$ of 1 patient. Shaded area indicates normal range for alveolar and arterial gas pressures. (Courtesy of McNicol, M. W., and Campbell, E. J. M.: Lancet 1:336-338, Feb. 13, 1965.)




7. Lancet 1:336-338, Feb. 13, 1965.

placement and antibiotic therapy. In hypotensive states associated with bacterial infection, the circulatory state must be assessed by the pulse volume and skin temperature rather than on the basis of blood pressure.

► [I agree that one seldom gets the impression that pressor compounds are lifesaving in shocklike states associated with infection Norepinephrine is considered to have a further disadvantage tendency to cause hepatic damage characterized by centrolobular necrosis We prefer metaraminol because of this —Ed.]

**Endotoxin-Like Activity of Serum from Patients with Severe Localized Infections.** Philip J. Porter, Alan R Spievack and Edward H. Kass (Harvard Med. School) sought evidence of endotoxemia in diverse clinical disorders using the method of Thomas, which consists of injecting endotoxin or endotoxin-containing materials intravenously into rabbits, with intradermal epinephrine given at the same time. Hemorrhagic necrosis develops in the skin within 8-10 hours

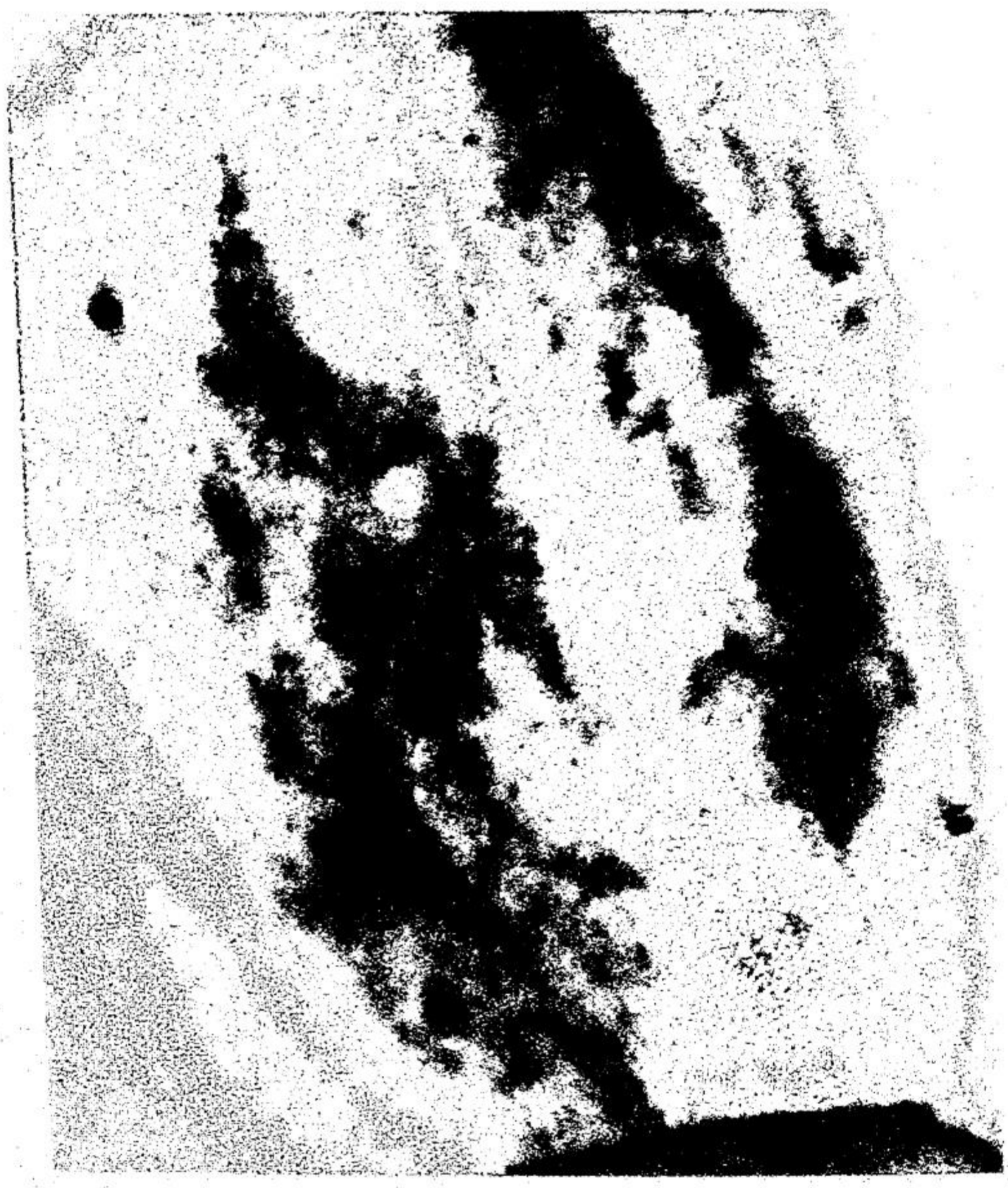


Fig. 3.—Positive test in rabbit given serum from patient with klebsiella aerobacter infection (Courtesy of Porter, P. J., *et al.* New England J. Med. 271:445-447, Aug. 27, 1964.)

(7) New England J. Med. 271:445-447, Aug. 27, 1964

DATA ON 18 CASES OF RESPIRATORY FAILURE

| Case no. | Age (yr.) | Sex | Days in hospital | FEV, VC, BTPS (litres per min.) | | $P_aco_2$ (mm. Hg) | | | | $S_ao_2$ (%) | | pH | | Blood-urea (mg. per 100 ml.) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Admission | Discharge | Re-breathing on admission | Rebreathing or arterial | | | Admission | Improved to | Admission | Discharge | Admission | Discharge |
| | | | | | | | Highest recorded | Lowest recorded | Discharge | | | | | | |
| 1 | 54 | M | 28 | 0 8 1 6 | 2 9 4 1 | 57† | 57 | 40 | 40 | 85 | 90 | 7 34 | 7 44 | 58 | 34 |
| 2‡ | 51 | M | 82 | 0 8 1 2 | 0 6 1 2 | 49 | 63† | . | 63† | 85 | 73 | 7·35 | 7 37 | 22 | 60 |
| 3 | 63 | M | 27 | 0 5 1 4 | 0 6 2 2 | 54 | 66† | 42 | 47 | 70 | 92 | 7 46 | 7 42 | 76 | 34 |
| 4 | 50 | M | 19 | 1 1 2 2 | 1 1 3 5 | 56* | 56 | 42 | 42 | 80 | 90 | 7 29 | 7·45 | 28 | . |
| 5 | 54 | M | 16 | 0 6 1 5 | 1 0 2 0 | 70† | 70 | 44 | 52 | 64 | 86 | 7 35 | 7 40 | 42 | 30 |
| 6 | 54 | M | 15 | 0 8 1 9 | 1 0 2 2 | 66† | 66 | 50 | 57 | 79 | N.D. | 7 33 | 7 40 | 35 | .. |
| 7 | 64 | M | 14 | 0 8 1 5 | 1 0 2 3 | 60 | 64† | 55 | 57 | . | 86 | 7 40 | | 36 | . |
| 8 | 72 | M | 8 | 0 8 1 9 | 0 9 2 0 | 56† | 61 | 46 | 46 | 82 | 86 | 7 40 | | 42 | 40 |
| 9 | 67 | M | 26 | 1 0 2 4 | 1 8/3 8 | 55† | 55 | 40 | 40 | 65 | 71 | 7 36 | 7 40 | 50 | 42 |
| 10 | 52 | M | 20 | 1 0/2 0 | 1 5/2 5 | 67† | 75 | 46 | 46 | 60 | 87 | 7·35 | 7 38 | 40 | 26 |
| 11 | 45 | M | 24 | 0 5 1 9 | 1 4 3 4 | 54 | 68§ | 40 | 47 | 61 | 78 | 7 28 | 7 39 | 44 | 46 |
| 12 | 54 | M | 35 | 0 7/1 2 | 0 95 1 4 | 59† | 63 | 51 | 51 | 78 | 87 | 7 37 | 7 39 | 62 | 46 |
| 13 | 60 | M | 19 | 0·6 1 7 | 0 7/2 0 | 58* | 70 | 39 | 44 | 76 | 92 | 7 27 | 7 48 | 33 | 22 |
| 14 | 63 | F | 16 | 0 3/0 8 | . | 70 | | | | | | | | | |
| 15 | 61 | M | 29 | 0 6/1 95 | 0 7/2 6 | 72† | 72 | 44 | 49 | 72 | 85 | 7 43 | 7 39 | 35 | . |
| 16 | 61 | M | 13 | 0 45/1 5 | 0 6/1 7 | 65† | 69 | 44 | 55 | 78 | 79 | 7·33 | 7 42 | 38 | |
| 17 | 64 | M | 24 | 0 4/1 4 | 0 4/1 4 | 73† | 73 | 48 | 55 | 61 | 77 | 7·35 | 7·41 | 50 | 34 |
| 18 | 59 | M | 19 | .. | 0 5/1 7 | 72† | 82 | 44 | 44 | .. | .. | .. | .. | 70 | 35 |

† Admitted to intensive care unit
‡ Died
§ Admitted to intensive care unit at 62 mm
‖ Died. Patient and husband refused all treatment

disease with diffuse airway obstruction Patients with arterial $Pco_2$ of 55 mm Hg or over were considered to have respiratory failure. These 18 patients had constant nursing, with attention to fluid balance, clearing of airways, encouragement of coughing, physiotherapy and keeping the oxygen mask in position Oxygen-enriched air was given with disposable Venturi masks to produce an inspired $Po_2$ about 50 mm Hg above that of air. A broad-spectrum antibiotic was given, as were bronchodilators (1% isoprenaline by inhalation, 0.25-0.5 Gm. aminophylline intravenously, 5% orciprenaline). Four patients had bronchial lavage through a bronchoscope Nikethamide or amiphenazole hydrochloride was given intravenously if the arterial $Pco_2$ was above 60 mm Hg or so or if it tended to rise despite treatment in the first few hours. Corticosteroids, diuretics and digoxin were given if indicated.

Two patients died, 1 after 2 months' active treatment, with Pseudomonas pyocyanea infection, and 1 after refusing all treatment. The other 16 patients did well (table) Only 5 patients had arterial $Pco_2$ levels over 70 mm. Hg, and all had levels below 80 mm. These patients are believed to be representative of those in other centers The arterial $Pco_2$ was measured before any oxygen therapy was given. More radical measures such as tracheostomy may be justified in patients who fail to improve or who deteriorate on this regimen, but not unless active methods have been unsuccessful

► [The low mortality is impressive if, as the author believes, these patients are representative of severe respiratory failure as seen in other centers, but with higher levels of $Pco_2$ recorded The key question is whether the observations, of initial exceedingly high $Pco_2$ values reported by others, were made only after oxygen had been given McNicol and Campbell (see preceding article) in a larger series found only 2 of 81 untreated patients to have had a $Pco_2$ above 80 mm Hg, whereas other authors cited by Doctor Lal have reported as many as 20 of 29, and 11 of 25 patients with initial values of 90 mm Hg or higher, most of which patients were known to have received oxygen Levels as high as 150 mm have been observed in patients receiving oxygen, and one instance is recorded of 228 mm Doctor Lal's experience is in agreement with that of Doctor Campbell and that of Hutchison *et al* (see this YEAR BOOK, p (121), that with controlled oxygen therapy these disasters can be avoided and that, moreover, most patients in respiratory failure can be treated successfully with oxygen, and without mechanical aids to ventilation More precision in the dosage of oxygen is required, however, than is customary in most hospitals – at least in the United States – Ed ]

**Oxygen and Carbon Dioxide Concentrations in Oxygen Tents.** In the Oxygenaire Mark V tent, carbon dioxide may be optionally washed out by the entrainment of ambient air, and the oxygen concentration is simultaneously reduced This

model accordingly was selected for a trial of its efficiency in permitting control of oxygen concentration and in maintaining a low carbon dioxide concentration.

Bernard J Freedman[9] (London) studied 5 patients with acute infective exacerbations of chronic bronchitis and 1 healthy volunteer subject The tent was used under normal working conditions Mattress overlays were covered by nonporous plastic envelopes Gas samples were aspirated at 10-minute intervals for periods of 4-5½ hours The zipper was opened during this time for meals, toilet and nursing procedures.

A reduction to about one fourth of pre-existing levels of carbon dioxide was found. Predictable oxygen concentrations of 26-30% were obtained with use of the washout in conjunction with various oxygen flow rates When the heavily built, young male volunteer subject was in the tent, oxygen and carbon dioxide values were 56 and 1.6%, respectively, at an oxygen flow rate of 8 L/minute with the carbon dioxide washout off, and 29.5 and 0.5% with the washout on. The carbon dioxide output was 291 ml. per minute, 55% greater than the mean for the 5 patients, carbon dioxide concentrations in the tent were proportionately higher The relative humidity in the six experiments varied between 40 and 45%.

A suitable mask is undoubtedly the first choice in oxygen therapy if its design will eliminate rebreathing and if it will give predictable oxygen concentrations. A properly set-up tent offers a degree of reliability in maintenance of suitable gas concentrations that is unobtainable with masks when patients are restless, fidgety, confused or intolerant of masks There is also the occasional male patient who tinkers with his giving-set. The discomfort experienced by some patients in tents is usually due to a high (1-2%) carbon dioxide content; the feelings of stuffiness, sweating, headache and restlessness are due to the ensuing hypercapnia. All these distressing symptoms are eliminated by the carbon dioxide washout.

Exercise Training with Aid of Portable Oxygen Supply in Patients with Emphysema. Alan K. Pierce, Pedro N. Paez and William F. Miller[1] (Univ. of Texas Southwestern Med School) assessed the physiologic responses to progressive

(9) Thorax 19:568-570, November, 1964
(1) Am. Rev. Resp. Dis. 91:653-658, May, 1965

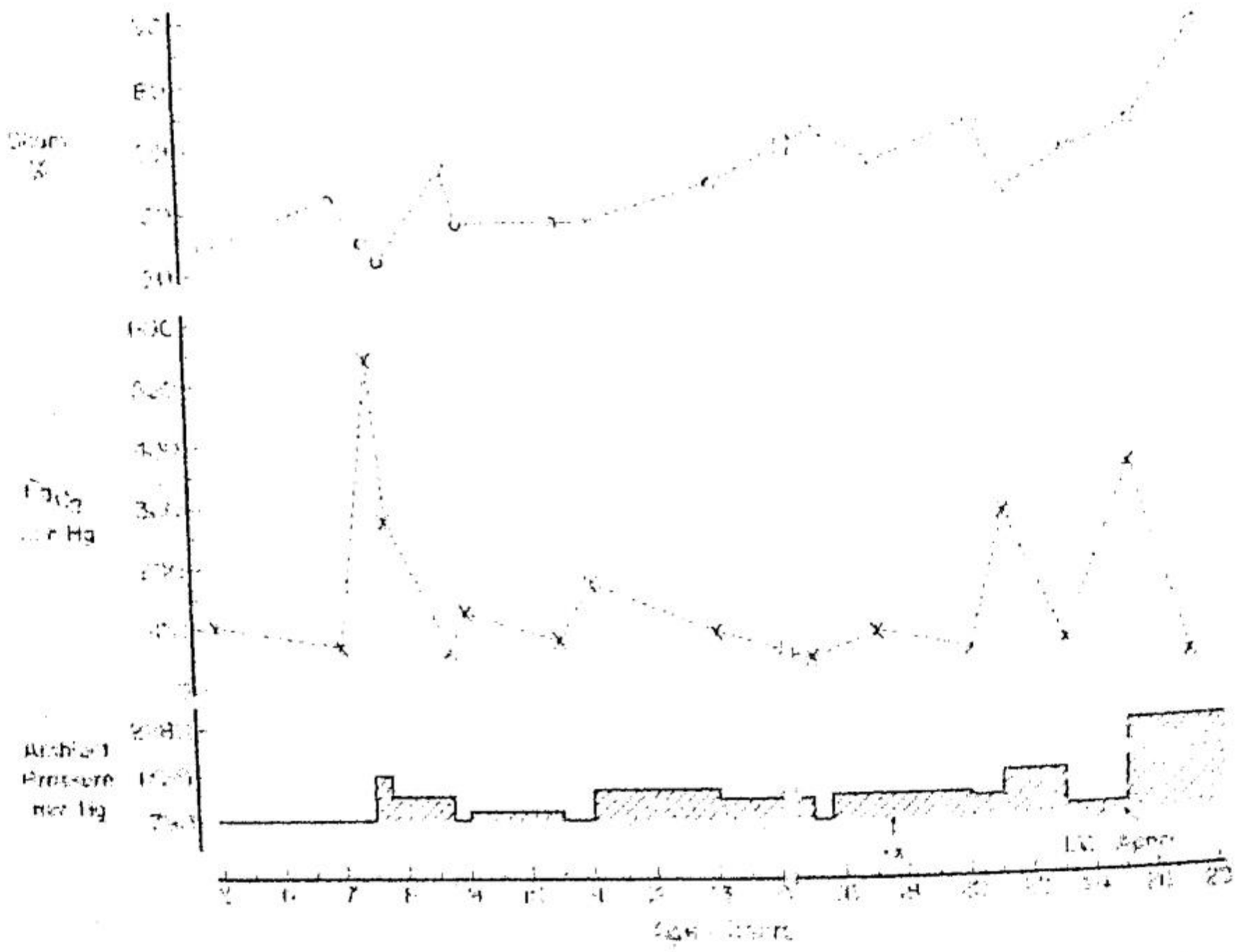


Fig 23 - Increase in arterial oxygen tension in 1695 Gm infant with respiratory distress syndrome on exposure to high oxygen pressure (Courtesy of Cochran W. D. *et al*: New England J. Med. 272:347-351, Feb. 18, 1965.)

arterial oxygen tension rose in all infants. Results in 1 patient are shown in Figure 23. Periods of apnea were often followed by relative hyperventilation and elevation of temporarily reduced oxygen tension. A slow increase in pressure was needed to maintain an arterial oxygen tension of 90-150 mm. Hg in all infants treated for over 3 hours. Apneic periods occurred with increasing frequency in the chamber in all infants but 1. All the infants died. Hyaline membranes were found at autopsy in 6, and all 8 studied showed severe atelectasis. The arterial blood carbon dioxide tension was well above normal in these patients and did not change measurably with high oxygen pressure. Critical lactate concentrations were exceeded in some cases before and after placement of the infants in high oxygen pressure. Serum sodium and potassium levels and hematocrit did not change.

The results give little reason for recommending the use of 100% oxygen at high pressures, though temporary elevation of blood oxygen was possible. Though calculated shunts fell minimally and briefly, they soon increased in high oxygen pressure. The clinical significance of the temporary improvement seen in arterial oxygen and color of the infants seemed dubious and could not be used to advantage in the babies.

of this was caused by a great reduction in 1 patient. Training resulted in decrease of the respiratory rate by 23%, minute ventilation by 29%, oxygen consumption by 24% and carbon dioxide production by 25%. Before training, each patient could perform more exercise while breathing oxygen than while breathing room air. After training, exercise with oxygen still produced less stress than room air exercise. With the patient breathing oxygen, the average reduction in heart rate was 7%, in respiratory rate, 23%, in minute ventilation, 25%, and in carbon dioxide production, 13%.

The results indicate that patients with chronic obstructive pulmonary disease with hypoxia have less stress during exercise both while breathing oxygen and after a period of physical conditioning. Physical training in these patients improves their efficiency in performing physical work.

▶ [The authors point out that they have not attempted to separate the effects quantitatively of physical training and of supplemental oxygen and that they regard the beneficial effects of each as additive. In clinical practice, they suggest assessing each patient by determining pulse rate, respiratory rate, degree of dyspnea and exercise ability with and without supplemental oxygen. The tendency to hypoventilation during oxygen breathing at rest should also be determined, and patients cautioned to use oxygen only during exercise. The authors give due credit to Barach, and to Cotes and Gilson, for earlier work on exercise training with supplemental oxygen.—Ed.]

**Clinical Trial of High Oxygen Pressure for Respiratory Distress Syndrome.** William D. Cochran, Henry Levison, Donald M. Muirhead, Jr., R. Wesley Boston, Catherine C. S. Wang and Clement A. Smith[4], (Harvard Med. School) studied 8 infants who had the clinical picture of respiratory distress, usually associated with hyaline membrane disease. A tank 30 in. in diameter and 36 in. long inside was designed to withstand pressures up to 12 atmospheres. Nitrogen was washed out with 100% oxygen, and a continuous flow of oxygen was maintained during use of the chamber, total pressure was regulated and carbon dioxide was removed. Infants were not usually placed in the chamber unless oxygen tension fell below 90 mm. Hg in 100% ambient oxygen at 1 atmosphere pressure. Five infants received intravenous glucose and bicarbonate and 7 received blood transfusions. One was given small doses of THAM. All had been given prophylactic penicillin, streptomycin and vitamin K.

When oxygen pressure in the chamber was first increased above 760 mm. Hg, cyanosis decreased or disappeared and

PYELONEPHRITIS INDUCED BY INTRAVENOUS INJECTION OF E COLI IN MICE INFECTED WITH MOUSE ADENOVIRUS

| INTRAPERITONEAL INJECTION | INTRAVENOUS CHALLENGE | GROSS PYELONEPHRITIC LESIONS |
|---|---|---|
| Adenovirus | E coli | 39/113* |
| Virus diluent | E coli | 4/100 |
| Adenovirus | Brain heart infusion | 0/110 |
| Virus diluent | Brain heart infusion | 0/36 |

* Numerator, number of mice bearing gross pyelonephritic lesions denominator, number of mice harvested

the host was challenged either intravenously or by the retrograde route with E. coli. The results of intravenous injection are shown in the table.

The extensive and persistent nature of the renal lesions raises the possibility that mouse adenovirus may cause chronic renal disease. Early in the course of adenovirus infection, increased susceptibility to E. coli challenge may result from increased renal tissue pressure produced by the extensive cellular infiltrate. Also, intracellular multiplication and the "toxic" action of adenovirus may decrease resistance to infection by interfering with tubular cell metabolism. Herpes simplex and vaccinia produced only minimal infiltrates in the renal cortex, but low titers seemed to decrease resistance to E. coli challenge significantly. The greater incidence (50%) of bacterial pyelonephritis seen in mice challenged with E. coli 12-64 days after adenovirus infection, as compared to that (33%) in mice challenged 3-9 days after, appears to reflect tubular obstruction and consequent increased renal tissue pressure.

► [A nicely conducted piece of investigation. People have wondered whether virus infection may sometimes play a part in human pyelonephritis. This work in animals shows a possible mechanism.—Ed.]

**Prevention of Pyelonephritis by Water Diuresis: Evidence for Role of Medullary Hypertonicity in Promoting Renal Infection.** The renal medulla is much more susceptible to infection than is the cortex. This has been ascribed in the past to its anatomic location and chemical composition.

Vincent T. Andriole and Franklin H. Epstein[3] studied experimental pyelonephritis in rats. Chronic water diuresis was induced in white female Sprague-Dawley rats by adding 5%

(3) J Clin Invest 44:73-79, January, 1965

**Detection of Asthma Epidemics in Seven Cities.** Epidemics of asthmatic attacks occurring simultaneously or nearly so in a number of persons have been reported The commonest outbreaks have been due to dust from milling of castor beans Stella Booth, Ido DeGroot, Robert Markush and Robert J M Horton (Cincinnati) discuss data obtained in the summer of 1961 by abstracting the 1960 emergency room records of 16 hospitals in 9 cities 10 hospitals in 7 cities yielded satisfactory material When visits for asthma were plotted graphically by day for each hospital, Charity Hospital in New Orleans showed the greatest range of variation in the number of visits Moreover, the peak days were distributed over a large part of the year, whereas they appeared clustered in the other hospitals Three hospitals, 1 in Chicago and 2 in New York, showed a rather even level of visits for the first two thirds to three fourths of the year, with a rise in the autumn. These were the 3 largest hospitals studied The daily graphs of the other hospitals were similar to those of the 3 hospitals except that the autumn increase was less pronounced and peaks tended to occur only in the fall In all hospitals, a rise in visits was apparent in the fall In most cities, this appeared after the plant-pollinating season Possibly, the autumn increase in asthma is multifactorial

► Recent studies on the epidemiology of asthma emphasize inhalational factors, which very probably are the most important. It seems likely that the autumn outbreaks are related to the temperature inversions which occur commonly in this season and cause exacerbations of air pollution of all kinds. Other sensitizing factors than those inhaled need also to be considered, since asthma can be invoked by a great variety of agents, some of them entering the body by other routes than the air passages. – Ed ]

**Iatrogenic Bronchospasm Occurring during Clinical Trials of New Mucolytic Agent, Acetylcysteine,** was investigated by I. Leonard Bernstein and Robert W. Ausdenmoore[1] (Univ. of Cincinnati). Acetylcysteine has a low oral toxicity in animals and has been found to liquefy effectively a variety of purulent and nonpurulent mucoproteinaceous secretions. It is used topically, as a 20% solution for aerosolization or as a 5% solution for direct instillation into the trachea.

(1) Arch Environ Health 10:152-155, February, 1965
(2) Dis Chest 46:468-473, October, 1964

Eleven patients with longstanding chronic asthma and 15 normal control subjects each received 1 5 ml of 20% acetylcysteine nebulized through a no 40 DeVilbiss nebulizer by compressed air at a pressure of 5 lb /sq in. for 5 minutes Eight patients developed obvious wheezing and, in most cases, a relative worsening of objective indexes (1-second timed vital capacity and peak expiratory flow rate). Two patients required epinephrine and aminophylline to control symptoms To determine whether the untoward effects were due to a reaction between acetylcysteine and rubber, the experiment was repeated 2 weeks later with the rubber stopper removed from the side vent of the nebulizer; 9 of 10 patients had wheezing, although less severe than in the first experiment.

The same group were exposed to an aerosol containing equal parts of 20% acetylcysteine and isoproterenol (1-200) 2 weeks later, and only 2 patients developed mild wheezing; these were the ones who previously had had the most severe symptoms. None of the normal subjects wheezed or showed significant over-all changes in respiratory indexes on exposure to acetylcysteine in contact with rubber Bronchospasm was not observed in 5 normal subjects or in patients with emphysema and cystic fibrosis on exposure to an aerosol of 20% acetylcysteine generated by an ultrasonic nebulizer which affords a particle size as small as 1 $\mu$.

Acetylcysteine is believed to exert a direct irritative effect on bronchiolar musculature It is postulated that patients with asthma display an unusual reactivity to hydrogen sulfide or other oxides of sulfur liberated from the sulfhydryl groups in the native compound

► [This observation merits emphasis because the drug presently is being administered as an aerosol to large numbers of patients with respiratory difficulties, of which doubtless asthma, asthmatic bronchitis and conditions not easily differentiated from asthma form a considerable proportion —Ed.]

## GRANULOMATOSES: DIFFUSE FIBROSES

**Role of Mycobacteriophages and of Cortisone in Experimental Tuberculosis and Sarcoidosis** was investigated by

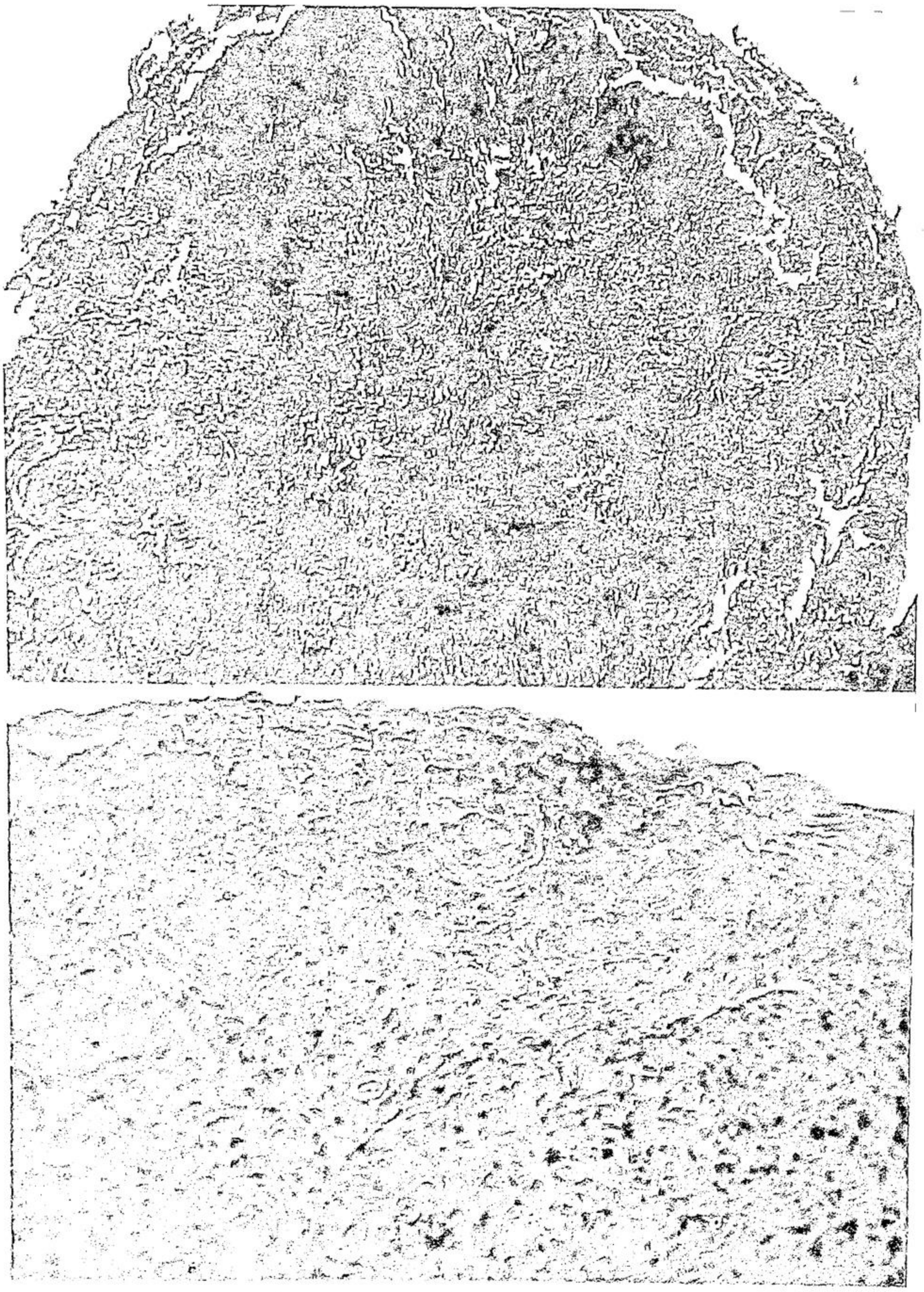


Fig. 24 (top). Section of lymph node almost completely replaced by a granulomatous inflammatory process referred to as a sarcoid like reaction. Hematoxylin phloxine safranine stain. ×100.

Fig. 25 (bottom). Higher power view of same section as in Figure 24 showing dense confluent granulomas without caseation necrosis. Lymphoid tissue is still present around the granulomas. ×250.

(Courtesy of Mankiewicz, E., and Boland, J. Am. Rev. Resp. Dis. 89:707-720, May, 1964.)

Edith Mankiewicz and Jean Béland (Montreal) Guinea pigs infected with only 1 $\mu$g of tubercle bacilli and with mycobacteriophage DS6A showed a smaller number of more discrete lesions than did those inoculated with the same amount of tubercle bacilli only However, animals in the former group died at a faster rate Administration of hydrocortisone orally, 1 mg/100 Gm. body weight every 2d day for 7 weeks, to the phage-infected animals increased the numbers of lesions but, at the same time, lowered their allergic state and lengthened the period of then survival

Simultaneous infection with tubercle bacilli and mycobacteriophage DS6A gave rise to homologous and heterologous phage antibodies The level of homologous antibodies was below detection in animals given cortisone However antibodies to bacteriophages with a broader lytic spectrum, and especially antibodies to phage Leo, can be demonstrated in the serum of these animals From the granulomatous sarcoid-like lesions of guinea pigs infected with DS6A and tubercle bacilli (Figs. 24 and 25), "atypical" strains of mycobacteria were isolated, either alone or with typical Mycobacterium tuberculosis. Some of these strains produced lytic phage particles When, after repeated subculturing, these bacteria were inoculated into normal guinea pigs, they determined inflammatory reactions, but no sarcoid-like lesions The observations suggest that sarcoid like lesions are caused by a transitory form of mycobacteria which emerges by lysogenization, and from the selective action of phage antibodies

▻ [The possibility of some pathogenetic relationship between mycobacteria and sarcoidosis has tantalized microbiologists and clinicians virtually since the disease was recognized as an entity distinct from tuberculosis Whether mycobacteria and mycobacteriophages are similarly related to human sarcoidosis as they are to these experimentally induced lesions is, of course, yet far from established but this approach to unraveling the mystery of sarcoidosis seems a promising one As the authors point out, recent epidemiologic observations of Edwards and Palmer indicate a preponderance of reactors to tuberculin prepared from atypical mycobacteria in areas of sarcoidosis prevalence, and Chapman (see the 1962 1963 YEAR BOOK, p. 170) has demonstrated antibodies against atypical (unclassified) strains in the serums of a high proportion of patients with sarcoidosis.—Ed.]

**Sarcoidosis Involving the Pleura** has been reported in 9 cases, only 1 of which was histologically confirmed Paul J Kovnat and Robert F Donohoe[6] (Washington, D. C.) report 2 additional histologically documented cases

(5) Am Rev Resp Dis 89:707-710, May, 1964
(6) Ann. Int. Med. 62:130-134, January, 1965

Woman, 23, had bilaterally symmetrical arthralgias in several joints, followed by monarthritis of the right ankle and cervical adenopathy. Hilar and bronchopulmonary adenopathy were noted on x-ray study. Liver biopsy showed noncaseating granuloma. After a 5 month remission, dyspnea on mild exertion developed, with x-ray evidence of a parenchymal pulmonary lesion. The dyspnea remained unchanged over the next 8 months, otherwise, the patient felt well. Left pleural effusion then developed. Coccidioidin skin tests were positive, previous tests had been negative. Pleural fluid contained 5 Gm. protein per 100 ml. and 4-8 red cells per high-power field; cultures were sterile. Biopsy of parietal and visceral pleura and lung parenchyma showed noncaseating granulomas, as did scalene node biopsy. Thoracotomy was done, and 2 months later, there was no reaccumulation of pleural fluid.

The other patient, a man aged 24, showed clearing of pleural effusions on corticosteroid therapy. The 3 histologically confirmed cases provide evidence that pleural involvement is an uncommon but occasionally prominent finding in sarcoidosis. If sarcoidosis has various causes, then perhaps the cases in which pleural effusion is present are related to one of the specific etiologic factors. If sarcoidosis is a single disease entity, these cases re-emphasize its protean manifestations.

► [The result of the Kveim test, if this was done, is not mentioned in either case report. Positive tests would have made these diagnoses more secure. The authors could find only 1 other case in the literature of pleural sarcoidosis diagnosed on histologic evidence, although there are others reported with pleural effusion without such "confirmation" of the character of the pleural involvement. Certainly, the pleural lesions in these 2 cases, as described and as shown in the photomicrographs, are compatible with sarcoidosis, but histologic evidence in sarcoidosis, as is well known, is not pathognomonic of the disease. Nevertheless, these findings, together with the negative tuberculin skin tests, lend support to the authors' diagnoses in each of these cases.—Ed.]

**Eosinophilic Granuloma [Histiocytosis X] and Its Variants with Special Reference to Lung Involvement.** J. G. Lewis[7] (Brompton Hosp.) reports 12 cases, all proved histologically. The 3 women and 9 men were aged 19-50 years at the time of clinical onset of the disease. Five patients had died at the time of study. The mean duration of illness was 5 years for those with primary pulmonary eosinophilic granuloma and 12 years for those with widespread lesions. Cough and dyspnea were the most common respiratory symptoms. Fatigue was an important complaint in 5 cases; weight loss was a feature in 3 cases and clubbing and occasional lung crepitations in 2 each. Bone lesions were present in 3 patients and suspected in 1, this being confirmed at autopsy. Recurrent

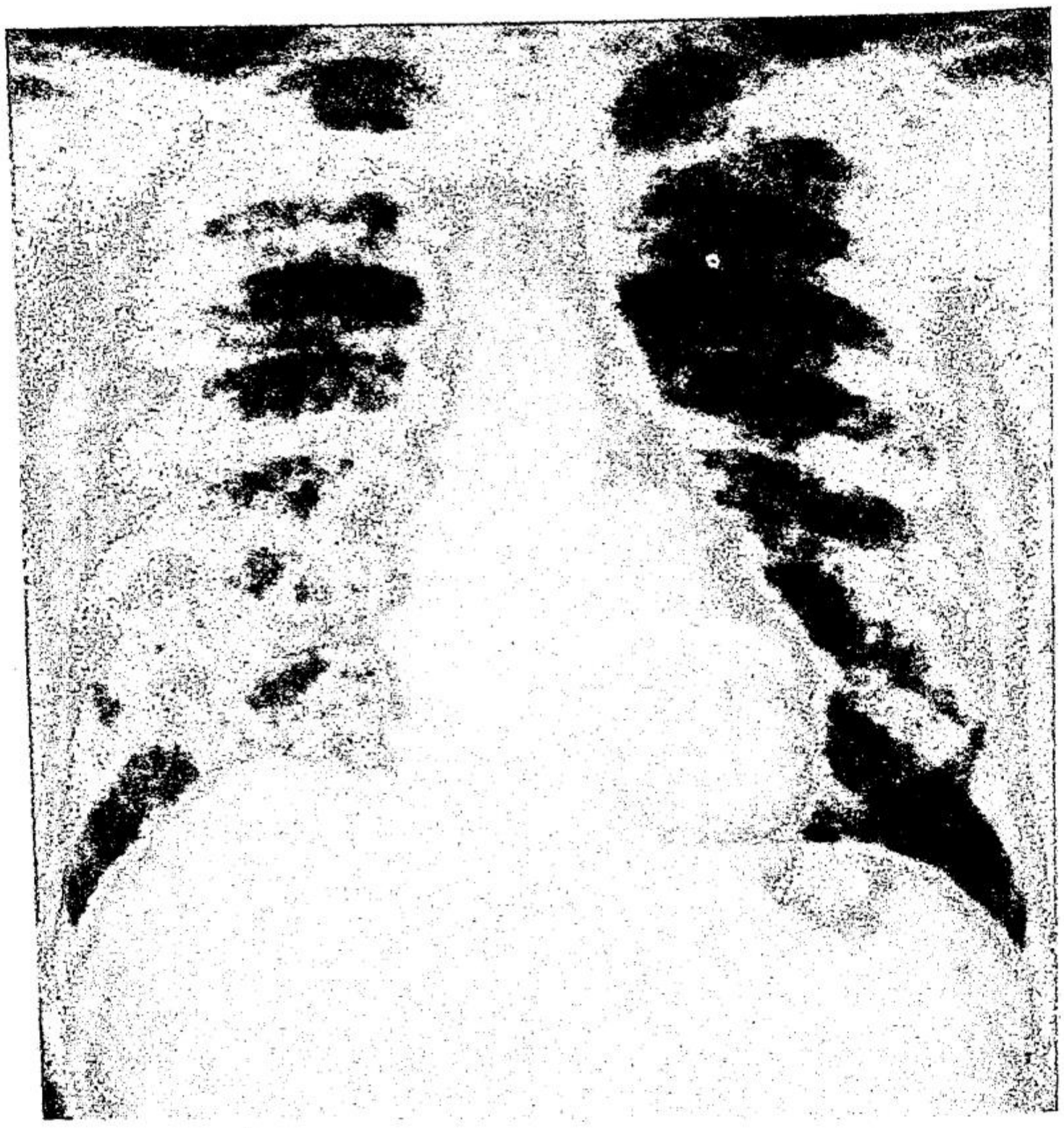


Fig. 26.—X ray showing mottling and ring shadows. (Courtesy of Lewis J. G. Quint, J. Med. 33:337-359, July, 1964.)

pneumothoraces occurred in 3 cases. Diabetes insipidus was found in 2 patients and panhypopituitarism with obesity and myxedema in 3. Two patients died of pulmonary suppuration and 2 in respiratory failure with right ventricular hypertrophy. A fifth patient was cyanotic and in respiratory distress before death.

Man, 28, was hospitalized with a history of tiredness and shortness of breath on exertion for about 6 months. He had developed a dry irritating cough on deep breathing and had lost 14 lb. Fever up to 100.4 F and night sweats had occurred, as had mild aching in the knees and occasional left-sided chest pain. A scalene node biopsy was normal. Much loss of hair was noted. The temperature was 99.99.5 F. Review of a chest x-ray taken before symptoms developed showed mottling in the left upper zone. Subsequent films showed the normal vascular pattern obscured in all zones, mottling throughout and an appearance of numerous ring shadows (Fig. 26). Blood studies showed the white cell count to be 13,000/cu. mm. with 2% eosinophils, wet eosinophil count, 300 cu. mm. sedimentation rate, 20 mm. per hour, and $\alpha_2$-globulin slightly elevated. The sputum contained 2% eosinophils.

On biopsy, the lung was poorly expanded and felt fibrotic. There were grayish subpleural and intrapulmonary 3-5 mm. nodules

throughout the excised part of the right upper lobe Microscopically, there was solid infiltration with histiocytes and some eosinophils There were areas of focal collections of eosinophils

Prednisone 40 mg daily for 6 weeks followed by 15 mg daily for maintenance, effected rapid subsidence of fever The patient himself stopped this medication The next year, radiography revealed slight clearing of the infiltration He remains well and working about 2½ years after admission

In these cases, high leukocyte counts occurred from neutrophilia in the absence of known infection X-ray study showed diffuse bilateral mottling in 10 cases and slight reticulation in another Progressive lung changes with formation of air spaces were conspicuous in 6 cases All 4 patients studied at autopsy showed conspicuous air spaces due to cysts or emphysema Fibrosis and histiocytic infiltration were prominent Eosinophils were absent or scanty in 3 cases, but focal aggregations were plentiful in 1 Review of 75 reported cases of pulmonary eosinophilic granuloma diagnosed by lung biopsy (table) showed that occasionally there was a localized mass or large nodule, but that usually there were nodules 1-20 mm in diameter spread evenly throughout the lungs

A significant proportion of patients with eosinophilic granuloma remain asymptomatic or improve spontaneously It is best to delay treatment until the patient becomes ill or is deteriorating. Steroid therapy is probably the best treatment when this is considered necessary However, steroids were of

Clinical Features of 75 Patients Diagnosed by Lung Biopsy as Having Eosinophilic Granuloma (Histiocytosis X)

| | |
|---|---|
| Asymptomatic | 5 |
| Cough | 51 |
| Sputum | 26 |
| Dyspnea | 31 |
| Fatigue | 25 |
| Weight loss | 26 |
| Fever | 11 |
| Chest pain (includes rib lesions, spontaneous pneumothorax) | 19 |
| Hemoptysis | 6 |
| Exhibiting | 3 |
| Bone lesions | 10 |
| Diabetes insipidus | 7 |
| Spontaneous pneumothorax | 18 |
| Diabetes insipidus and pneumothorax | 6 |
| Diagnosis by routine chest radiography | 26 |
| Published mortality | 3 |
| Age range | 15–60 years |
| Men | 63 |
| Women | 12 |

possible value in only 2 of the 7 cases in the present series in which they were used They should be given at a stage when the disease is potentially reversible and should be given a trial when there is doubt about reversibility Occasionally, they appear to be life-saving. For patients with permanent fibrous or cystic disease, symptomatic treatment may be necessary for cor pulmonale, superimposed infection or pneumothorax The prognosis for life seems fairly good, but follow-up in reported cases has been limited.

► [This report of 12 new cases and analysis of other published cases provide a most authoritative clinical description of the disease and discussion of the diagnosis, treatment and prognosis It will serve as the standard informational reference for a considerable time – Ed ]

**Agricultural Dusts and Diffuse Pulmonary Fibrosis.** John Rankin, Mosaburo Kobayashi, Robert A Barbee and Helen A Dickie[8] (Univ. of Wisconsin) report results of studies done in the last 10 years. Most subjects were agricultural workers. Inhalation of a variety of moldy organic dusts has resulted in serious acute, recurrent or chronic lung disease in several occupational groups. The characteristic syndrome seen in 73 agricultural workers consisted of chills, fever and dyspnea within a few hours of exposure and subsequent development of acute, diffuse, granulomatous, interstitial pneumonitis. In acute cases, physiologic study shows the syndrome of a stiff lung with reduced diffusing capacity, nonuniform distribution of regional ventilation and blood flow and no significant change in airway or vascular resistance. Lung biopsy shows epithelioid cells, poorly defined tubercles and Langhan's giant cells, along with thickening of alveolar septa, which are infiltrated with plasma cells and lymphocytes. The lesions are usually reversible, but recurrent episodes may lead to progressive and fatal pulmonary fibrosis.

Trichloroacetic acid was generally used as solvent for extraction of antigens. Serum of affected patients appeared to contain one to three antibodies that specifically reacted with one to three antigens in extracts from moldy hay. Precipitins were found only in the γ-globulin fraction. Antibodies appeared to persist in the blood for 1-5 years after the last recorded illness and in several instances, at least 3 years after any possible exposure to moldy organic dusts. In most of 17 samples of moldy hay studied, antigenicity appeared related to the presence of large numbers of thermophilic

(8) Arch Environ Health 10 278 282 February, 1965

actinomycetes growing at incubator temperatures up to 60 C The most potent natural source of antigen contained large amounts of Thermopolyspora polyspora Antigens extracted from this sample produced qualitatively similar illness in susceptible farmers but no respiratory symptoms in healthy urban controls.

Evidence seems to indicate that the pneumonitis results from an acquired hypersensitivity to relatively simple polysaccharide or glycopeptide antigens formed by the growth of thermophilic actinomycetes and perhaps other organisms on a variety of plant materials

► [This is a convincing demonstration that a granulomatous interstitial pneumonitis which may lead eventually to diffuse disabling pulmonary fibrosis results from antigen-antibody reactions in hypersensitive individuals to inhaled dusts Doctors Rankin and Dickie, with their colleagues, suggest that many other diffuse pulmonary diseases may arise through similar mechanisms —Ed ]

**Beryllium Lung Disease and Its Registry** are discussed by Howard S Van Ordstrand, Joseph M DeNardi and John F Zielinski[1] (Cleveland). Beryllium has been used mainly in the forms of the metal beryllium, beryllium oxide and beryllium-copper alloys The primary commercial application has been as beryllium windows in x-ray tubes It is used in reactor systems and in the aerospace industry Exposure to the element principally affects the skin and respiratory tract, resulting in acute and chronic lung disease and dermatitis. Of 700 cases of beryllium lung disease on file in the Beryllium Case Registry at the Massachusetts Institute of Technology, 211 are considered acute only, 445 chronic and 44 both acute and chronic. There have been 185 deaths

Acute chemical pneumonitis is produced by inhalation of beryllium-containing materials as dust or fumes The water soluble salts are preponderantly implicated There is a direct relationship to amount of exposure, and hypersensitivity may play a significant role. Symptoms may appear within 72 hours of brief but large exposure or may be quite insidious. The disease is characterized by progressive, usually nonproductive, spasmodic cough, dyspnea, anorexia, general malaise and weakness. Except for respiratory embarrassment and possible cyanosis, findings on examination may not be remarkable. The disease may last from a few weeks to 4 months. Laboratory findings in uncomplicated cases are essentially normal. The predominant reaction is

[1] Postgrad Med 36 491-504, November, 1964

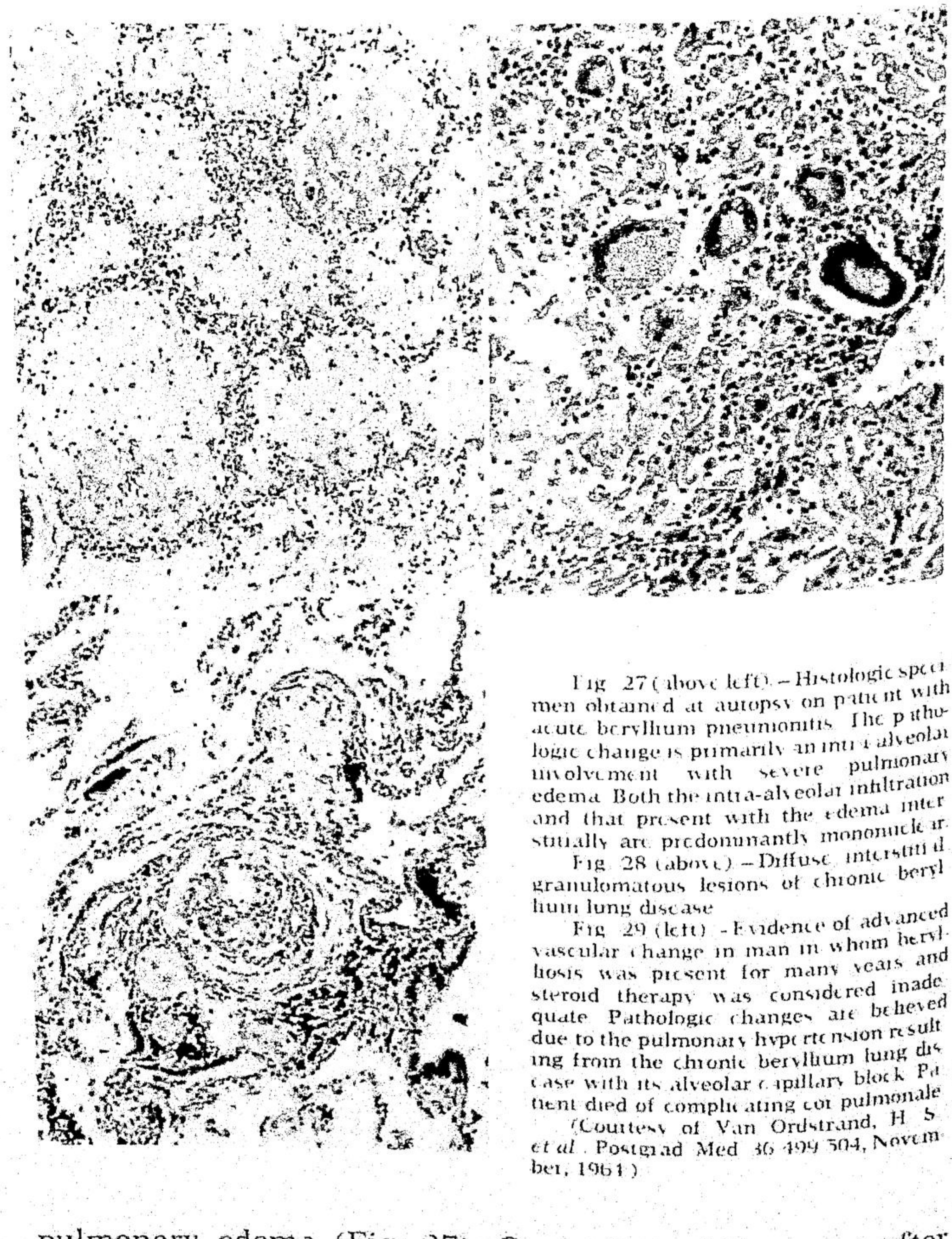


Fig. 27 (above left). – Histologic specimen obtained at autopsy on patient with acute beryllium pneumonitis. The pathologic change is primarily an intra-alveolar involvement with severe pulmonary edema. Both the intra-alveolar infiltration and that present with the edema interstitially are predominantly mononuclear.

Fig. 28 (above). – Diffuse interstitial granulomatous lesions of chronic beryllium lung disease.

Fig. 29 (left). - Evidence of advanced vascular change in man in whom berylliosis was present for many years and steroid therapy was considered inadequate. Pathologic changes are believed due to the pulmonary hypertension resulting from the chronic beryllium lung disease with its alveolar capillary block. Patient died of complicating cor pulmonale.

(Courtesy of Van Ordstrand, H. S. *et al*. Postgrad. Med. 36: 499-504, November, 1964.)

pulmonary edema (Fig. 27). Cor pulmonale, present after only 3 weeks of illness, is the cause of death in fatal cases. The disease has been virtually eliminated in recent years by application of good industrial hygiene and engineering safeguards. No known fatalities have occurred since the advent of adequate steroid therapy. Of 93 patients seen since 1941, 10 died.

Berylliosis, or chronic beryllium lung disease, is due to inhalation of beryllium dust or fumes over a variable period.

Beryllium oxide and other compounds are suspect. There is a latent period of 1-20 years between termination of exposure and onset of clinical disease The illness is related to hypersensitivity The usual symptoms are chronic, relatively nonproductive cough, shortness of breath, decreased appetite and weight loss. Pulmonary function studies usually show an alveolar-capillary block Relative hypergammaglobulinemia is found X rays show generalized fine nodulation or stippling with minimal hilar adenopathy Later, superimposed linear and reticular densities may be seen The lungs show diffuse, chronic, interstitial, granulomatous pneumonitis (Fig 28), which is sometimes indistinguishable from sarcoidosis However, in berylliosis, involvement is usually more diffuse and confluent, the granulomas are more loosely arranged, plasma cells more prominent and sclerosing granulomas less common than in sarcoidosis Patch tests with beryllium compounds and the Kveim test help differentiate between the two conditions. The most frequent complication is cor pulmonale, the disease itself causes pulmonary hypertension (Fig 29) Experience with low-dosage, long-term steroid therapy has been most rewarding Twelve of 81 patients have died Only 2 patients died since institution of steroid therapy in 1950 and there is some question as to the adequacy of treatment in these 2 cases

► [Dr. Van Ordstrand and his colleagues here present a succinct account of beryllium lung disease based on their own extensive experience of 174 cases and on information on file in the Beryllium Case Registry established by Dr Harriet L. Hardy in 1952. A description of some unusual pulmonary patterns was published recently (Weber, Stoeckle and Hardy, Am J Roentgenol 93:879, 1965) by Doctor Hardy and her colleagues at the Massachusetts General Hospital. – Ed]

**Familial Interstitial Pulmonary Fibrosis.** E. W. Hughes[1] (England) reports 3 cases of diffuse interstitial pulmonary fibrosis from one family.

Woman, 30, was admitted to Tehidy Hosp., Camborne, England, because of progressive breathlessness on exertion. When hospitalized elsewhere, she was acutely ill and had a slight productive cough. Central cyanosis and crepitations at the bases of both lungs were noted. The temperature occasionally reached 105 F., and the pulse rate was 140. The erythrocyte sedimentation rate was 131 mm in 1 hour. The chest x-ray showed generalized fine mottling throughout both lungs and dilatation of the pulmonary artery. Broad-spectrum chemotherapy did not help the fever, which settled by lysis when the antibiotics were withdrawn during the 3d week. Breathlessness had worsened so that speech was barely possible, and the patient was transferred to this hospital.

1. Thorax 19:515-525, November, 1964

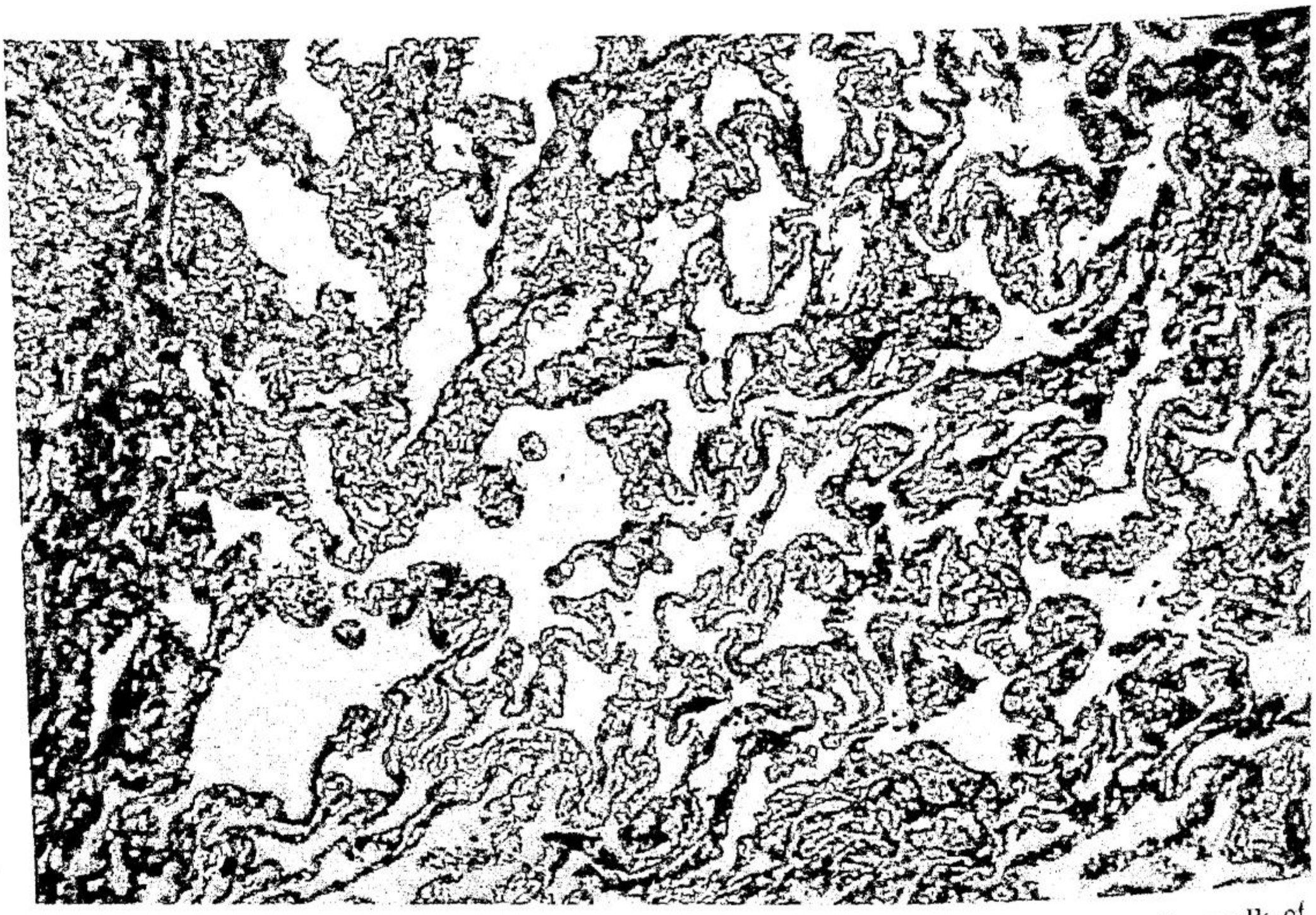


Fig 30 —Section of lung showing reticulin increase causing thickening of the walls of the air spaces characteristic of all three cases Silver impregnation, ×90. The photograph was taken by Mr P Stinchcombe from a section prepared by Professor J Gough of the Welsh National School of Medicine (Courtesy of Hughes, D W Thorax 19 515 525, November, 1964 )

The respiratory rate was 40 per minute The hemoglobin was 54% and the red blood cell count 2,550,000/cu mm The sedimentation rate was 77 mm in 1 hour Chest x-rays showed extension of mottling with areas of confluence in the left middle and right lower zones Empirical ACTH therapy gave improvement A month after admission, lung biopsy showed chronic inflammation that was mainly interstitial There was dense accumulation of lymphocytes, plasma cells and histiocytes which, together with increase in reticulin, produced great thickening of the walls of the alveoli and other distal air spaces (Fig 30) There also were inflammatory cells and fibrosis obliterating some of the air spaces

Progress was maintained on 15 mg prednisolone daily When the patient was discharged about 3 months after admission, exercise tolerance had returned to 75% of normal The radiologic impression was one of resolution, although some fine punctate mottling was still evident Breathing improved further after discharge, and x-rays showed clear lung fields and a normal-sized pulmonary artery Corticosteroids were stopped, and the patient returned to work

In the next year, refractory anemia was noted during pregnancy Dyspnea, cough and lethargy recurred within 6 months of delivery of a healthy child. Clinically, obvious pallor and toxemia were evident, and crepitations were present on auscultation The hemoglobin was 53%, and the polymorphonuclear alkaline phosphatase score. 302

(normal, 14/100) A leukemoid reaction was diagnosed Conventional methods for correction of the anemia failed Corticosteroids were again given, and the patient felt much better within 2 days The lungs were clear after another month, and the hemoglobin had risen to 67% The patient has remained clinically well so long as corticosteroid treatment was continued There has been susceptibility to descending respiratory tract infection The hemoglobin varies from 70 to 80 Gm /100 ml

The illness appeared in the patient described, her sister and their mother within 18 months, when all three had lived apart from one another in different surroundings for a number of years The 3 patients each had a different form of the disease The first patient had the acute form and would almost certainly have died within 6 months of onset of symptoms but for corticosteroid therapy Her sister was never acutely ill and was thought to have the subacute form of the illness The mother had chronic interstitial pulmonary fibrosis which followed a progressive, slowly downhill course leading to death The refractory anemia in the first daughter appears to be related in some way to the pulmonary condition

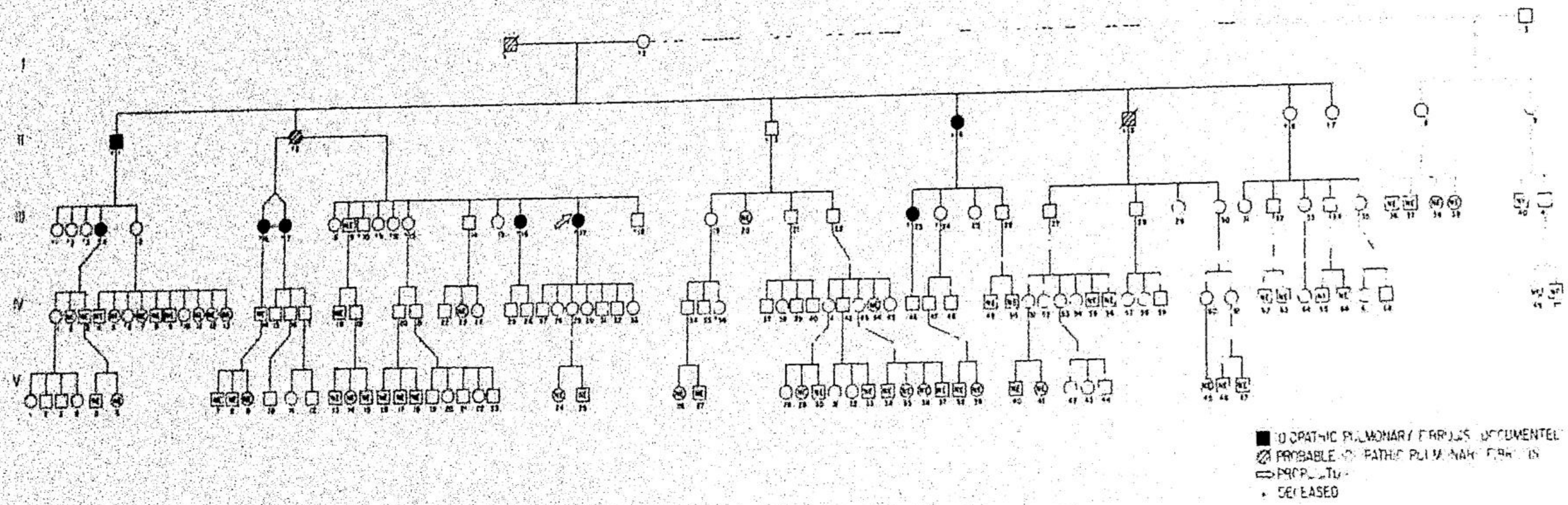
The total of recorded familial cases is now 31 There is clearly sufficient evidence to show that liability to diffuse interstitial pulmonary fibrosis can be inherited and warrants, in such cases, the present descriptive term

**Family Study of Idiopathic Pulmonary Fibrosis: Possible Dysproteinemic and Genetically Determined Disease.** Ralph F. Jacox, John Frymoyer, Philip Bonanni and L. E. Young[2] (Univ. of Rochester) recently studied a patient with interstitial pulmonary fibrosis. Study of her family revealed 7 other autopsy-proved cases with remarkably similar features.

The propositus, a woman aged 46, had a 6-month history of progressive dyspnea and mild productive cough. Chest x-rays showed a diffuse, nodular-appearing infiltration widely disseminated throughout the lungs. Blood studies revealed persistent eosinophilia and pulmonary function studies, an alveolar-capillary block associated with restricted ventilation. Serum protein electrophoresis demonstrated a sharp peak within the $\gamma$-globulin. Immunoelectrophoresis suggested that this represents a monoclonal $\gamma_2$-globulin abnormality. The clinical course deteriorated despite treatment with prednisone and isoniazid. At autopsy, the lungs showed widespread deposition of interstitial connective tissue, marked increase in elastic material in alveolar septa and congestion with histiocytic infiltration within the alveoli and in the septa.

See accompanying chart for genealogy. The mother and

(2) Jr. A. Am. Physicians 77: 232-240, 1964




Pedigree through 5 generations. Note that all individuals with idiopathic pulmonary fibrosis have an affected parent (NE was not examined) (Courtesy of Jacox, R. F., *et al.*: Tr. A. Am Physicians 77:232-238, 1964 )

grandfather of the propositus are suspected cases of pulmonary fibrosis. The mother bore identical female twins who lived in widely separated areas and died within a year of one another of proved interstitial pulmonary fibrosis. None of 82 family members examined had either x-ray changes suggesting early disease or abnormal pulmonary physical findings. Six members had some type of serum protein abnormality, and 13 had eosinophilia of over 6%. Four relatives had a positive latex test for rheumatoid factor. Two members had Raynaud's disease, 1, ulcerative colitis; and 1, classic rheumatoid arthritis. One had a history of Schonlein-Henoch purpura and 1 a history of acute rheumatic fever.

No definitive predictive marker for interstitial fibrosis was found in the study. The pattern of distribution of cases suggests transmission as an autosomal dominant abnormality.

**Regulation of Ventilation in Diffuse Pulmonary Fibrosis.** Ruy V. Lourenco, Gerard M. Turino, Lindsay A. G. Davidson and Alfred P. Fishman[1] (Columbia Univ.) studied 9 males and 10 females, aged 20-69 years, with diffuse pulmonary fibrosis, granulomatosis or both. Each had a history of pulmonary disease for at least 1 year, and none had bronchial obstruction or heart disease. There was no evidence of bronchopulmonary infection at the time of study. Seven patients had Boeck's sarcoid and 2 had asbestosis. All patients but 1 reported breathlessness, and all but 4 had cough. In general, x-ray appearances were those of diffuse fibrosing granulomatosis. Physiologic features are shown in the table. Total lung capacity was abnormally low in all but 2 patients, and this was due to reduction in both vital capacity and residual volume. In 9 of 16 patients the ratio of residual volume to total lung capacity was abnormally high. Maximal breathing capacity was normal in 10 patients, slightly below normal in 4 and below normal in 5. The response to exercise was studied in 15 patients and the ventilatory response to breathing 40% oxygen in 8. The response to breathing of 5% carbon dioxide was studied in 15 patients, and 7 received intravenous THAM. The work of breathing was measured in 7 patients during breathing of 5% carbon dioxide.

Minute ventilation was greater than predicted in all patients, because of increases in respiratory frequency rather than in tidal volume. Breathing 40% oxygen did not change

VENTILATION AND GAS EXCHANGE† AT REST AND DURING EXERCISE IN 19 PATIENTS WITH DIFFUSE PULMONARY FIBROSIS

| Patient | State* | $V_E$ (L./min./M²) | f (per min.) | $V_D/V_T$ | $Vo_2$ (ml./min./M²) | $R_E$ | $D_{CO}$ (ml./min./M²) | Arterial Blood | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | O Saturation (%) | pH | $pCO_2$ (mm. Hg) |
| D. I. | Rest | 8.56 | 28 | 0.54 | 196 | 0.78 | 5 | 91 | 7.42 | 33 |
| | Exer.(Step) | 20.00 | | | 427 | 0.74 | | 89 | 7.40 | 32 |
| | Exer.(S.S.) | 13.80 | 36 | 0.43 | 288 | 0.94 | 6 | 93 | 7.45 | 30 |
| T. S. | Rest | 6.73 | 18 | 0.53 | 143 | 0.83 | | 95 | 7.42 | 33 |
| | Exer.(Step) | 18.75 | | | 441 | 0.76 | | 93 | 7.45 | 30 |
| A. S. | Rest | 4.41 | 19 | 0.65 | 129 | 0.77 | | 96 | 7.42 | 38 |
| | Exer.(Step) | 14.80 | | | 479 | 0.77 | | 89 | 7.42 | 38 |
| I. I. | Rest | 4.74 | 17 | 0.56 | 123 | 0.76 | | 96 | 7.42 | 38 |
| | Exer.(Step) | 11.23 | | | 304 | 0.71 | | 78 | 7.36 | 37 |
| G. K. | Rest | 4.98 | 15 | 0.41 | 168 | 0.73 | | 95 | 7.42 | 39 |
| | Exer.(Step) | 14.70 | | | 518 | 0.67 | | 88 | 7.40 | 40 |
| M. L. | Rest | 6.12 | 18 | 0.54 | 157 | 0.85 | | 98 | 7.40 | 41 |
| | Exer.(Step) | | | | | | | 75 | | ... |
| A. H. | Rest | 6.46 | 33 | 0.49 | 122 | 0.78 | 2 | 92 | 7.42 | 39 |
| | Exer.(S.S.) | 15.00 | 48 | 0.61 | 303 | 0.88 | 3 | 91 | 7.41 | 38 |
| W. B. | Rest | 4.10 | 16 | 0.37 | 116 | 0.88 | 8 | 97 | 7.43 | 36 |
| | Exer.(S.S.) | 8.95 | 23 | 0.37 | 274 | 0.94 | 10 | 95 | 7.41 | 39 |
| G. M. | Rest | 5.27 | 26 | 0.52 | 150 | 0.75 | 2 | 95 | 7.39 | 41 |
| | Exer.(Step) | 16.40 | | | 377 | 0.82 | | 72 | 7.40 | 36 |
| | Exer.(S.S.) | 9.32 | 41 | 0.61 | 176 | 0.99 | 3 | 74 | 7.37 | 43 |
| W. L. | Rest | 3.92 | 23 | 0.53 | 120 | 0.82 | 6 | 97 | 7.41 | 39 |
| | Exer.(S.S.) | 21.17 | 30 | 0.31 | 525 | 1.00 | | 97 | 7.41 | 34 |
| D. H. | Rest | 5.10 | 13 | 0.53 | 142 | 0.79 | | 93 | 7.43 | 37 |
| C. L. | Rest | 4.60 | 18 | 0.54 | 130 | 0.83 | 4 | 97 | 7.42 | 40 |
| | Exer.(S.S.) | 22.40 | 34 | 0.44 | 510 | 1.08 | 14 | 95 | 7.48 | 43 |
| G. J. | Rest | 5.10 | 23 | 0.58 | 124 | 0.79 | | 98 | 7.40 | 40 |
| L. S. | Rest | 4.20 | 19 | 0.44 | 132 | 0.70 | 4 | 95 | 7.40 | 35 |
| | Exer.(S.S.) | 16.40 | 26 | | 450 | 0.91 | | 95 | | ... |
| E. P. | Rest | 7.71 | 40 | 0.63 | 132 | 0.75 | 5 | 79 | 7.41 | 36 |
| J. B. | Rest | 4.72 | 15 | 0.41 | 122 | 0.87 | 12 | 97 | 7.39 | 34 |
| | Exer.(Step) | | | | | | | 94 | 7.37 | 36 |
| J. A. | Rest | 4.43 | 13 | 0.45 | 137 | 0.79 | 5 | 95 | 7.42 | 34 |
| F. T. | Rest | 4.81 | 23 | 0.50 | 119 | 0.86 | 3 | 97 | 7.40 | 37 |
| | Exer.(S.S.) | 13.23 | 38 | 0.56 | 267 | 1.02 | 4 | 91 | 7.40 | 34 |
| J. I. | Rest | 4.70 | 22 | 0.44 | 104 | 0.82 | | 92 | 7.42 | 36 |
| | Exer.(S.S.) | 12.12 | 35 | 0.43 | 302 | 1.12 | | 88 | 7.43 | 38 |

†$V_E$, minute ventilation at body temperature and ambient pressure saturated with water vapor (BTPS); f, respiratory frequency; $V_D$, volume of physiologic dead space, BTPS; $V_T$, tidal volume, BTPS; $Vo_2$, oxygen consumption at standard conditions, dry; $R_E$, respiratory exchange ratio; $D_L$, steady state diffusing capacity of lungs for carbon monoxide; arterial $Pco_2$, partial pressure of carbon dioxide in arterial blood.

*Exer.(Step), exercise step test; Exer.(S.S.), exercise steady state.

the minute ventilation or the respiratory pattern. The increase in minute ventilation on breathing of 5% carbon dioxide averaged 218%; the increment was not significantly different from that seen in normal subjects. Respiratory frequency during carbon dioxide breathing was significantly greater in the patients, and tidal volumes represented abnormally large fractions of the vital capacity. Oxygen uptake increased in all patients during carbon dioxide breathing. There were abnormally large increments in arterial $Pco_2$ and arterial hydrogen ion concentration. These changes may

result from an abnormally low buffering capacity and an abnormally high dead space ventilation

The pattern of change in minute ventilation on infusion of THAM was the same qualitatively as that in normal subjects, but the plateau reached was only 15% below the value before infusion, compared with 50% in controls Carbon dioxide decreased in both groups, and respiratory exchange ratios were markedly low Work of breathing was abnormally high during breathing of both ambient air and 5% carbon dioxide in the patients The abnormally high work per minute involved not only an increase in respiratory frequency but also in the work done during each breath The abnormally high work per breath done by the patients was a result of the abnormally low compliance of their lungs.

The high minute ventilation of patients with diffuse fibrosis ordinarily arises from an abnormally large number of afferent nerve impulses reaching the respiratory center from the lungs, respiratory muscles or both In some patients this heightened ventilation may be further increased by chemical stimulation The abnormally high work of breathing does not appear to limit ventilatory response The results suggest that in chronic obstructive pulmonary emphysema, the total work of breathing does not limit the ventilatory response At least part of the limitation in patients with this condition may arise from a functional depression of the respiratory center during carbon dioxide retention.

[The point relative to chronic obstructive pulmonary emphysema is that if the limitation of ventilatory response in emphysema were limited primarily by the inordinate increase in work of breathing (as has been suggested by others) one would expect a similar limitation in these patients with diffuse fibrosis, but this was not found. In making this observation, the authors point out, however, that the comparison applies to *total* work of breathing, which is increased mainly against nonelastic resistance in obstructive emphysema, whereas in diffuse fibrosis, the increased work is against elastic resistance.—Ed.]

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## MUCOVISCIDOSIS

New Method of Iontophoresis and Analysis of Sweat Electrolyte is described by Edwin Glenn Troutman[4] (Fort Worth, Texas). The procedure was developed to eliminate the overlapping ranges of electrolyte values noted between nor-

4. Am Rev Resp Dis 90:740-741, November, 1964

mal subjects and patients with cystic fibrosis and the consequent uncertainty occurring in the "band of confusion"

METHOD.—A constant-current generator which delivered a precisely timed current at a preset amperage with a variation of less than 1%, regardless of changes in resistance between electrodes, was used. A plain 2x2 in. gauze square was saturated with fresh pilocarpine hydrochloride and placed under the positive electrode. Gauze saturated with physiologic saline was placed under the negative electrode. Sweat samples were collected at 6 successive 5-minute intervals, beginning immediately after stimulation was completed. Collections were made on ashless filter paper under a watch glass. Analysis of total electrolyte was carried out with an alternating-current Wheatstone bridge after dilution and elution of the sweat with triple-distilled water.

Excretion curves, obtained by plotting weight and electrolyte concentration, showed varying patterns with various levels of stimulation. The most consistent curves were obtained by a stimulus lasting 2 minutes at a level of 2 ma., using 0.2% pilocarpine hydrochloride. Abnormal electrolyte concentrations were often produced in control subjects by understimulation or overstimulation. The most statistically significant values were obtained when samples from the last 20 minutes of collection were totaled.

An index was developed which reflected not only the amplified significance of absolute electrolyte content times concentration, but also a standard area of collecting surface (1 sq. m.) and collecting time (1 minute). The formula was:

$$\frac{\text{mEq./L.} \times \text{absolute excretion in mEq.} \;\Big/\; \frac{\text{1 sq. m}}{\text{area of electrode}}}{\text{Time of collection in minutes}}$$

Computer analysis of data from numerous groups showed that only patients with cystic fibrosis had significantly high values of sweat electrolyte concentration. Excretion in absolute milliequivalents was sometimes more significant than concentration. Symptomatic relatives of patients with cystic fibrosis had a significantly higher absolute excretion and index than asymptomatic relatives. The data did not confirm the presence of a forme fruste of mucoviscidosis and failed to support the concept of simple mendelian recessiveness.

**Ocular Changes in Pulmonary Insufficiency** were studied

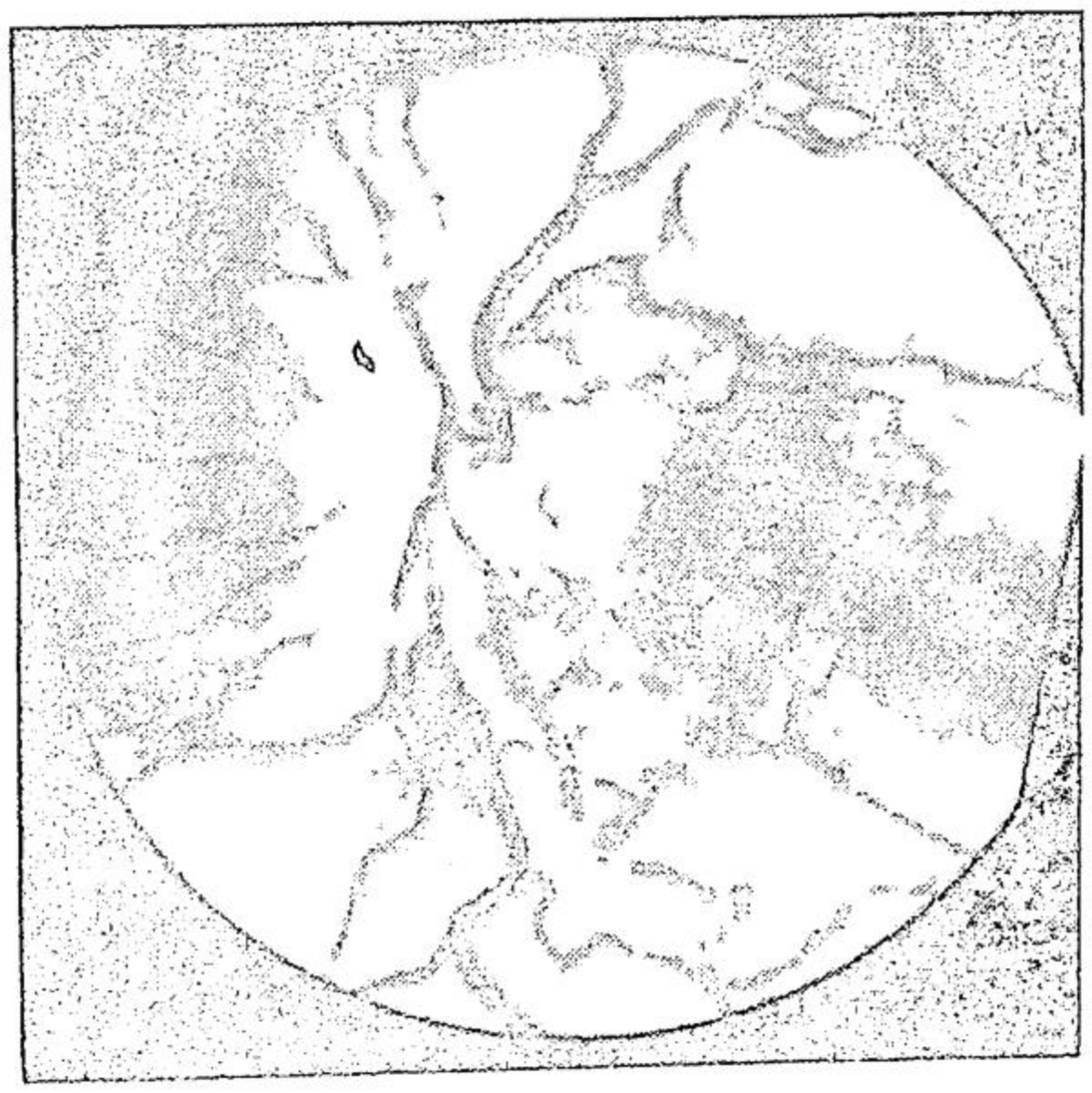

Fig. 31. – Photograph of fundus of left eye of patient, aged 20, with cystic fibrosis during episode of respiratory failure. Mild papilledema, retinal hemorrhages and venous dilatation are present. (Courtesy of Spalter, H. F., and Bruce, G. M.: Ir. Am. Acad. Ophth. 68: 661-676, July-Aug., 1964.)

by Harold F. Spalter and Gordon M. Bruce[5] (New York). The globes of 16 patients with cystic fibrosis of the pancreas were examined after death, and definite evidence of pathologic changes in the ocular tissues was noted in 12. In most instances, this was manifested by papilledema, macular edema or retinal hemorrhages. In 10 of the 12 patients, the retinopathy of cystic fibrosis was noted before death. A review of laboratory findings showed that hemoglobin levels and venous pressure levels were not directly related to the ocular changes, and cerebrospinal fluid pressure was elevated clinically in only 1 patient. Generalized cerebral edema was not found in patients studied at autopsy. Patients with minimal clinical respiratory problems or those who died of terminal acute respiratory insufficiency without a background of chronic respiratory failure were those in whom no pathologic ocular changes were noted. Four of the 5 patients who died of causes other than chronic respiratory failure had normal globes.

In a living patient, aged 20, respiratory difficulties increased with the rather sudden development of recurrent pulmonary infections. Retinal changes were first noted during hospitalization due to $CO_2$ retention (Fig. 31). With treatment, the respiratory insufficiency slowly cleared and $CO_2$

5 Ir. Am. Acad. Ophth. 68: 661-676, July-Aug., 1964.

levels returned to normal. Within 3 months, the retinopathy almost entirely disappeared. Five patients with respiratory failure and $CO_2$ retention were studied. Two had chronic pulmonary emphysema, 2, kyphoscoliotic pulmonary disease, and 1, the Pickwickian syndrome. Four of these patients had retinal vascular changes, 1 showing frank papilledema and macular edema. The abnormalities were similar to those seen in patients with cystic fibrosis. The spectrum of changes varied from venous dilatation to marked vascular tortuosity, in addition to retinal hemorrhage, macular edema and papilledema.

Findings suggest that the retinopathy observed in patients with cystic fibrosis and in adults with chronic pulmonary insufficiency of different origins is in large part a reflection of $CO_2$ retention with its physiologic influence on cerebral blood flow. Respiratory failure may serve as a possible explanation for previously unexplained retinal hemorrhages. Respiratory insufficiency should be considered in the differential diagnosis of papilledema.

► [The occurrence of retinopathy, including papilledema, in respiratory insufficiency has been known for many years, but the present authors were the first in 1960 to describe it in association with mucoviscidosis. In the present important article, they report autopsy findings, compare the retinal changes in the pediatric group with those found in adults (with respiratory insufficiency secondary to other causes, of course, than the pulmonary disease associated with cystic fibrosis of the pancreas) and discuss the possible pathogenetic mechanisms. In an addendum, Doctor Bruce further draws attention to the question of differentiating visual disturbances due to hypercapnia from possible toxic effects of antibiotic medications and describes several cases of failing vision which he attributes to a specific optic neuritis caused by chloramphenicol. Idiosyncrasy to the drug, he believes, is necessary to produce this syndrome. –Ed.]

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## MYCOSES

**Histoplasmosis Cooperative Study: II. Chronic Pulmonary Histoplasmosis Treated with and without Amphotericin B.** In the Veterans Administration-Armed Forces Cooperative Study on Histoplasmosis,[6] patients found to have chronic pulmonary disease with Histoplasma capsulatum demonstrable on sputum culture were assigned randomly to receive

(6) Am Rev Resp Dis 89:641-650, May, 1964

hospital treatment with or without amphotericin B therapy. Of the 31 patients observed for 27 months, 17 were so treated One who had acute pulmonary histoplasmosis had a satisfactory response Only a few patients were confined to bed. Among the 30 males, predominantly in the 5th and 7th decades of life. the mean ages were 55 and 52 years, respectively, for patients not given and those given amphotericin B The mean durations of disease were 5 years 7 months and 5 years 10 months, respectively

Pulmonary lesions were bilateral in 9 control and 11 drug treated patients All 14 control subjects and 13 of the 16 drug-treated patients had cavities Progressing lesions were found in 6 control and 7 drug-treated patients and regressing lesions in 6 and 4, respectively A solution of 50 or 65 mg of the drug in 500 ml 5% glucose was given intravenously for 6 hours, beginning with a 10 mg dose, 3 times weekly Acetylsalicylic acid was given before each infusion, and hydrocortisone was given when necessary The "target" dosage was 1 2 Gm. in 6 weeks, or 3 3 Gm in 4 months, actual dosage approximated this in all but 3 instances The average follow-up period was 11 months in control cases and 30 months in drug treated cases.

Only 3 of the 14 control subjects developed negative sputum cultures, and 2 had mycologic relapse All cultures in drug-treated patients became negative There was one permanent and one temporary relapse H capsulatum disappeared from sputum cultures in 26 days or less after drug therapy was begun and sometimes much more promptly Stable lesions had increased in treated patients at 6 weeks and at 4 months; these patients unlike control subjects, continued to improve after 4 months. In treated patients, densities at the circumferences of cavities became less marked and the outlines of the cavities became clearer Only 2 of 12 control subjects showed a 4-fold fall in serologic titer, noted at 4 months. Seven drug-treated patients showed falls in titer, 4 of them at 6 weeks. Three control subjects died from active histoplasmosis and 1 from other causes Three drug-treated patients died, without active histoplasmosis, of pulmonary and systemic complications.

It was concluded that amphotericin B has a definitely beneficial effect on the course and prognosis of chronic pul-

monary histoplasmosis. In patients with chronic pulmonary lesions and sputum cultures positive for H. capsulatum, it is inadvisable to withhold amphotericin B

► [This cooperative study demonstrates convincingly the superiority of treatment with amphotericin B over no treatment for cases of chronic infiltrative and cavitary histoplasmosis with positive sputum cultures. The question of surgical excision as an ancillary or alternative measure in cases of sufficiently limited and localized disease is not a subject of the report. It is stated by Utz in *Modern Treatment* (1:321, 1964) that amphotericin therapy is especially important before and after surgery, but the indications for excision if there still are any except for diagnosis, are not given. Nevertheless, earlier reports (prior to the introduction of this drug) have indicated successful results with surgery alone in selected cases. The impediment of drug toxicity has been cited as a reason to use amphotericin only when the diagnosis is certain. This consideration suggests also that its *routine* use after relatively complete excision even of cavitary lesions may not be advisable, as it probably is not after excision of isolated noncavitary granulomas. Further experience, no doubt, will clarify this question.—Ed.]

**Laboratory-Acquired Histoplasmosis.** After discovery that a medical student had acute histoplasmosis and that several classmates had positive histoplasmin skin tests, John F. Murray and Dexter Howard[7] (Univ. of California, Los Angeles) carried out a survey of an entire class of students. Data were obtained on 62 of the 66 persons who worked in the microbiology laboratory in which exposure presumably occurred. Twenty six subjects had positive histoplasmin skin tests. In 10 of these, the positive skin tests were associated occasionally with severe reactions. Most of these showed multiple areas of calcification on chest x-rays which antedated laboratory exposure, and all 10 had lived for many years in the known endemic area (Mississippi-Missouri River basin). Histoplasmin precipitins were found in only 1 subject, the student first to be discovered with histoplasmosis and the only one to become severely ill. Nineteen students had a complement fixation titer of 1:8 or higher to yeast or histoplasmin antigen, all had positive skin tests. Several students with positive skin tests and complement fixation results had generalized aches, malaise, fatigability, chest pain or cough.

Man, 22, complained of chest pain and fever present for 9 days. The pulse rate was 140 and the temperature 100.4 F. The area of cardiac dullness was enlarged to the left, and a loud multiphasic pericardial friction rub was heard over the precordium. The white blood cell count was 16,050 cu. mm. and the sedimentation rate was 36 mm. per hour. Electrocardiographic findings were consistent with pericarditis. Skin tests showed a 12-mm. area of induration with

(7) Am. Rev. Resp. Dis. 89:631-640, May, 1964

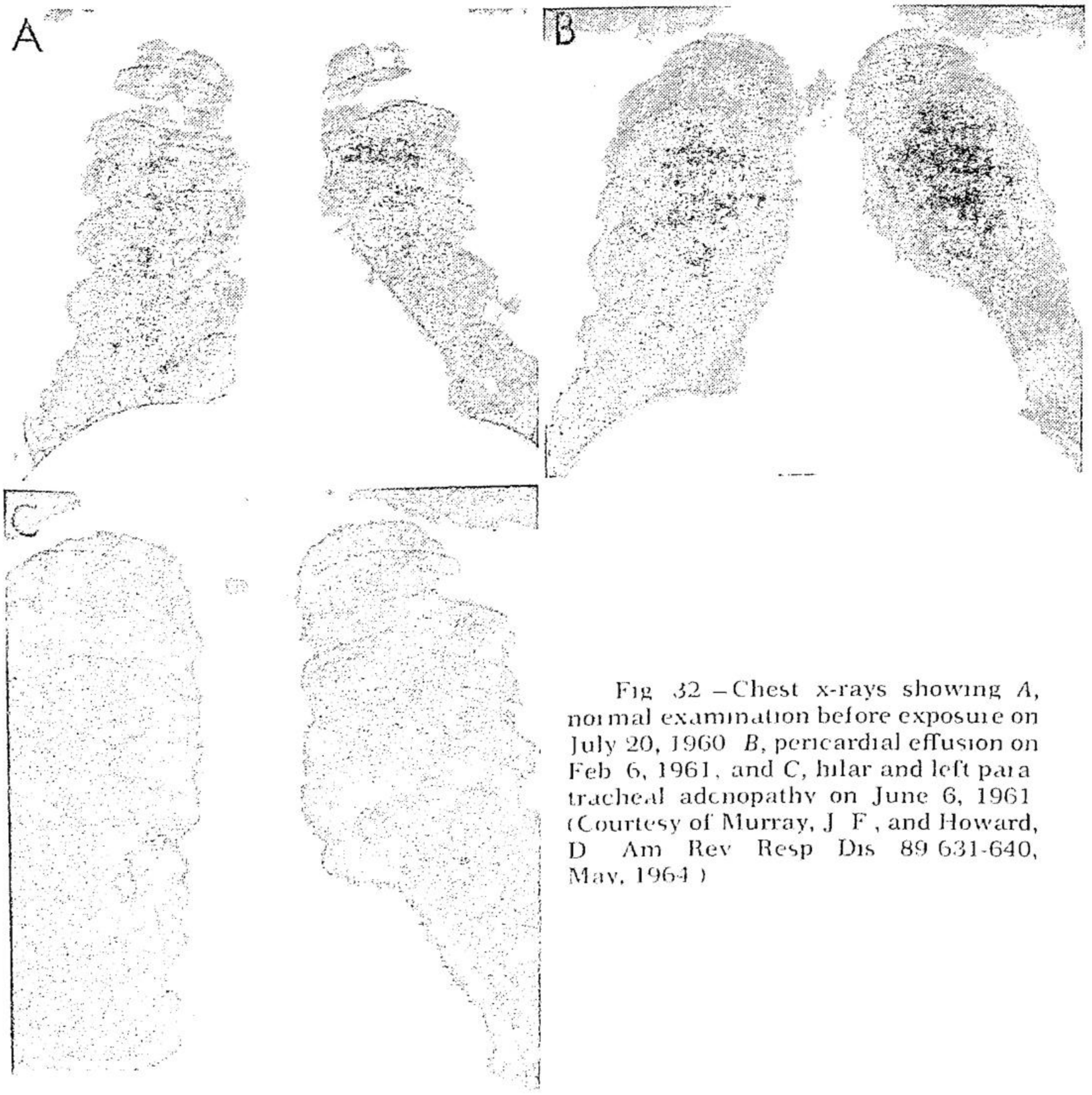


Fig 32 —Chest x-rays showing *A*, normal examination before exposure on July 20, 1960 *B*, pericardial effusion on Feb 6, 1961, and *C*, hilar and left paratracheal adenopathy on June 6, 1961 (Courtesy of Murray, J F, and Howard, D Am Rev Resp Dis 89 631-640, May, 1964 )

coccidioidin and a 20-mm area with histoplasmin Chest x-rays showed two infiltrations in the right lower lung field (Fig 32). In the next month, fever diminished, the pericardial effusion decreased, and the friction rub disappeared. The student returned to class work. At 4 months after the initial illness, x-rays showed bilateral hilar lymphadenopathy Positive agar gel precipitin and complement fixation reactions were obtained to histoplasmin and yeast. Bone marrow study was negative Later, a 2-cm subcutaneous nodule developed over the right lower chest Biopsy showed a caseating granulomatous lesion without organisms The histoplasmin precipitins disappeared, and the complement fixation titer decreased to 1 64 The most recent chest x-rays showed complete resolution of all abnormalities

All personnel should handle histoplasma organisms with care and respect Inactivated cultures are recommended for most teaching purposes Although most laboratory infections are mild, significant illness can occur.

**Clinical Usefulness of Fungal Serologic Testing** was evaluated by Edward E Mays, Joseph A Hawkins and Ludwig R Kuhn[8] (Fitzsimons Gen'l Hosp.). Since 1959, fungal complement fixation tests have been performed relatively routinely on the serums of patients admitted to the pulmonary disease service. Of about 2,100 patients having 2,928 examinations, 111 had positive serologic reactions (titer of 1:8 or greater) to one or more of the fungal antigens used The records of 102 patients were analyzed. Positive reactions to histoplasmin were obtained in 92, to blastomyces antigen in 35 and to coccidioidin in 12. Of the histoplasmin reactions, 58% were in titers over 1:8; 84% were mycelial phase reactions alone or combined, and 35% were yeast phase reactions alone or combined.

Of the 47 cases in which tuberculosis was diagnosed, 37 (79%) were bacteriologically proved All 47 patients had positive histoplasmin titers, and Mycobacterium tuberculosis was isolated in 11 of the 12 patients with titers of 1:32 or greater. Cross reactions with blastomycin were noted in 14 cases, but none occurred with coccidioidin. Histoplasmin skin tests were positive in two thirds of the patients tested, and all the tuberculin skin reactions were positive, almost all being either purified protein derivative no. 1 or intermediate strength. Only 3 of the patients in whom tuberculosis was presumptively diagnosed had histoplasmin titers of 1:16 or greater Six of 22 cases in which histoplasmosis was diagnosed were mycologically proved. All 22 patients had positive titers against histoplasmin; all but 4 had titers of 1:16 or greater The mycelial phase antigen was the most reactive Four of the 7 patients showing cross reactions with blastomyces antigen were proved to have histoplasmosis. There were no coccidioidin cross reactions. Of the 16 patients with a presumptive diagnosis, 14 had 2+ or stronger histoplasmin skin reactions. Only 5 patients had positive tuberculin skin reactions.

Of 10 patients with coccidioidomycosis, 9 had positive coccidioidin complement fixation titers, and five titers were 1:16 or above. Nine of the 10 cases were mycologically proved. Six patients showed cross-reactions with blastomyces antigen and 4 with histoplasmin. Seven patients had positive coccidioidin skin reactions and 6 positive tuberculin

COMPARISON WITH VA COOPERATIVE STUDY ON HISTOPLASMOSIS

| | VA | PRESENT STUDY |
|---|---|---|
| Per cent records available for study | 97 8 | 91 9 |
| Per cent cases diagnosed histoplasmosis | 24 | 21 5 |
| Per cent histoplasmosis cases with positive histoplasmin skin tests among those recorded | 86 6 | 90 |
| Per cent of all patients with histoplasmin serology 1 8 or above with diagnosis of histoplasmosis | 8 | 6 6 |
| Per cent histoplasmosis diagnosis presumptive | 66 | 72 7 |
| Per cent cases diagnosed tuberculosis | 51 | 46 |
| Per cent tuberculosis diagnosis presumptive | 25 | 21 |
| Per cent cases diagnosed other diseases | 24 8 | 32 3 |
| Per cent other diseases with positive histoplasmin skin test | 52 | 58 8 |
| Proved cases coccidioidomycosis | 8 | 10 |

skin reactions None of 35 patients with serums reactive to blastomyces antigen had a diagnosis of blastomycosis Cross reactions occurred in 60% of the coccidioidomycosis group and 66% of the proved histoplasmosis group The 1 patient with blastomycosis had negative serologic studies Of 23 patients with nonfungal, nontuberculous diseases but positive fungal serologic studies, 5 had sarcoidosis, 4, nontuberculous pleuritis 3, pneumonia, 2, pulmonary fibrosis, 2, carcinoma of the lung, and 7, miscellaneous conditions

A comparison of the present study with a Veterans' Administration cooperative study is presented in the table Positive complement fixation tests for fungal disease, regardless of titer, are worthwhile screening devices in the diagnosis of pulmonary disease

► [This evaluation should be of appreciable help to the clinician. The authors mention that prior skin testing may elevate the titers of the serologic tests, which should therefore be done first whenever possible —Ed ]

**Blastomycosis: I. Review of 198 Collected Cases in Veterans Administration Hospitals** is reported by the Blastomycosis Cooperative Study of the Veterans Administration.[9] In a review of records of 170 hospitals for 1946-57, 198 proved cases were found in 51 hospitals in 30 states Mean age of the patients was 42: half were aged 30-49 There were 143 whites, 54 Negroes and 1 American Indian The highest incidence was in the southeastern United States. Occupations relating to contact with the soil predominated. Symptoms pertaining to diseases of skin or lungs were the usual causes for seeking medical attention. No single symptom or combination of symptoms could be considered diagnostic.

(9) Am Rev Resp Dis 89 659-672, May, 1964

DEMONSTRATION OF BLASTOMYCES DERMATITIDIS

| Source | Microscopy | | | Culture | | | Histologic Examination | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total Number of Patients Tested | *B. Dermatitidis* Demonstrated | | Total Number of Patients Tested | *B. Dermatitidis* Demonstrated | | Total Number of Patients Tested | *B. Dermatitidis* Demonstrated | |
| | | Cases | Per Cent | | Cases | Per Cent | | Cases | Per Cent |
| Material from skin lesion | 60 | 49 | 81.7 | 72 | 57 | 79.2 | 79 | 71 | 89.9 |
| Sputum | 70 | 40 | 57.1 | 82 | 61 | 74.4 | 22 | 19 | 86.4 |
| Bone (abscess, biopsy, drainage) | 23 | 19 | 82.6 | 31 | 30 | 96.8 | | | |
| Mucous membrane biopsy | 5 | 3 | | 8 | 6 | | 10 | 10 | |
| Bronchoscopic material | 5 | 3 | | 13 | 8 | | | | |
| Prostatic secretions | 5 | 5 | | 8 | 6 | | | | |
| Urine | 5 | 3 | | 11 | 6 | | | | |
| Gastric content | | | | 6 | 6 | | | | |
| Lymph node | 2 | 1 | | 3 | 2 | | 8 | 3 | |
| Lung tissue or chest fluid | | | | 2 | 1 | | 3 | 3 | |
| Cerebrospinal fluid | | | | 3 | 0 | | | | |
| Aspirate of brain abscess | 1 | 1 | | | | | | | |
| Blood | | | | 6 | 1 | | | | |
| Abdominal fluid (aspirate) | 1 | 0 | | 1 | 1 | | | | |
| Liver biopsy | | | | | | | 1 | 1 | |
| Bone marrow | | | | 4 | 1 | | 1 | 0 | |
| Prostate biopsy | 1 | 1 | | 1 | 0 | | 1 | 1 | |
| Testicle biopsy | | | | | | | 1 | 1 | |

Diagnosis was established by tissue biopsy or culture of materials from many sources (table). In 19 cases, diagnosis was made only after exploratory thoracotomy. Often blastomycosis was confused with tuberculosis. In many cases, pulmonary illness previously had been present. No particular type of coexisting disease preponderated. Pulmonary involvement was found in 118 cases and skin lesions in 118. The genitourinary tract was involved in 32 cases, the skeleton in 46 and the mucous membranes in 11. Nine patients had central nervous system disease, whereas the spleen, lymph nodes and thyroid were involved in 8 each. The adrenal was involved in 3 cases and the gastrointestinal tract in 2. The commonest pulmonary lesion was infiltration, but nodular, pneumonic, miliary and linear densities were also seen (Fig. 33). Cavities were found in 30 patients; the largest was 8 cm. in greatest diameter (Fig. 34). Only one system was involved in 81 cases. The disease had been present for 5 years or less in 82% of cases. Positive skin tests were found in 41% of cases and positive complement fixation results in 48%.

Diamidine therapy was given 120 patients, some of whom received potassium iodide. Stilbamidine was the chief drug in 39 patients, whereas 66 received 2-hydroxystilbamidine. Twenty patients received amphotericin B. Thoracic operations were carried out in 30 patients, and an equal number

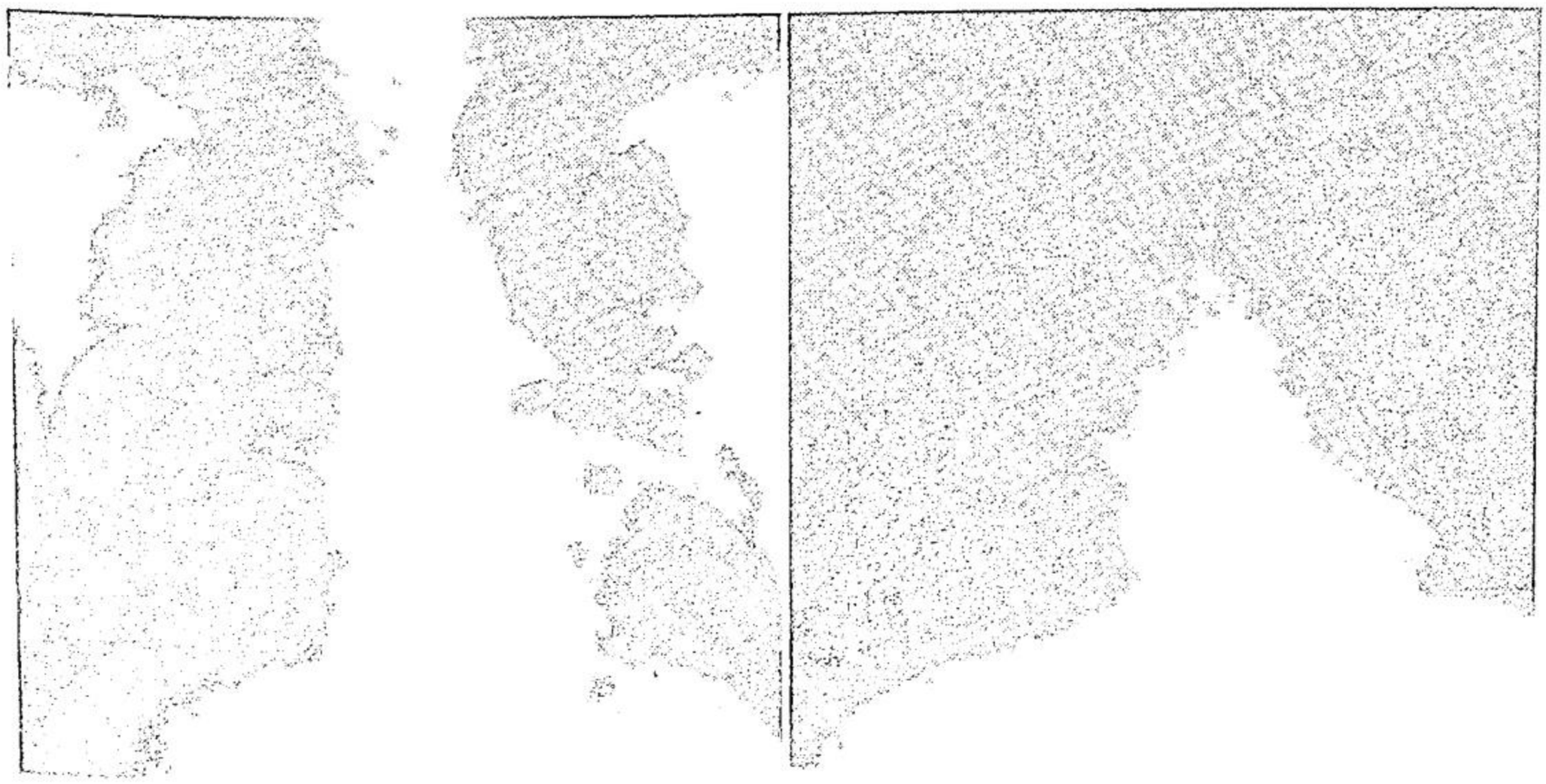

Fig. 33 (left) – Roentgenogram showing widespread pulmonary infiltrate.

Fig. 34 (right) – Roentgenogram showing a large cavity in the chest

(Courtesy of the Blastomycosis Cooperative Study of the Veterans Administration Am Rev Resp Dis, 89 659-672, May, 1964 )

required nonthoracic operations. Follow-up was 1 year or longer in 117 cases. There were 23 relapses within 1 year of apparently effective therapy, but recurrences were observed after much longer and variable periods of remission. Of 53 deaths occurring in 16 years, only 25 (13%) were directly attributable to blastomycosis.

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## TUBERCULOSIS

**Tuberculosis in Ancient Egypt.** According to Dan Morse, Don R. Brothwell and Peter J. Ucko,[1] there are many artistic representations from ancient Egypt that have, at one time or another, been claimed to show some kinds of deformity, including hunchback. An example is shown in Figure 35. Assuming that not all the cases were due to conventions of style or artistic ineptitude, the type of deformity portrayed, an angular kyphosis, is what would be expected to occur in patients who recover from spinal tuberculosis without treatment by surgery or splinting. In 1891, Grebart discovered 44 well-preserved mummies from the 21st dynasty. In 1,

1 Am Rev Resp Dis 90 524-541 October, 1964

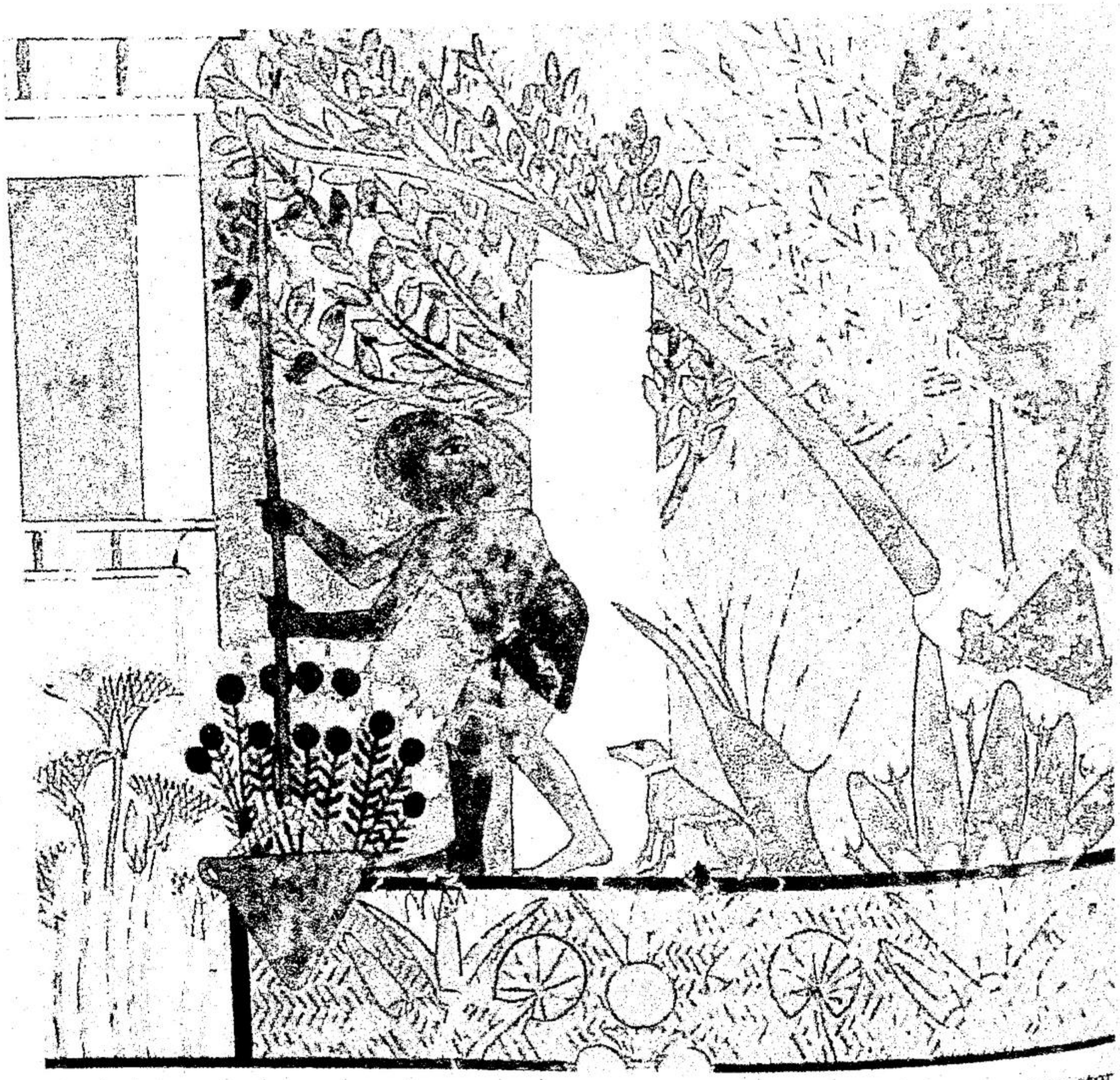

Fig. 35 – Photograph of painting furnished by Henry G. Fischer, associate curator department of Egyptian art Metropolitan Museum of Art New York The original painting is still on the tomb wall of Ipuy near Thebes It is dated XIXth Dynasty The subject is a deformed (?) gardener engaged in raising water with a shadul (water elevator (Courtesy of Morse, D. *et al* Am Rev Resp Dis 90 524-541, October, 1964) (Reproduced by permission of The Metropolitan Museum of Art)

unmistakable evidence of tuberculosis was present. Partial destruction of the lower thoracic and upper lumbar vertebrae had created an angular kyphotic deformity In addition, a huge abscess occupied the area of the right psoas muscle (Figs. 36 and 37). The authors review 31 cases in which skeletal and mummy specimens, possibly dating from 3700 to 1000 B.C., showed pathologic changes resembling tuberculosis. It seems very likely that tuberculosis was established by predynastic times, but further evidence is needed.

It is impossible to say whether tuberculosis has affected the hominid line throughout its evolution. Clearly, some form of tuberculosis has been with man since Neolithic times, and

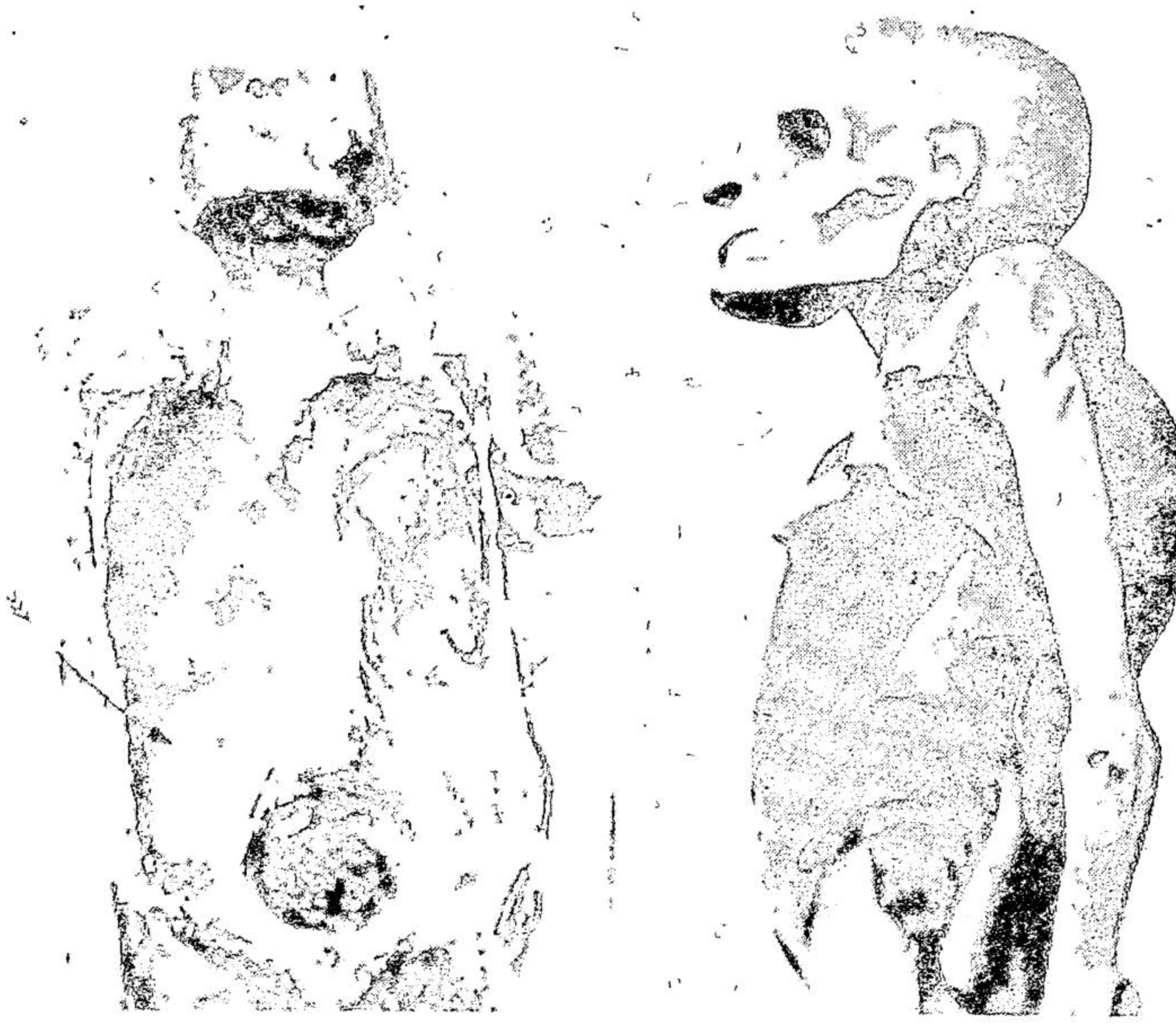

Fig 36 (left) – Photograph of an Egyptian mummy after front body wall was removed (21st dynasty about 1000 B C ) There is partial destruction of the lower thoracic and upper lumbar vertebrae A huge abscess (*arrow*) occupies the right psoas muscle

Fig 37 (right) – Artist's drawing showing spine deformity

(Courtesy of Morse, D , *et al* Am Rev Resp Dis 90 524 541, October, 1964 )

it is conceivable that the closer contact of man with livestock after the Neolithic Revolution provided a satisfactory "bridge" over which an early mutant variety of the tubercle bacillus was able to cross and survive.

The mummy with the large psoas abscess was studied many years ago by Ruffer and the famous archaeologist Elliott Smith Ruffer's fascinating book, *Studies in the Paleopathology of Egypt* (Chicago University of Chicago Press, 1921) contains an extensive description of this find It was attempted, but not successfully, to demonstrate acid fast bacilli The failure, according to my recollection, was attributed to the abscess having been evacuated post mortem and filled with foreign matter in the embalming process. Other microorganisms, however, have been demonstrated in mummies of similar or even greater age by modern histologic staining methods. Morse in an earlier report (Am Rev Resp Dis 83 489, 1961) emphasized the difficulties of differential diagnosis on the basis of skeletal remains and concluded from studies of such material from New World diggings that the existence of tuberculosis in the Americas before Columbus has not been demonstrated unequivocally In the present communication, he and his colleagues make the interesting observation that, despite much evidence from art representations

and human remains of the existence of tuberculosis in ancient Egypt, the literature of the period contains little apparent reference to such a disease.—Ed.]

**Puvalluttuq: Epidemic of Tuberculosis at Eskimo Point, Northwest Territories.** "Puvalluttuq" is the Eskimo term for tuberculosis or "lung sickness." P. E. Moore[2] (Dept. of Nat'l Health and Welfare, Ottawa) describes an outbreak of tuberculosis that occurred in the small Eskimo village of Eskimo Point in the winter of 1962-63.

The precipitating cause of the outbreak was probably a case of active, highly infectious disease in a popular and friendly person with many village contacts. The basic underlying causes include overcrowding, marked increase in the number of susceptible young people and possibly nutritional factors not yet investigated. The debilitating effect of three epidemics of virus diseases (measles, mumps, German measles) also played a role. Overcrowding derives from the necessity of pooling limited housing resources to combat the effect of extreme cold in winter. The size of dwellings is limited by the great expense of keeping them warm and by the need for mobility to seek new hunting and fishing areas. Thus it appears that, despite efforts of the government to-

SUMMARY OF ACTIVE CASES OF TUBERCULOSIS

| *Item* | *All ages* | *Age groups* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *0-4* | *5-9* | *10-19* | *20-29* | *30-39* | *40-49* | *50-59* | *60+* |
| Eskimo population | 329 | 61 | 37 | 77 | 52 | 39 | 28 | 19 | 16 |
| Pulmonary cases: | | | | | | | | | |
| Primary | 49 | 23 | 16 | 10 | | | | | |
| Miliary | 6 | 1 | 1 | 1 | 3† | | | 1 | |
| Minimal | 6 | | 1 | 3 | 1 | | | | |
| Moderately advanced | 4 | | | 2 | 1 | | 1 | | |
| Far advanced | 4 | | | | 3 | 1 | | 1 | |
| Total pulmonary | 69 | 24 | 18 | 16 | 8 | 1 | 1 | | |
| % all cases | 86 | | | | | | | | |
| Extrapulmonary cases: | | | | | | | | | |
| Pleural effusion | 9 | | 1 | 4 | 2 | 2 | | | |
| Others | 2 | 1 | 1 | | | | | | |
| Total extrapulmonary | 11 | 1 | 2 | 3 | 2 | 2 | | | |
| % all cases | 14 | | | | | | | | |
| Total cases | 80 | 25 | 20 | 20 | 10 | 3 | 1 | 1 | |
| % of population | 24 | | | | | | | | |

*All Eskimos †Two of these patients died

(2) Canad. M. A. J. 90:1193-1202, May 23, 1964

ward improvement of dwelling standards, overcrowding will continue to exist.

A case-finding survey during January-April, 1963, among the 329 Eskimos and 16 white persons produced 80 cases of active tuberculosis involving 55% of all households, half the children under age 10 years and 24% of the entire population. Sixty patients (61%) were considered to have active primary disease and 20, reinfection tuberculosis. Sixty-nine patients had pulmonary and 11 extrapulmonary disease. The age distribution is shown in the table.

The increase in number of susceptible young people is a result of case-finding surveys and removal of individuals with infectious disease to the hospital, thus removing most of the natural stimuli to development of immunity. These will have to be replaced by artificial stimuli to keep the number of susceptible persons at a low level.

Programs to improve nutrition and vaccination appear to be complementary to case-finding, isolation and treatment in development of a good antituberculosis program in the Canadian North.

► [A further account of this same outbreak by S L. Carey appears in the *American Review of Respiratory Diseases* (91.1, 1965). Several other local epidemics of tuberculosis have been documented in recent years, but none quite so explosive as this one at Eskimo Point – Ed.]

**Diagnostic Usefulness of Marrow Biopsy in Disseminated Tuberculosis** is evaluated by E. W. Heinle, Jr., W. N. Jensen and M. P Westerman[3] (Univ. of Pittsburgh) on the basis of review of results of marrow biopsy performed in 9 patients in the preceding 4½ years, using a needle biopsy technic. In 6 patients, acute disseminated tuberculosis was the primary diagnosis.

Tuberculous granulomas were found in the marrow in 5 of the 9 patients. Of the 4 without evident marrow granulomas, 1 had a marrow culture positive for Mycobacterium tuberculosis, and 1 had tuberculous meningitis and granulomatous involvement of the liver. One patient had negative marrow and liver biopsies for 53 days before finding of the classic lesions in the same organs at autopsy. Marrow tissue was insufficient for diagnosis in 1 case. Multiple biopsies were obtained in 4 cases and showed regression or disappearance of granulomas 12-27 days after initiation of antituberculotic

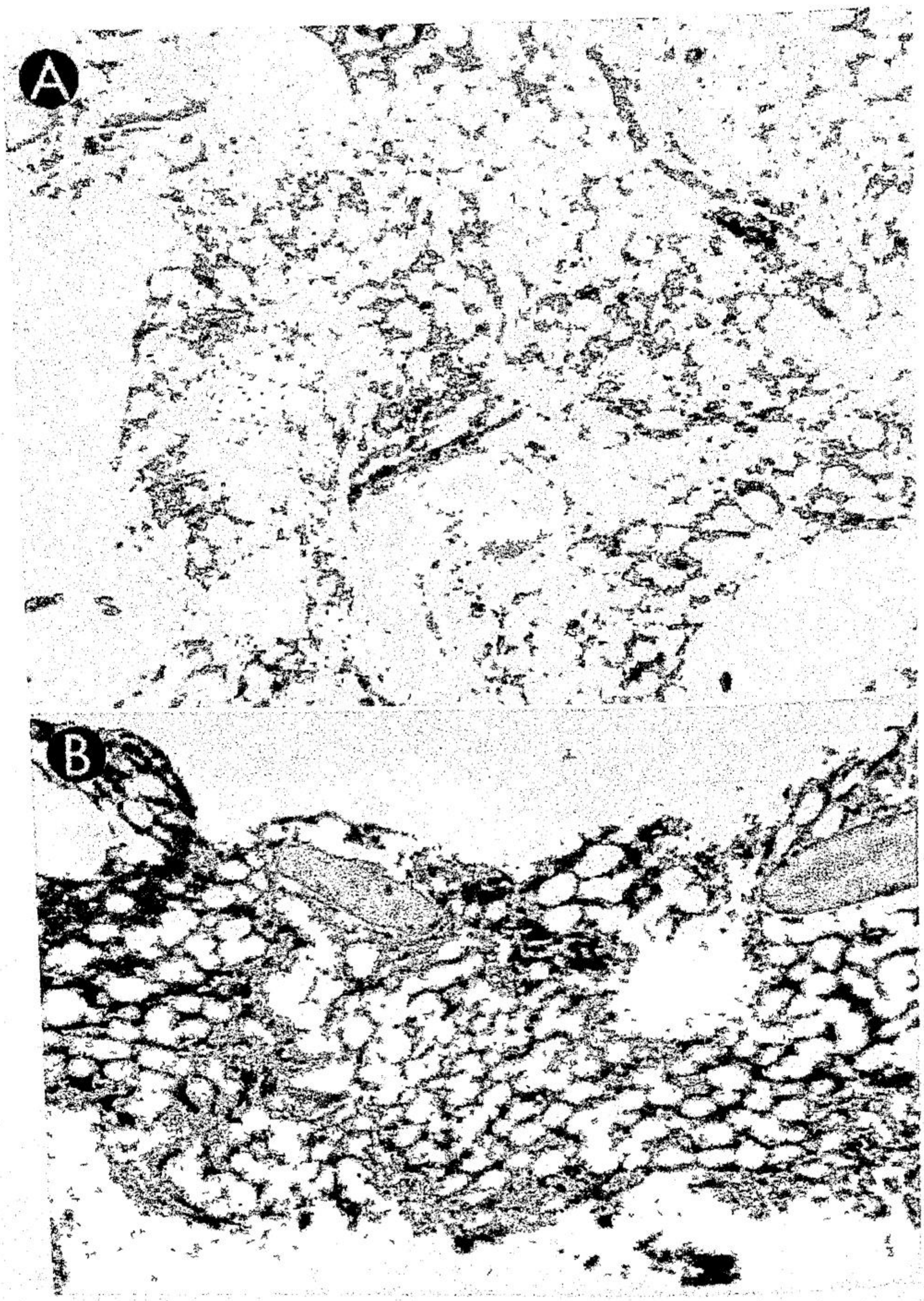


Fig 38 —Serial marrow biopsy sections A, initial biopsy with presence of tubercle and B, repeat biopsy with absence of tubercles 4 weeks after initiation of therapy (Courtesy of Hemle, L W , Jr , *et al* Am Rev Resp Dis 91 701-705, May 1965 ) 87 5 (Cont

therapy in 3 Eradication of the disease was confirmed at autopsy in 1 case Serial marrow biopsy sections are shown in Figure 38 Mycobacterium tuberculosis was recovered on culture of the marrow in 4 of 7 cases, in 3 associated with granulomas on marrow sections. Liver biopsy showed granulomas in all 3 patients studied Chest films showed miliary infiltrates in 3 cases

The bone marrow is often involved in miliary tuberculosis, and marrow biopsy is valuable in diagnosis of disseminated disease Marrow biopsy, in association with liver biopsy when possible, should provide early diagnosis in most patients with miliary tuberculosis

▻ [The recommendation of liver biopsy "when possible" means when not contraindicated by bleeding tendencies, by "the patient's precarious clinical state" or when the patient cannot render the "greater degree of physical cooperation" that is needed for this than for bone marrow biopsy The latter is considered by these authors a less dangerous procedure and not hazardous even in the presence of hemorrhagic disorders It would seem preferable since bleeding tendencies when present are not always obvious, always to reserve liver biopsy for those instances in which the marrow biopsy is unsuccessful and the clinical suspicion high of disseminated tuberculosis Even in these instances the decision whether or not to give isoniazid may often be made advantageously on the total clinical picture and without entailing the hazards of liver biopsy Moreover, toxic effects from isoniazid alone are extremely infrequent, the drug is highly specific for tuberculosis and its effectiveness alone is little, if at all, inferior to combined therapy in such a situation of obscure disseminated tuberculosis as is postulated —Ed.]

**Adrenal Corticosteroids in Life-Threatening Pulmonary Tuberculosis.** David G. Simpson and John H McClement[1] (Columbia Univ.) studied 39 patients with far-advanced, active, acute pulmonary tuberculosis who had not had more than 1 month of previous treatment and were judged in imminent danger of death. Control and study patients received 1 Gm. streptomycin daily and 800 mg isoniazid daily, with 15 Gm. para-aminosalicylic acid daily added as soon as it was tolerated. Study patients also received 250 mg. hydrocortisone intravenously on the 1st day, 60 mg prednisone on the 2d and 3d days and 40 mg. daily from the 4th day until satisfactory improvement was being maintained. Treatment was given for at least 3 weeks if no complications developed. Fluid and electrolyte imbalance were corrected, and an adequate fluid and caloric intake was maintained. Vitamin supplements, vasopressor agents and transfusions of whole blood were given when necessary; nontuberculous infections were treated with appropriate antimicrobial

[1] Am Rev Resp Dis 90 754-759, November, 1964.

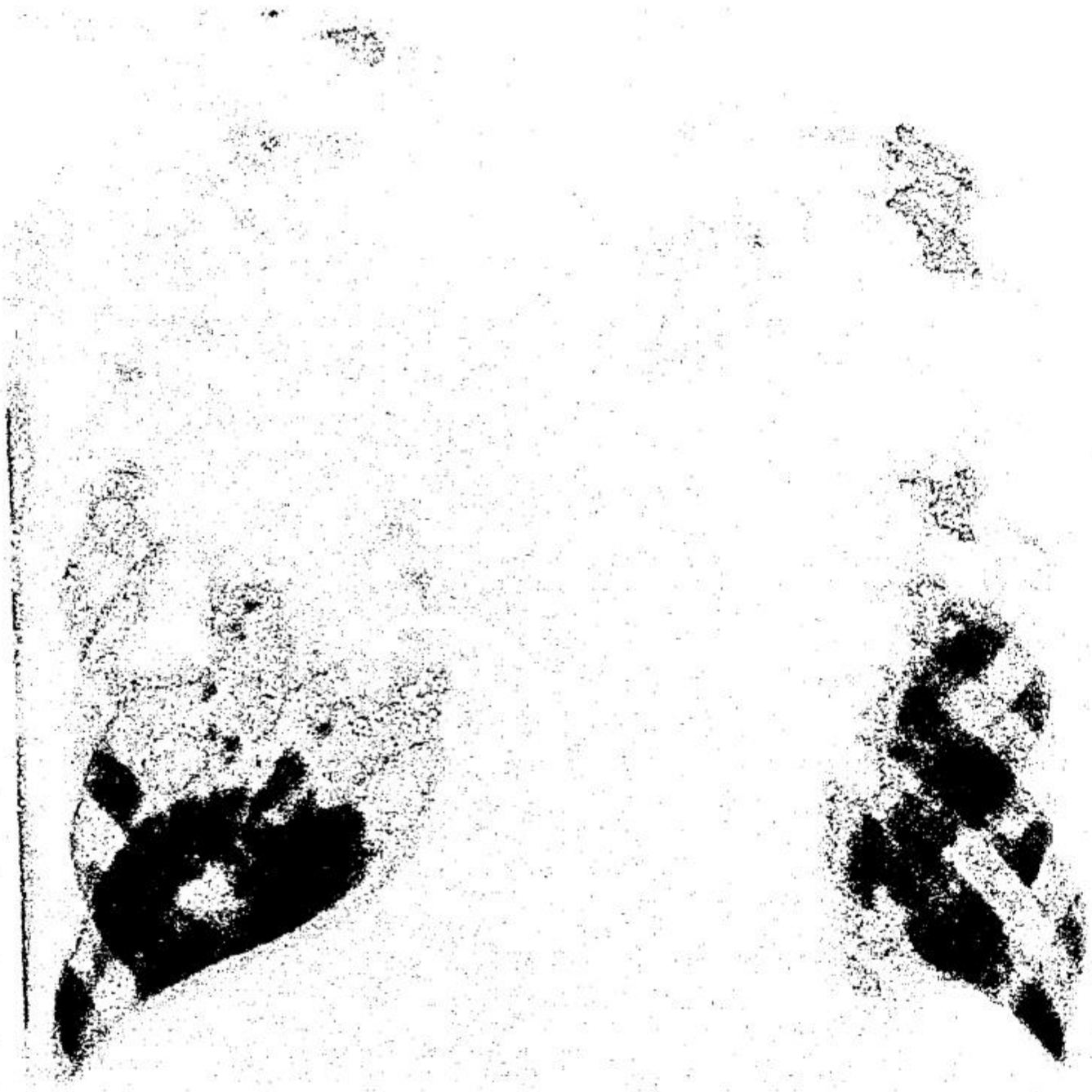

Fig. 39.—X-ray in illustrative case. (Courtesy of Simpson, D. G., and McClement, J. H., Am. Rev. Resp. Dis., 90: 754-759, November, 1964.)

agents. Respiratory insufficiency was prevented or treated by measures directed mainly at removal of tracheobronchial secretions. Average age of the 21 male control subjects was 54, and of the 15 male and 3 female study patients, 47. The duration of symptoms and the extent of tuberculosis were similar in the two groups. A representative chest x-ray is shown in Figure 39. Treatment was usually begun within 24 hours of admission.

The mortality in the two groups (table) was not significantly different. Two thirds of patients who died did so within 1 week. In 4 of 8 patients treated with steroids for an average of 40 days, fewer recurred when the dose of prednisone was reduced; in 3, there was x-ray evidence of worsening. Corticosteroid treatment was stopped because of gastrointestinal hemorrhage in 2 patients. A third patient died of staphylococcic septicemia thought to be a superinfection to which the steroid probably contributed. Three control patients had significant gastrointestinal bleeding and 1, spontaneous pneumothorax. One patient in the study group had pneumothorax on admission and died 3 weeks later, but pneumothorax contributed little, if anything, to death. In

MORIALITY AND TIME OF DEAIH IN RELATION TO ADMISSION TO STUDY

| Interval between Time of Admission to Study and Time of Death | Control Group (Total 21) | Treatment Group (Total 18) |
|---|---|---|
| 21 48 hours | 5 | 2 |
| 2 7 days | 5 | 3 |
| 7 14 days | 1 | 3 |
| after 14 days | 1 | 0 |
| Total | 12 (57%) | 8 (45%) |

both groups, death was more common among older patients, those with the most extensive tuberculosis and those with associated diseases The primary cause of death was tuberculosis or its complications in all 20 patients who died Decreased ventilation was commonly observed clinically in patients with abundant tracheobronchial secretions. Respiratory failure of this type was present in 8 of the 12 control patients and in 3 of the 8 study patients who died

The advantage of corticosteroid therapy added to the standard treatment of tuberculosis was small and not of statistical significance Inanition was believed the most important single factor in failure to survive Respiratory failure caused by retention of tracheobronchial secretions was a prominent contributing cause of death Prevention and treatment of this complication in seriously ill patients are extremely difficult but are a very important aspect of their management

► The failure here to demonstrate a statistically significant advantage in survival rate may be more indicative of the difficulty of selecting patients for such a control study than it is that the treatment is not sometimes highly effective to the extent of being in fact a life preserving measure The authors, indeed, concede that investigation of a larger group might demonstrate a significant difference Prior reports albeit mostly without control comparisons have included instances of such a dramatic and prompt improvement in patients with disease of fulminating character that an immediate beneficial influence cannot reasonably be doubted. That an immediately fatal outcome, despite adequate antimicrobial therapy, cannot be reliably predicted is evidenced by the survival of nearly half the patients of the present series who were in the control group Doctors Simpson and McClement have shown nevertheless many of the factors which determine an early fatal outcome, as they have also demonstrated the risks of adrenocorticosteroid therapy in this kind of clinical situation and the value of certain other ancillary therapeutic measures. - Ed ◄

**Drug-Resistance in Patients with Pulmonary Tuberculosis Presenting at Chest Clinics in Hong Kong.** In the course of a Hong Kong Government Tuberculosis Service—British Medical Research Council Cooperative Investigation,[5] sputum specimens were obtained from 869 patients considered likely to have bacteriologically positive pulmonary tuberculosis. In all, 247 (28.4%) specimens were negative on smear and culture, 47 (5.4%) were positive on smear but negative on culture and 571 (65.7%) grew on culture. Only 4 (0.5%) cultures were contaminated. There were 5 anonymous mycobacteria. All 564 strains of Mycobacterium tuberculosis were classed as the human variety. Smear-positive but culture-negative results were obtained in 23% of specimens that were scantily positive on smear Climatic conditions, time in transit, loss of viability of isoniazid-resistant organisms and previous courses of chemotherapy did not explain this incidence.

Of the 564 patients with sensitivity test results, 302 (54%) had no history of previous chemotherapy, 54 (10%) had a history of probable chemotherapy and 208 (37%) had a history of definite previous chemotherapy. Of the 302 with no previous chemotherapy, 20% had resistance to one or more drugs. The total resistance to isoniazid was 14%, to streptomycin, 11%; and to para-aminosalicylic acid (PAS), 3%. Resistance to both isoniazid and streptomycin occurred in 5% of patients. Of the 208 patients with a history of definite chemotherapy, 70% had resistance to one or more drugs. The total resistance to isoniazid was 62%; to streptomycin, 41%; and to PAS, 13%. Resistance to both isoniazid and streptomycin occurred in 23% of patients, to isoniazid and PAS in 1% and to streptomycin and PAS in 0.5%.

Isoniazid resistance was found in 14% of patients with no history of chemotherapy, 40% of those with a history of chemotherapy that did not include isoniazid and 67% of those with a history including isoniazid therapy. Streptomycin resistance occurred in 11% of patients with no history of chemotherapy, 27% of those who had received courses of injections and 43% of those with a history of a course of streptomycin. PAS resistance was found in 3% of patients with no history of chemotherapy, 10% of those with a history of chemotherapy not including PAS and 20% of those with a

(5) Tubercle 45 77 93, June, 1964

history of definite PAS therapy Patients whose sputum smears were heavy or moderate on direct examination were more likely to be excreting drug-resistant organisms than were patients whose smears were scanty or negative

In Hong Kong, a careful history on patients newly registered at a clinic is a valuable guide to the likelihood of finding drug-resistant strains

► The very high incidence of primarily drug resistant tuberculosis here reported is sharply at variance with recently reported findings in the United States (see the article presented by U S P H S Cooperative Investigation, 1964-65 YEAR BOOK, p 188), where primary resistance to any one of the three principal drugs is in the 2-3% range and to two or more, less than 1% The nearly 10-fold discrepancy may, as the investigators of the present report themselves point out, be due in part to concealment by patients of a history of prior treatment Strenuous efforts were made, by repeated interrogation to eliminate this source of error, but there is no way of estimating its actual magnitude —Ed ◄

**Response to Treatment in Silicotuberculosis: A 10-Year Survey.** Kirby S Howlett, Jr , and Frederick C Warring, Jr [6] (Laurel Heights Hosp , Shelton, Conn ) reviewed results in 69 patients with proved active silicotuberculosis who were treated, usually for prolonged periods, with various combinations of antituberculosis drugs and discharged during 1953-63. Average follow-up was 4 years 8 months The median age at admission was 63 The silicotuberculosis was inactive or quiescent in 65% of patients after initial treatment and in 41% at end of follow-up. Sixteen per cent of patients died of progressive silicotuberculosis (13% during initial treatment and 3% after later relapse). Even among patients whose disease was successfully controlled, deaths from other causes were numerous. An additional 11% of patients died of causes related to chronic impairment of pulmonary circulation and function, and 29% died of causes unrelated to the silicotuberculosis.

Results were considerably better in patients treated initially with the combined regimen of isoniazid and para-aminosalicylic acid than in those given streptomycin and para-aminosalicylic acid. However, in many patients, especially those with more extensive cavitary disease, the tuberculous infection subsequently became resistant to one or more of the initial drugs and required a change of regimen to other appropriate drug combinations. Silicotuberculosis became inactive in 94% of patients in whom treatment was begun before cavitation developed, and there were no deaths from

(6) Arch Environ Health 9:343-356, September, 1964.

CORRELATION OF RESULTS WITH VARIOUS FACTORS

| | No. of Cases | Became Inactive or Quiescent | Died of Progressive Silicotubere |
|---|---|---|---|
| Extent of silicotubere | | | |
| Minimal | 2 | 2 (100%) | 0 |
| Moderately adv | 26 | 21 (81%) | 3 (12%) |
| Far adv | 41 | 22 (54%) | 8 (20%) |
| Cavitation | | | |
| Present | 53 | 30 (57%) | 11 (21%) |
| Absent | 16 | 15 (94%) | 0 |
| Initial drug regimen | | | |
| Streptomycin-aminosalicylic acid | 26 | 15 (58%) | 7 (27%) |
| Isoniazid-aminosalicylic acid | 38 | 29 (76%) | 3 (8%) |
| Other | 5 | 1 (20%) | 1 (20%) |

progressive silicotuberculosis in this group Results are correlated with various factors in the table.

When medical treatment was inadequate, surgical resection of the refractory lesions yielded excellent results. In all patients so treated, an inactive status was achieved and maintained, the only death resulting from a totally unrelated cause 7 years later. Unfortunately, however, only a minority of patients who needed pulmonary resection were acceptable risks for this operation

**Cervical Adenitis in Children Due to Human and Unclassified Mycobacteria.** Bob G. Black and John S. Chapman (Southwestern Med. School) review findings in 30 patients diagnosed as having mycobacterial lymphadenitis during 1956-62, representing a sixth of all coded cases of lymphadenitis. Of 20 positive cultures found among 29 patients, 13 yielded unclassified mycobacteria and 7 Mycobacterium tuberculosis. The 10 cases not supported by culture were diagnosed on the basis of comparative skin tests, histologic study, lack of contact with animals and a negative response to cat-scratch antigen. In all but 4 patients, the diseased node was unilateral, being located just posterior and inferior to the angle of the mandible. Three patients had generalized adenopathy due to M. tuberculosis, and 1 had unilateral axillary adenopathy. None of the 15 patients on intensive and varied antibiotic regimens before admission showed resolution of the adenitis.

(7) Pediatrics 34 887-893, June, 1964

RACE AND SEX INCIDENCE*

| | *Negro Male* | *Negro Female* | *Total* | *Caucasian Male* | *Caucasian Female* | *Total* | |
|---|---|---|---|---|---|---|---|
| Unclassified | | | | | | | |
| Group I | 3 | 1 | 4 | 1 | 3 | 4 | ♂ |
| Group II | 0 | 0 | 0 | 2 | 1 | 3 | 14 |
| Group III | 0 | 0 | 0 | 1 | 1 | 2 | |
| M. tbc. | 1 | 3 | 4 | 2 | 1 | 3 | ♀ |
| Unproven | 1 | 2 | 3 | 3 | 4 | 7 | 16 |
| Total | 5 | 6 | 11 | 9 | 10 | 19 | |

* Clinic ratio of Negro to Caucasian, 2.5:1, population ratio, 1.5:1

In children with unclassified disease, the node is usually freely movable; if it is attached to the skin, the overlying tissue varies from hyperemic to an attenuated parchment-paper appearance. Draining sinuses occasionally develop. Involvement of other nodes is slow and late and would seem to be by contiguity.

Of the 19 white and 11 Negro patients, 14 were males and 16 females. Race and sex incidence are shown in the table, in which unclassified cases are indicated as group I (photochromogen), group II (scotochromogen) and group III (nonchromogen). Duration of adenitis was of no value in differentiating the mycobacterial type. Three of the 7 patients from whom M. tuberculosis was cultured had a history of contact with tuberculosis. White cell counts ranged from 5,000 to 25,000/cu. mm. in each group. Although there was considerable cross reaction, no patients with unclassified disease produced a reaction against human tuberculin on agar gel diffusion study. Of 22 histologic studies, 19 showed typical granulomas. All patients with M. tuberculosis adenitis but only 1 with unclassified disease had active pulmonary parenchymal disease.

Surgical treatment consisted of total excisional biopsy in 26 cases, incision and drainage in 2 and needle aspiration only in 1. One patient was not treated surgically. Chemotherapy in 25 cases consisted of isoniazid, 5 mg./kg. daily, and para-aminosalicylic acid, 200 mg./kg. daily, for a total of 18 months. Four patients also received short courses of streptomycin, 20 mg./kg. daily. Two patients did not receive chemo-

therapy after surgery, and 3 had no record as to whether it was instituted. Of 26 patients followed from 6 months to 7 years, only 1 has had a recurrence, this was due to a scoto-chromogen. One patient who had needle aspiration has had persistent drainage for 5 months, although the size of the node has decreased markedly; the agent was a photochromogen. The incision site becomes more indurated with delayed healing and breaks down frequently when chemotherapy is not instituted at an early date. All biopsy incisions healed rapidly and by primary intention when para-aminosalicylic acid and isoniazid were started immediately after surgery, and no late spread or breakdown has occurred

A negative history of contact with tuberculosis, large reactions to unclassified skin test antigen with concomitant weakly positive or negative tuberculin skin tests, the absence of a tuberculin band on agar diffusion in the face of reaction to unclassified antigens, and the absence of active pulmonary parenchymal disease in the preschool age group (predominantly age 1-3) point toward an unclassified mycobacterial cause. Intensive search among adult contacts of patients with unclassified disease revealed no case of pulmonary disease Contact investigation of the child with tuberculous nodes is quite productive The treatment of both types of mycobacterial disease of lymph nodes yielded good results, and recurrence was relatively uncommon

► [This high proportion of cases associated with unclassified mycobacteria raises some questions regarding the causes of scrofula in the past, when this condition was so much more common In 1910, Park and Krumwiede typed the acid-fast bacilli in 54 cases of cervical lymph node tuberculosis operated on by Dowd, and they found one-third to be of the bovine strain They reported the human type to predominate except in the age group under 5 years Since such typing of strains was carried out by animal inoculation, the possibility is ruled out that a large proportion of cases could have been due to the unclassified mycobacteria (then unrecognized as pathogenic), because these are not pathogenic for guinea pigs, as are both the human and the bovine varieties of M. tuberculosis In Glasgow, as recently as 1932, Griffith found as high as 64% bovine infection in children with tuberculous lymphadenitis Gale, reporting in 1952, found among 210 patients of all ages seen in a Canadian sanatorium over a 20-year period with superficial lymphadenitis (mostly of cervical nodes) that 88% had tuberculosis elsewhere in the body The relative preponderance of unclassified mycobacteria in children now, as reported here by Doctors Black and Chapman, must, it seems from these retrospective data, be a reflection of the decline in the prevalence of infection with M tuberculosis, bringing to prominence the cases due to unclassified mycobacteria which in the past must have constituted a very small proportion of the total, if this form of lymphadenitis indeed existed prior to its recognition in the past decade, which there is little reason to doubt – Ed ]

## Three Cases in Same Family of Fatal Infection with My-

PATHOGENICITY AND VIRULENCE*
(HIGHEST DEGREE OF VIRULENCE RECORDED)

| Strain no | Year | Animal | Dose & route | Death weeks | Lung affection | | Organs | | Joints and tendon sheaths | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Macr. & micr. | Culture | Macr. & micr. | Culture | Macr. & micr. | Culture |
| 1 | 1959 | Rabbit | 5 i.v. | 2 | n.e. | n.e. | Spleen | + | 0 | n.e. |
| | 1959 | Rabbit | 1 i.v. | k. 12 | n.e. | n.e. | Liver | + | + | + |
| | 1959 | Hen | 1 i.v. | 6 | n.e. | n.e. | 0 | + | n.e. | n.e. |
| | 1959 | Guinea pig | 1 i.v. | k. 8 | n.e. | n.e. | 0 | Spleen + | n.e. | n.e. |
| | 1962 | Guinea pig | 1 i.p. | k. 8 | 0 | n.e. | 0 | Spleen + | n.e. | n.e. |
| | 1965 | Guinea pig | 0.1 × 2 i.c. | k. 8 | + | n.e. | 0 | 0 | n.e. | n.e. |
| 2a | 1963 | Rabbit | 5 i.v. | 2 | n.e. | n.e. | Spleen | + | 0 | - |
| | 1962 | Hen | 5 i.v. | 4 | n.e. | n.e. | Liver Spleen | + | n.e. | n.e. |
| | 1962 | Guinea pig | 1 i.v. | k. 8 | n.e. | n.e. | 0 | +, ++ | n.e. | n.e. |
| | 1962 | Guinea pig | 1 i.p. | k. 8 | + | + | Liver | + | n.e. | n.e. |
| | 1962 | Guinea pig | 0.1 × 2 i.c. | k. 8 | + | n.e. | 0 | 0 | n.e. | n.e. |
| 2a | 1962 | Rabbit | 5 i.v. | 2 | n.e. | n.e. | Spleen | + | + | - |
| | 1962 | Hen | 5 i.v. | 4 | n.e. | n.e. | 0 | + | n.e. | n.e. |
| | 1962 | Guinea pig | 1 i.v. | 4 | n.e. | n.e. | 0 | + | n.e. | n.e. |
| | 1962 | Guinea pig | 1 i.p. | k. 8 | + | + | 0 | + | n.e. | n.e. |
| | 1962 | Guinea pig | 0.1 × 2 i.c. | k. 8 | + | n.e. | 0 | 0 | n.e. | n.e. |

* +, ++ = degrees of positivity. k. = killed. n.e. = not examined.

eobacterium Avium are reported by H. C. Engbaek* (Copen-
hagen). In a family of 5 members, the mother and 2 daugh-
ters became seriously ill within about a year as the result of
infection with M. avium. The disease lasted from 5 months
to about 2½ years and was fatal in all 3 patients. On the whole,
the strain was very similar to one another and all grew

* Acta pathol. microbiol. scand. 49, 165–172, 1960.

relatively slowly After 3 weeks' growth at 37 C., the colonies were moderately eugonic and dome-shaped, with a smooth entire rounded margin and a shiny, smooth surface The pigmentation was pale yellow and did not change after short exposure to light The strains grew densely and diffusely on Dubos fluid medium with Tween 80. The niacin test was negative and the catalase test positive, as were tests with nicotinamide and pyrazinamide. The strains were strongly resistant to most drugs tested: only treatment with cycloserine was considered practicable Results of studies on pathogenicity and virulence are shown in the table.

There can be little doubt that the myocbacteria isolated caused the progressive disease that led to the death of the 3 patients. The results of the studies justify the classification of the bacteria as M. avium. The family was in close contact with their poultry, which wandered about freely in the home Infections with M. avium were known to exist in the district among poultry on small holdings similar to the holding owned by the family studied. It must be assumed that the family's attitude toward poultry resulted in the hens being allowed to live for a long time, thus favoring the development and spread of infection.

► [The pathogenicity criteria for M avium are that it produce progressive disease in chickens and rabbits but not in guinea pigs These criteria, it is claimed, were fulfilled, though I must confess to finding some difficulty in making this out from the table – Ed ]

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## PULMONARY NEOPLASMS

**Age at Onset of Lung Cancer: Significance in Relation to Effect of Smoking.** M. C. Pike and Richard Doll[9] (London) examined the death rates among British doctors to see what effect smoking different numbers of cigarettes daily has on the "life-span" average age at death from lung cancer, which in this disease provides a close estimate of the age at onset.

The physicians were studied during 1951-61. They were classified into groups according to the number of cigarettes smoked daily: 1-14; 15-24; and 25 and more. The relationship

(9) Lancet 1 665 668, Mar 27, 1965

TABLE 1.—AVERAGE AGE OF OCCURRENCE OF LUNG CANCER IN RELATION TO NUMBER OF CIGARETTES SMOKED

| Passey's (1962) data * | | | British doctors starting smoking at age 17 years† | |
|---|---|---|---|---|
| Cigarettes per day | No. of men | Average age at onset (yr.) | Cigarettes per day (group mean) | Average age at death (yr.) |
| 1–10 | 90 | 58 6 | 8·4 | 71 8 |
| 11–20 | 178 | 57·0 | 18 6 | 70·5 |
| 21–30 | 132 | 57 1 | .. | .. |
| 31–40 | 52 | 55 9 | 30 7 | 69 3 |
| 41–80 | 43 | 56 6 | .. | .. |

Similar results have been reported from the United States by Buechley (1964)
†Corresponding to w=20, in formula given

can be represented by use of two formulas. That for lung cancer is

$$y = \rho\, Nk(x-w)^{k-1}$$

where y is the age-specific death rate; x, the age in years; w, a constant equal to age at beginning of smoking plus a few years' minimal "induction period"; N, the number of cigarettes smoked daily; k, 5; and $\rho$ is a constant. This formula provides a reasonably close fit to the observations. The formula for all other causes of death is:

$$y = e(\alpha + \beta x)$$

where y is the age-specific death rate; x, the age in years; and $\alpha$ and $\beta$ are constants that vary with amount smoked and are chosen to provide lines of best fit.

The results for N equal to 8.4, 18.6 and 30.7 and for w of 20-45 years were compared with those obtained by Passey from study of 499 men with lung cancer during 1948-56 (Tables 1 and 2). His principal results—that neither the

TABLE 2.—AVERAGE AGE OF OCCURRENCE OF LUNG CANCER IN RELATION TO AGE AT STARTING TO SMOKE

| Passey's (1962) data | | | British doctors smoking 15–24 cigarettes a day (mean 18 6) | |
|---|---|---|---|---|
| Age at starting to smoke | No. of men | Average age at onset (yr.) | Age at starting to smoke (yr.)* | Average age at death (yr.) |
| 6–14 | 117 | 57 9 | 17 | 70 5 |
| 15–19 | 285 | 55 9 | 22 | 72 0 |
| 20–24 | 69 | 59 6 | 27 | 73 5 |
| | | | 32 | 75 0 |
| 25–11 | 25 | 62 0 | 37 | 76 5 |
| | | | 42 | 78 0 |

*Corresponding to values of w equal to age in years plus 3, in formula given

amount smoked nor the age at starting makes any substantial difference to the "period" average age at onset of the disease—are valid also for the "life-span" average under the conditions in which lung cancer is produced in man, and follow directly from the observed relations between age-specific mortality rates and duration of smoking. The results do not imply that the number of cigarettes smoked daily has no significant clinical effect on life expectancy.

The observed relation between age of occurrence of lung cancer and number of cigarettes smoked as well as age at beginning of smoking justify the conclusion that smoking 30 cigarettes daily is not equivalent to exposure to a "strong" carcinogen. They do not justify the conclusion that cigarette smoke does not act as a carcinogen. Whether cigarette smoke acts as a weak carcinogen cannot be decided on the basis of present evidence alone.

► [This study was stimulated by Passey's interesting suggestion (see the 1963-64 YEAR BOOK, p 160) that smoking in relation to cancer acts as a nonspecific irritant and not as a direct carcinogen, because the average age at onset appears to be much the same irrespective of the amount smoked Doctors Pike and Doll first take issue with Passey for drawing conclusions from observations of the average age at death (or onset) taken at a specific time (period average), rather than the average which would be found if the group were followed from first exposure until death of all members (life span average) Their own calculations, to arrive at the latter, are based on the relationship between age and mortality from lung cancer and from all other causes, for each level of smoking Applying the formulas which express these relationships to their own observational data, their results agree with Passey's to the extent that neither the amount smoked nor the age at starting made any substantial difference to the average age at death Somewhat larger differences were found by this method of calculation, but these were still small While agreeing that these results indicate that smoking is not equivalent to exposure to a "strong" carcinogen, the present authors do not concede that they justify the conclusion that cigarette smoke does not act as a carcinogen They make estimates of what would be observed if doses were increased to levels which might produce cancer in a large enough proportion of subjects to provide comparability with the experimental effects of known carcinogens The estimates are made by inserting larger values for N (the number of cigarettes smoked per day) in the equation than can be observed in practice (i e, values for N of 300 and 3000) The results of these extrapolations indicate that under such conditions differences would appear comparable with those observed experimentally when the dose of a carcinogen, or the age at which it is given, is changed They do not, however, draw the conclusion that cigarette smoke does in fact act as a weak carcinogen, but only that the question cannot be decided on such data alone On other grounds, they regard it as reasonable to suppose that it acts as a promoting agent, which position conflicts little with Doctor Passey's, although arrived at from different considerations than the relationship between age and age specific death-rates which is here under discussion.—Ed ]

**Presurgical Irradiation in Bronchogenic Carcinoma, Superior Sulcus Type,** is assessed by John T. Mallams, Don-

ald L. Paulson, Richard E. Collier (Baylor Univ.) and Robert R. Shaw[1] (Southwestern Med. School) on the basis of results in a series of patients treated since 1936. No biopsy was done. Radiotherapy was designed to serve as an adjuvant. A dosage which would sterilize the peripheral portions of the tumor only, allow for recognizable residual tumor in the

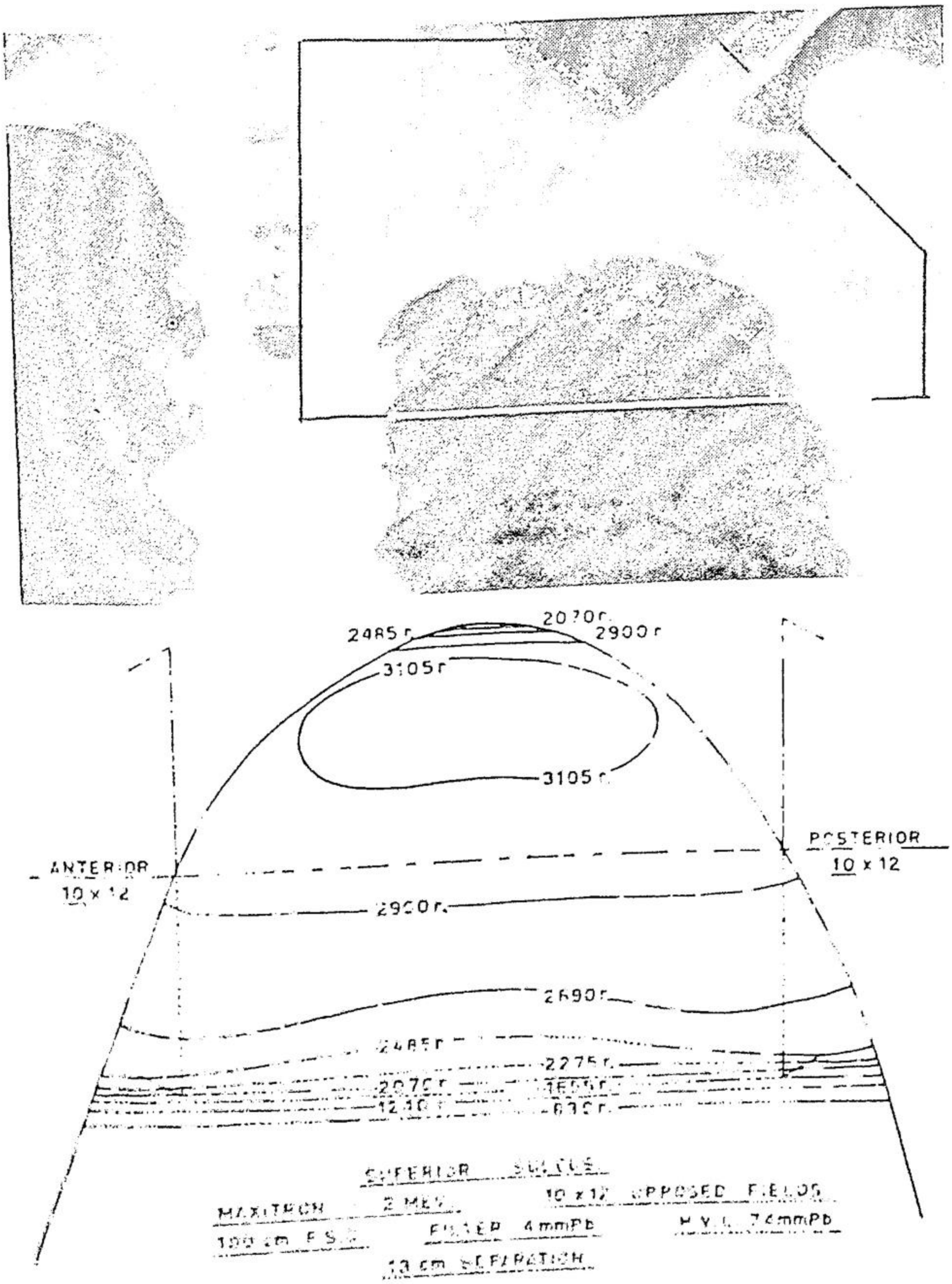



FIG. 40 (top). – Usual zone of irradiation.
FIG. 41 (bottom). – Composite isodose curve of usual situation.
(Courtesy of Mallams, J. T., *et al.*: Radiology 82:1050-1054, June, 1964.)

(1) Radiology 82:1050-1054, June, 1964.

center for pathologic confirmation and minimize the possibility of interference with operative procedures and complications was selected. A midplane tumor dose of 3,000 rads was given in 10 treatments over 12 days, using simple parallel opposing-field technics Supervoltage was preferred. Occasionally, a dose of 3,000-3,500 rads in 15 treatments over 19 days was given. Unless obvious evidence of mediastinal extension was present, only the mediastinal area immediately adjacent to the tumor was treated (Figs. 40 and 41). En bloc total surgical resection was attempted 4 weeks after completion of irradiation except in patients who showed distant disease during the interval and those in whom an intercurrent permanent medical contraindication to surgery occurred.

Of the 42 patients with a clinical diagnosis of bronchogenic cancer, superior sulcus type, 5 (12%) represented errors in diagnosis: 3 had chronic tuberculosis and 2 metastatic disease. The combined approach was applicable in 28 of the 37 proved cases. Surgical specimens showed a zone of peripheral sclerosis, an intermediate zone of fibrosis and ghost cells and a center zone with apparently still viable tumor. Response to irradiation could not be correlated with either surgical resectability or survival. Eighteen of the 28 patients showed definite evidence of bone destruction; 6 of the 18 are alive and well. One death in the series was due to gastric hemorrhage and adrenal insufficiency secondary to prolonged steroid therapy for arthritis. Eight complications in 6 patients included 2 instances of drainage of cerebrospinal fluid, 3 of prolonged air leak and 3 of empyema. All these were eventually completely controlled, and none could be attributed directly to irradiation. Two patients are alive and well after 6 and 7 years, respectively. Of 9 evaluated after 4 years, 5 were alive and well and 4 dead due to recurrent disease. Of 24 evaluated after 2 years, 8 were alive and well and 16 dead due to recurrent disease.

In view of the pathologic findings and the previously reported radioresistance of these tumors, this approach is believed valid. A significant increase in radiation dose might significantly increase the morbidity rate, and there is no indication that it would result in a greater survival rate The low incidence of diagnostic error and the favorable results justify this approach on the basis of clinical diagnosis alone.

▷ [Perhaps the most radical aspect of this approach is the giving of preoperative radiation therapy on the basis of a clinical diagnosis without biopsy confirmation The authors find justification for this practice in the 33% 2-year survival rate balanced against the relatively low (12%) incidence of diagnostic error Some will disagree, but it may be pointed out in support that (1) there is no comparably successful experience recorded in cases of this type treated by other methods and (2) the preoperative radiation therapy was not given in massive dosage, nor did the therapy affect adversely the conditions which at subsequent operation proved not to be bronchogenic carcinoma For the rationale behind the authors' opinion that biopsy should not be done in these cases the reader is referred to the original article – Ed ]

**Significance of Carcinoma Cells in Blood Relative to Surgery of Pulmonary Carcinoma.** Yoshihiro Hayata, Motonobu Hayashi, Kenkichi Oho and Kingo Shinoi[2] (Tokyo Med. College) examined cancer cells in the blood of 160 patients with histologically confirmed lung cancer. Cell collection was carried out by Sandberg's, Moore's or Munakata's method. First examinations were performed within a week of admission, and 20.6% were positive. The rate rose to 33.5% after an average of 6.6 examinations. The rate was 28.1% for carotid arterial specimens, 25% for femoral artery specimens and 18.6% for cubital vein specimens. The rate in 14 symptom-free patients was 7.1%, compared with 55.7% in 34 patients with hemoptysis, 83.3% in 12 with evident symptoms of hematogenous metastasis and 81.3% in 16 with cervical lymph node metastasis. Circulating cancer cells were found in 64% of 25 patients with positive prescalene fat pad biopsies and 37 5% of 32 with negative ones. The relationship between x-ray findings and the incidence of circulating cancer cells is shown in the table. The rate of positivity in patients with tumors in the main and lobar bronchi, segmental bronchi and peripheral bronchi was 25.4, 21.4 and 15 9%, respectively. The rate was 37.5% for the undifferentiated lesion, 24.3% for the adenocarcinoma and 9.4% for the squamous cell carcinoma group. There was no definite

X-RAY FINDINGS VS POSITIVE RATE

| | No of Cases | Positive Cases | Per Cent |
|---|---|---|---|
| Coin lesion | 7 | 0 | |
| Nodular type | 75 | 14 | 18 6 |
| Infiltrating type | 16 | 6 | 37 5 |
| Atelectasis | 32 | 7 | 21 8 |
| Hilar type | 13 | 3 | 23 0 |
| Others | 17 | 3 | 17 6 |

2. Jpn J Clin Med 45 53 60 July 1964

relationship between the rate of positivity and the period between onset of symptoms and hospitalization

The rate of positivity was 10.8% in 47 patients in whom radical operations could be performed, compared with 30.1% in 53 inoperable patients. In 66 patients without circulating cancer cells preoperatively, blood samples were taken from the pulmonary vein during operation. The rate of positivity was 31.9% after exploration of the thoracic cavity and 43.6% by the time the pulmonary vessels were ligated. On the whole, the incidence of cancer cells in the pulmonary veins during operation was 40.9% Of the 47 patients undergoing radical resection, 28 were followed about 40 days or more. Negativity was always maintained in patients without circulating cancer cells before and during operation. In the others, the rate dropped to 35% on the 1st postoperative day and declined gradually thereafter, being about 6% on the 20th day. The incidence of cancer cells in the pulmonary veins was 48.3% in patients in whom the pulmonary arteries were ligated first, compared with 22.2% in those in whom the veins were ligated first. More than a few of 69 patients without circulating cells before irradiation showed positivity as the radiation dose was increased When the dose exceeded 2,000 r, some of those who showed positivity again showed negativity.

Studies were carried out on Yoshida ascites sarcoma labeled with $P^{32}$ and injected transthoracically into the lungs of rats. It was concluded that almost all cancer cells in the blood are ineffective as metastatic matrices, but that a few circulating cancer cells still present an important problem in lung cancer therapy.

**Mediastinoscopy in Bronchogenic Cancer.** H. Reynders[3] (Univ. of Amsterdam) reports that mediastinal extension of lymph node metastases or invasive growth of the primary tumor was found to be the cause of nonresectability in 86% of 100 consecutive cases of lung cancers proved nonresectable by exploratory thoracotomy. The postoperative mortality was 9%. The number of exploratory thoracotomies done in vain varies from 20 to 50%. In detecting inoperability, the Daniels biopsy gives rather good results, but many patients show nonresectability despite a negative prescalene fat pad resection (table). Carlens introduced the technic of mediasti-

(3) Dis Chest 45 606-611 June 1964

NON RESECTABLE LUNG LESIONS
AFTER NEGATIVE DANIELS BIOPSY

| Author | Year | Negative Biopsy | Non-resectable Lesions |
|---|---|---|---|
| Shelts | 1953 | 7 | 2 |
| Skinner | 1955 | 21 | 9 |
| Ottoser | 1956 | 19 | 8 |
| Scott | 1957 | 54 | 19 |
| Smith | 1959 | 4 | 3 |
| Boerema | 1961 | 31 | 14 |
| Morgan | 1962 | 87 | 50 |
| | | 223 | 105 |
| | | | or 47.5 per cent |

noscopy, in which a channel is made on the ventral surface of the trachea through a small low collar incision in the jugulum, reaching up to the tracheal bifurcation. The mediastinal structures can be palpated and tissue biopsies done on suspicious-looking tissues. This technic is now practiced in several countries, and results are reported as satisfactory.

At the Wilhelmina Hospital in Amsterdam, over 250 mediastinoscopies have been done since 1960 on patients with all kinds of chest diseases. Included was a series of 122 consecutive routine examinations on patients with cancer of the lung and no clear evidence of inoperability. Forty-five (36.9%) of the 122 explorations were positive and 77 (63.1%) negative. The 77 patients underwent exploratory thoracotomy, and 70 (91%) were shown to have resectable cancer. The 7 nonresectable cancers were centrally located tumors, in 4 cases, the cause of nonresectability was felt during mediastinoscopy, but biopsies failed to show metastatic growth. The percentage of pneumonectomies dropped from 84% to 60% after selection by mediastinoscopy, and the percentage of lobectomies rose from 16 to 40%.

The author believes that mediastinoscopy should be performed if there is no evidence of incurability and the patient shows a central lesion on x-ray examination; a diffuse, poorly demarcated lesion or atelectasis; oat cell carcinoma; or dubious operability. In cases of right-sided incurable lung cancer with hypertrophic osteoarthropathy, vagotomy on the right side is possible through the mediastinoscope.

► [This procedure has been practiced with apparent success in Europe for several years but has not yet been widely adopted in the United States. The results here reported by Doctor Reynders would seem to recommend it as an innovation of real value. – Ed.]

**Coexistence of Carcinoma and Tuberculosis of Lung.** S. Donald Greenberg, Daniel E. Jenkins, David Bahar, H Irving Schweppe, Jr., and Harold Block, Jr.[4] (Jefferson Davis Hosp., Houston) reviewed the 8 cases of coexistent pulmonary tuberculosis and carcinoma found among 1,232 patients treated for pulmonary tuberculosis during 1957-63. In 4 cases, the carcinoma was adjacent to the tuberculosis and in 2, adjacent to a parenchymal scar. In 1 case, both diseases were in the same lung but anatomically separate, and in 1, the tuberculosis and carcinoma were in opposite lungs (Fig 42). All patients were men (mean age, 62 years), and all were chronic cigarette smokers. None had a history of exposure to radiation or to industrial carcinogens.

In general, it appears that carcinoma of the lung may, by direct extension, destroy fibrous tissue walls that contain quiescent foci of tuberculosis and thus permit dissemination

Fig 42.—Diagrams of lungs illustrating sites of origin of carcinomas (Courtesy of Greenberg, S. D., *et al.*: Am. Rev. Resp. Dis. 90:67-76, July, 1964.)




(4) Am. Rev. Resp. Dis. 90:67-76, July, 1964

of the granulomatous disease Between 6 and 10% of patients dying with lung carcinoma have been reported to have accompanying pulmonary tuberculosis The apparent increase in association of the two diseases is influenced by the increasing incidence of lung cancer in the older age groups, especially in males, by the relatively high death rate from tuberculosis in older age and by the increasing age of the general population In the presence of other proved disease, such as tuberculosis, coexisting carcinoma is apt to be unrecognized until it has advanced beyond resectability and the advantages of a peripheral origin have been lost

**Cavitary Pulmonary Metastases.** Metastatic carcinoma is often not considered in the differential diagnosis of multiple, thin-walled cavitary lesions in the lung, and yet, in the New England area, such lesions are more apt to be caused by carcinoma than by fungal diseases Marjorie LeMay and Anthony J Pirofsky report 9 cases recorded at the Boston Veterans' Administration Hospital over the last several years (table) Eight patients received neither chemotherapy nor irradiation before the appearance of cavitation, and the other received a course of x-radiation to the neck 2 years before cavities

PATIENTS WITH CAVITARY PULMONARY METASTASES

| Patient | Primary Site | Histopathology of | | Lesions | | Cavity Size | Cavity Wall Thickness | Sputum for Tumor Cells |
|---|---|---|---|---|---|---|---|---|
| | | Primary | Metastasis | Cavitary | Solid | | | |
| | | | | no. | no. | mm. | mm. | |
| (1) CHR 39703 | Rectum | Adenocarcinoma (partly mucus secreting) | Not proven | 22 | 4 | 8–23 | 1–4 | Negative |
| (2) 111381 | Rectum | Adenocarcinoma | Adenocarcinoma, metastatic | 20 | 1–a | 10–? | ? | Negative |
| (3) 137109 | Colon | Adenocarcinoma | Adenocarcinoma, metastatic | 1 | 0 | 40, 36, ?? | 2 | Negative |
| (4) 129913 | Colon | Adenocarcinoma | Not proven | 15 | ? | 5–20 | 1–3 | — |
| (5) 160356 | Colon | Adenocarcinoma (colloid) | Colloid carcinoma, metastatic | | ? | 20 | 3–5 | — |
| (6) 130172 | Larynx | Epidermoid carcinoma | Epidermoid carcinoma, vessel necrosis | 18 | 2 | 5–35 | 3–15 | — |
| (7) 144424 | Unknown primary | Undifferentiated carcinoma | Not proven | 4 | 18 | 6–22 | 1–7 | Negative |
| (8) 133964 | Bladder | Transitional cell cancer | Transitional cell cancer | 2 | 15 | 15–25 | 2–6 | — |
| (9) 129353 | Larynx | Epidermoid carcinoma | Epidermoid carcinoma | 5 | 3 | 20–30 | 1–5 | — |

(5) Ann Int Med 62:59-68, January, 1965

appeared. The number of cavitary lesions in each patient ranged from 1 to 25 and the size from 2 mm. to 7 cm. in diameter. Most lesions had walls 1-6 mm. thick and appeared ringlike The inner surfaces were usually smooth, but many showed an irregular appearance, and in 2 patients, the inner surfaces were nodular In 7 patients, the lesions were bilateral

Most metastatic pulmonary lesions do not communicate with a bronchus, and Papanicolaou smears from the sputum of patients with such lesions, solid or cavitary, are usually negative. The authors suggest that physicochemical changes in the center of the metastatic lesions may determine whether the appearance of the lesion will be cavitary or solid on x-ray study

► [Doctors LeMay and Puo mention also 4 cases of cavitary pulmonary lymphoma they have seen but did not include because such lesions are not usually defined as metastases

Doctor Steel (see next article) describes 4 cases of cavitating Hodgkin's disease of the lung seen at the Brompton Hospital The cavities are less likely to be multiple than in the instances of cavitating metastatic carcinoma —Ed]

**Hodgkin's Disease of Lung with Cavitation.** S. J. Steel[6] saw a patient with a cavitated pulmonary lesion but with no extrathoracic manifestations of Hodgkin's disease in whom the diagnosis was only made on histologic examination. He then reviewed all cases of Hodgkin's disease seen at the Brompton Hospital and London Chest Hospital during 1952-62. Of 36 patients with proved intrathoracic Hodgkin's disease, 14 had pulmonary lesions at the onset, and in 3 of these, cavitation was demonstrated on x-ray study.

Woman, 31, had been feeling tired for 6 months and had lost a few pounds in weight She had had a cough and scanty sputum, twice blood streaked, for 2 months and occasional pleuritic pain in the left side of the chest The temperature was 99-100 F The chest x-ray showed infiltration and cavitation in the left upper lobe (Fig 43) The blood count showed hypochromic anemia and a white cell count of 30,400/cu mm The sedimentation rate was 124 mm. per hour Serum albumin and globulin levels were 3.3 and 3 7 Gm./100 ml , respectively, the γ-globulin fraction was slightly elevated. Bronchoscopy showed only nonspecific inflammatory changes in the left upper lobe bronchus Infiltration in the left lung increased despite penicillin therapy Thoracotomy revealed consolidation in the left upper lobe, nodules in the left lower lobe and a mass of hilar and paratracheal lymph nodes Radical pneumonectomy was performed, all masses of nodes being removed Histologic study showed fairly acute Hodgkin's disease, with necrosis, cavitation and suppurative bronchopneumonia. The hilar nodes showed relatively early involvement of a secondary pattern.

(6) Am Rev Resp Dis 89 736-744, May, 1964

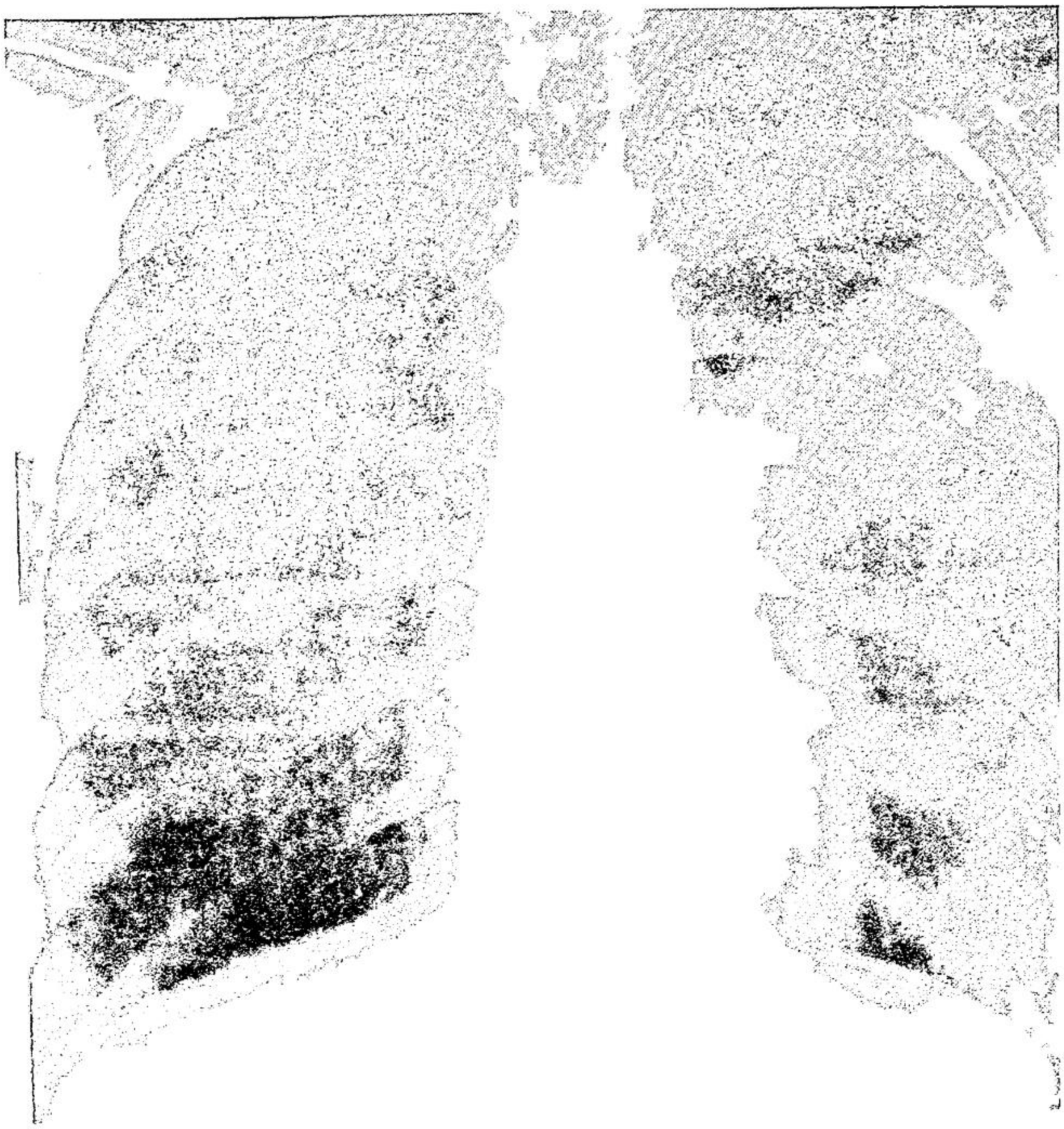


Fig. 14. X-ray showing infiltration involving the anterior and apicoposterior segments of the left upper lobe and cavitation in the anterior segment. (Courtesy of Steel, S. J. Am. Rev. Resp. Dis. 89:736-744, May, 1964.)

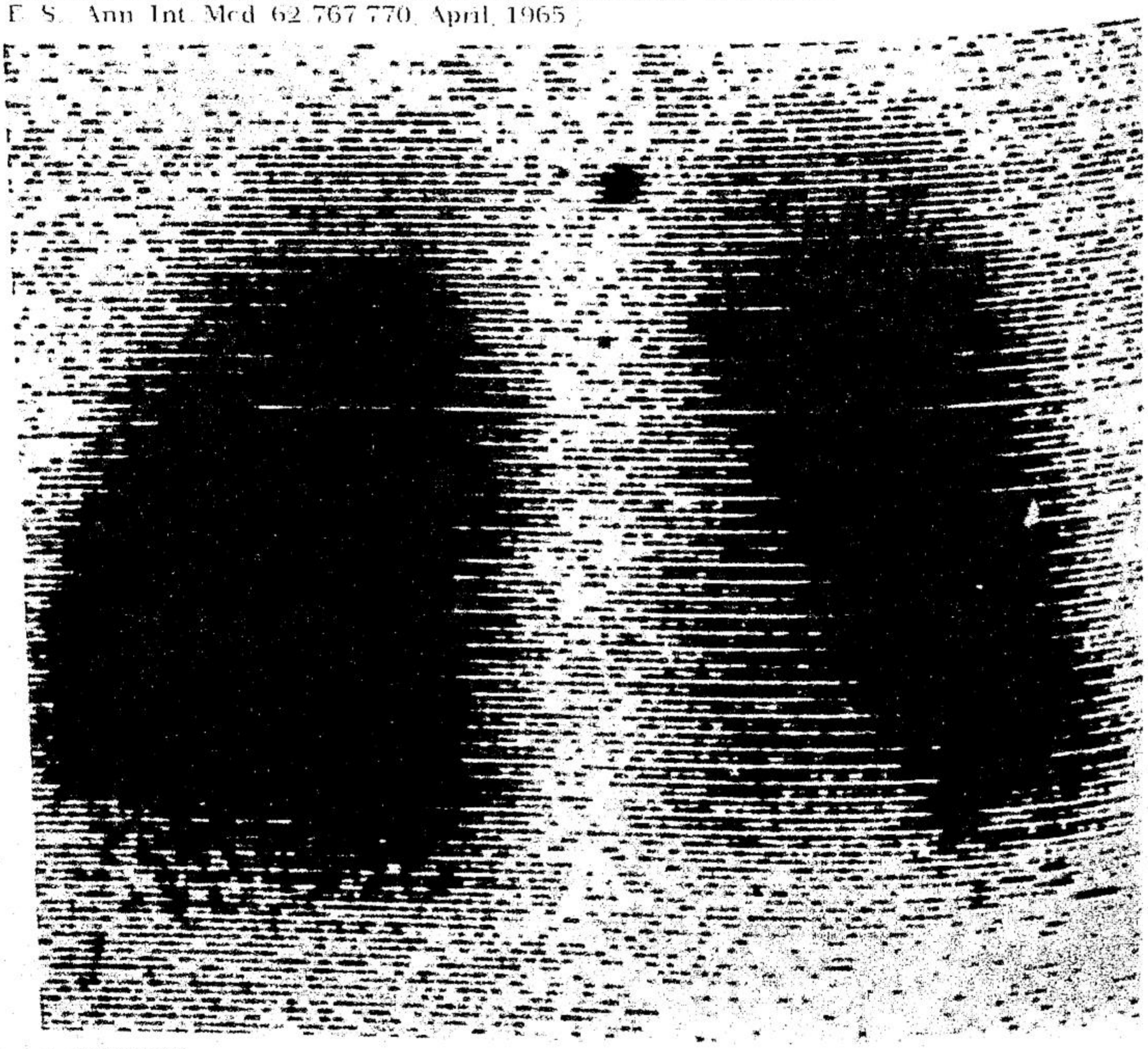
Despite a 6-week course of chlorambucil, enlarged left supraclavicular nodes developed, and chest x-rays showed gradual extension of new infiltration with cavitation in the right upper lobe. Improvement followed radiotherapy and administration of cytotoxic drugs. Subsequently, deposits developed in the pelvis, lumbar spine and left hip. Further radiotherapy and cytotoxic drug therapy resulted in relief of pain and shrinkage of an enlarged axillary node. Later, cavitation recurred in the right upper lobe, but responded to radiotherapy. The patient died 2½ years after her first admission.

The special features in the 4 cases with cavitation include pruritus, alcohol-induced pain, anergy to tuberculin, anemia, leukocytosis, neutrophilia, eosinophilia, a raised erythrocyte sedimentation rate and increase in serum γ-globulin. It is suggested that the treatment of choice should be resection of damaged lung tissue followed by radiotherapy and cytotoxic drugs.

**Pulmonary Metastases from Thyroid Carcinoma: An Unusual Case** is reported by O'Neill Barrett, Jr., and Edwin S Stenberg The chest x-ray was completely normal despite widespread pulmonary involvement demonstrated on a scintiscan

Man, 40, had a 1-cm nodule in the right thyroid lobe. This lobe and the isthmus were removed and a diagnosis of follicular carcinoma with papillary features was made Three months after operation, multiple anterior cervical nodes were found on the right but biopsy showed reactive hyperplasia A dose of 30 mc $I^{131}$ was administered and 100 $\mu$g l-triiodothyronine was given daily A scintiscan obtained about 9 months after treatment with radioiodine was begun showed extensive diffuse uptake throughout both lung fields (Fig 44) A chest x-ray was normal A total dose of 90 mc $I^{131}$ was given A scan 2 months later showed disappearance of uptake in the presumptive areas of tumor About 6 months later, a scintiscan again showed

Fig 44.—Chest scintiscan about 9 months after a single dose of $I^{131}$ showing diffuse bilateral pulmonary uptake of radioiodine (Courtesy of Barrett, O N., Jr., and Stenberg E S Ann Int Med 62 767 770, April, 1965)



(7) Ann Int Med 62 767-770 April 1965

diffuse bilateral uptake throughout the lung fields At exploratory thoracotomy with wedge biopsy of the right lower lobe areas of diffuse fine nodularity throughout all lobes were noted Metastatic carcinoma was confirmed on microscopic study A dose of 100 mc $I^{131}$ was given, and scintiscans showed complete clearing of the lesions Repeated scans since then, the latest 4 years after the first operation, and chest x rays have been normal

Evidence of pulmonary metastases from thyroid carcinoma cannot be excluded on the basis of a routine chest x ray alone, and a chest scintiscan using radioiodine should be obtained in all cases

**Intrathoracic Plasmacytomas: Presentation of 21 Cases and Review of Literature.** Teodoro Herskovic, Howard A Andersen and Edwin D Bayrd (Mayo Clinic and Found ) reviewed the records of 303 patients with multiple myeloma seen during a 5 year period Intrathoracic plasmacytomas were present in 21 patients (6 9%), and, occasionally, the thoracic mass was the first manifestation Symptoms referable to the thorax were the presenting complaints of 11 of the 21 Nineteen of the 21 had disseminated plasma cell myeloma at diagnosis One of the other 2 had a plasmacytoma of one rib and a region of cystic destruction in another The other patient most likely had multiple plasmacytomas The plasmacytomas presumably originated in the ribs in 16 patients, the vertebrae in 3, the subcutaneous tissue of the thoracic cage in 1 and the mediastinum in 1 On x ray study, rib tumors appeared to be soft tissue masses associated with destruction of the rib, 11 were located laterally The vertebral tumors appeared as paravertebral masses.

A review of the literature revealed 33 cases of plasmacytomas with intrathoracic extension. Eight patients were thought to have solitary thoracic lesions and were alive without evidence of multiple myeloma 9 months to 8 years after diagnosis. Seven of the 8 patients had undergone surgery with or without radiotherapy, and 1 had radiotherapy alone. Two other patients with apparently solitary lesions died of other causes after 3½ and 5 years, respectively, without evidence of diffuse disease. Two patients with multiple lesions had no evidence of disseminated disease after 7 and 25 years, respectively. Of the 21 patients with multiple myeloma at diagnosis of the plasmacytoma or soon thereafter, 1 died of myeloma 2 years after resection of an apparently

solitary plasmacytoma of a rib; 1 had evident diffuse disease 1 month after biopsy of a costal lesion; 1 who had irradiation subsequently underwent gastrectomy and died 26 months later of diffuse disease; and 1 died of pneumonia 9 months after diagnosis of a costal lesion and multiple myeloma. Two patients died of complications of the tumors. Periodic study of patients with plasmacytomas is indicated.

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## PLEURAL TUMORS AND EFFUSIONS

**Electron Microscopic Study of a Solitary Pleural Mesothelioma** was conducted by Sarah A Luse and Harlan J Spjut (Washington Univ.) to obtain evidence for or against the mesothelial origin of this lesion.

Man, 71, had a mass in the left posterior part of the thorax, found at thoracotomy to be a subpleural tumor in the upper lobe of the left lung The tumor was attached to the visceral pleura, it "shelled out" easily from the surrounding lung. Grossly, it was ovoid, firm and well circumscribed and weighed 60 Gm. Microscopically, the lesion had the features of a mixed pleural mesothelioma. The major portion of the lesion was formed of cellular, dense fibrous tissue. There were scattered slits lined by plump cuboidal to columnar epithelial cells, especially at the periphery. In some areas, the tumor was hyalinized

Electron microscopic study showed the epithelial lining of slits in the tumor to consist of a single cell layer of cuboidal to columnar cells separated from the stroma by a basement membrane. Often there were distended interconnecting spaces between the lateral margins of adjacent tumor cells, into which microvilli extended not infrequently The luminal surface of the epithelial cells was covered by numerous delicate microvilli. Their apical cytoplasm protruded into the lumen of the slit and was distended with electron-dense inclusions, which were often lamellar, whorled structures similar to myelin figures and separated from the surrounding protoplasm by a delicate membrane. In some cells, the inclusions appeared to have caused rupture of the cells, with free inclusions in the lumen. Occasionally, empty-appearing vacuoles and lipid droplets were present in the cytoplasm. Mitochondria were small and perinuclearly congregated. The endoplasmic reticulum was usually vesicular. Ribonucleoprotein particles were free in the cytoplasm Nuclei tended to be basally located and sometimes were irregular in shape. Some epithelial cells closely resembled normal mesothelial cells The tumor cells were attached to one another by overlapping cytoplasmic fingers that occasionally were the site of a desmosome.

The fibrous portion of the tumor was composed of interlacing

layers of collagen and fibroblasts The fibroblastic nuclei were sometimes quite elongated and even doubled back on themselves Occasionally, nuclei were irregular, with scalloped outlines

This study showed that the epithelial component of a solitary pleural mesothelioma has the characteristics of a hyperplastic mesothelial cell and that it in no manner resembles other epithelia so far described except for the highly phagocytic lining cells of the yolk sac. This lends support to the thesis that these tumors are mesothelial and discounts, at least in this case, the possibility of an occult carcinoma with pleural metastasis.

**Pathology of Mesotheliomas and Analysis of Their Association with Asbestos Exposure.** Dermot O'B Hourihane[1] (London Hosp) reviewed findings in all cases of primary diffuse tumors of the pleura or peritoneum encountered during 1917-62 The morbid anatomy and histologic findings were exactly typical of mesothelioma in 7 of the 17 cases of primary pleural mesotheliomas, and asbestos bodies were found in the lung in 6 of the 7 (table) Only 1 patient was known to have had asbestosis during life Four of the other patients showed peribronchial and interstitial fibrosis in addition to asbestos bodies In several patients, only very small numbers of bodies were found All 7 patients had tumor plaques in the peritoneum in addition to the main pleural lesion, 5 showed lymph node metastases Invasion of soft tissue was found in 2 cases Tumor was found in the pancreas in 1 case and in an adrenal gland in another Asbestos

INCIDENCE OF ASBESTOS BODIES OR FIBERS*

| Group | Lungs Available | Asbestos Bodies or Fibers | Fibrosis of Lung | Cases with Asbestos Bodies or Fibers (%) |
|---|---|---|---|---|
| A | 7 | 6 | 3 | 85 |
| B | 19 | 11 | 3 | 16 |
| C | 11 | 7 | 6 | 63 |
| D | 12 | 1 | 0 | 8 |
| E | 16 | 1 | 0 | 6 |
| F | 50 | 3 | 0 | 6 |
| G | 80 | 0 | 0 | 0 |

*Group A, certain pleural mesotheliomas; group B, probable pleural mesotheliomas; group C, certain peritoneal mesotheliomas; group D, probable peritoneal mesotheliomas; group E, selected from pleural series; group F, rejected from peritoneal series; group G, consecutive autopsy cases of carcinoma of lung; group H, consecutive autopsy cases excluding tumors in chest

homa and asbestos fibers in the underlying lung of a man who worked in a dry-cleaning plant in which asbestos workers' clothes were handled A recent publication from the Pneumoconiosis Research Unit, Council for Scientific and Industrial Research, Johannesburg (Webster, I, South African M J 38 870, 1964) analyzes the question of air pollution by asbestos and the possibility that "neighborhood" cases of asbestosis may occur Preventive measures against aerial pollution have been taken by the asbestos industry in South Africa in recent years —Ed]

**Eosinophilic Pleural Effusion: Review with Presentation of Seven New Cases.** Guy D. Campbell and Watts R. Webb[3] report findings in 7 cases of pleural eosinophilia recorded at the Veterans' Administration Center, Jackson, Mississippi, since 1961. The initial pleural fluid findings are summarized in Table 1. On admission, effusion was the only significant finding in the chest x-rays of 6 patients; the other patient had pneumonitis on the same side as the effusion. The tuberculin skin test was positive in 5 patients, and the histoplasmin skin test was positive in 6. The effusion cleared within 6 weeks after initial thoracentesis in 4 patients but persisted for 3 months in 2 and for 4½ months in 1. One patient had a recurrence 1 year later.

A review of the English literature revealed 94 other cases of pleural eosinophilia, 72% of which are grouped according to associated disease in Table 2. The wide variety of diseases associated with pleural eosinophilia suggests multiple eosinotactic agents.

One conclusion regarding the diagnostic significance of pleural eosinophilia can be drawn from this study, namely, that it militates greatly against tuberculosis, malignancy and fungal disease.

TABLE 1 – PLEURAL FLUID ANALYSES ON INITIAL THORACENTESIS

| Patient | Effusion Associated With | Erythrocyte Count | Leukocyte Count | Eosinophils | Protein | | Glucose | | Absolute Blood Eosinophils | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *per cent* | *gm per 100 ml* | | *mg per 100 ml* | | *number* | *per cent* |
| Case 1 | Histoplasmosis | Blood tinged | 40,000 | 94 | 3 2 | | | | 820 | 7 |
| Case 2 | Heart failure | 1 600 | 5,600 | 30 | 2 8 | | | | 378 | 4 |
| Case 3 | Pneumonia | 4,250 | 4,500 | 49 | 3 4 | | 100 | | 1,440 | 10 |
| Case 4 | Idiopathic | 340,000 | 5,700 | 46 | | | | | 690 | 6 |
| Case 5 | Rheumatoid arthritis | Amber | 5,700 | 8 | 2 9 | | 51* | | 510 | 6 |
| Case 6 | Pneumonia | 700 | 2,100 | 4 | 4 9 | | 36* | | 732 | 5 |
| Case 7 | Idiopathic | 18,000 | 5,600 | 26 | 4 7 | | 73* | | 0 | |

*Performed on AutoAnalyzer

Fig. 45.—Asbestos body (*arrow*) in area of pulmonary fibrosis, ×440 (Courtesy of Schikoff, I. J., *et al.* New England J. Med. 272: 560-565, Mar. 18, 1965.)

tient. No correlation was evident between the occurrence of mesothelioma and the severity of asbestosis. Six of the 7 men with mesothelioma in the autopsy series also had histories of prolonged employment in the asbestos industry. One man denied exposure to asbestos but was found to have asbestos bodies and fibers in lung tissue at autopsy (Fig. 45).

It appears that mesothelioma must be added to the neoplastic risks of asbestos inhalation, and it joins lung cancer and probably cancer of the stomach and colon as a significant complication of such industrial exposure in the United States.

[The association between mesothelioma and asbestos exposure was noted first in South Africa, later in Germany, Australia and England (see preceding article), and this report establishes the connection in the United States also. One observation of special interest made by the present authors is that crocidolite, a special type of asbestos mined in North Western Cape Province of South Africa and which it was thought earlier might alone be concerned in the association, has been imported into the United States in but very small quantities until quite recently. Here the more widely used type of asbestos fiber has been chrysotile. Since the interval between first exposure and the appearance of neoplasia from asbestos is thought to be long (the authors mention 20-40 years), the present findings indicate that the problem is not limited to just the one type of asbestos. Another observation of interest, and one reminiscent of a similar circumstance which occurs with berylliosis, is the finding of mesothe-

TABLE 2 – DISEASES ASSOCIATED WITH EOSINOPHILIC PLEURAL EFFUSION

| | Number of Cases | Per Cent |
|---|---|---|
| 1 Idiopathic | 28 | 28 |
| 2 Infection | | |
| a Pneumonia | 14 | |
| b Fungi | 3 | |
| c Empyema | 2 | |
| d. Tuberculosis | | |
| Pleural effusion (tuberculosis subsequently developed, after one and five years) | 2 | |
| Tuberculous peritonitis and tuberculous pleural effusion | 1 | |
| Pulmonary tuberculosis and tuberculous pleural effusion | 2 | 21 24 |
| 3. Trauma | | |
| a Following therapeutic pneumothorax | 12 | |
| b. Following thoracotomy | 1 | |
| c. Following rib fracture | 1 | |
| d Following spontaneous pneumothorax | 2 | 16 16 |
| 4. Hypersensitivity | | |
| a. Asthma and vascular allergy | 5 | |
| b Dermatitis | 1 | |
| c. Transitory pulmonary infiltration | 4 | |
| d. Periarteritis nodosa | 4 | 14 14 |
| 5. Malignancy | | |
| a. Hodgkin's disease | 1 | |
| b. "Neoplasm" | 4 | |
| c. "Cancer of the lung" | 1 | 6 6 |
| 6. Pulmonary infarction | | 5 5 |
| 7. Heart failure | | 4 4 |
| 8. Cirrhosis of the liver | | 1 1 |
| 9. Sarcoidosis | | 1 1 |
| 10. Rheumatoid arthritis | | 2 2 |

## DROWNING: UNDERWATER ACCIDENTS

**Management of Drowning Victims.** On the basis of experiments carried out in dogs, Joseph S. Redding and J. W. Pearson[1] (Baltimore City Hosp.) developed a plan for treatment of submersion victims which has proved effective in clinical situations. Most victims of submersion either are removed

(1) GP 20:100-104, June, 1959.

from the water early so that they require little or no treatment or have been submerged so long that attempts at resuscitation are hopeless. However, the apparent duration of submersion is an unreliable guide to the physiologic state of the victim.

As sea water contains 3.5% mixed salts, it is strongly hypertonic to blood. If a patient taken from sea water is conscious and no cyanosis is noted, he should be hospitalized for a chest x-ray and hematocrit determination. If no breathing movements are seen, the patient's head should be tilted back maximally and the jaw lifted forward; the rescuer, with his own lips, should then make a tight seal around the victim's open mouth and blow forcefully (Fig. 46). No attempt should be made to drain the lungs. If the chest does not expand, the rescuer should clear the pharynx with his fingers, readjust the head position and blow more forcefully. Positive-pressure inflations of the lungs are continued with bag-mask-oxygen when possible and are not stopped even if breathing movements return. The victim should be taken to a hospital, where positive-pressure ventilation with oxygen is continued until a hematocrit determination and a chest x-ray have been made. Tracheal intubation or tracheotomy facilitates prolonged treatment and removal of secretions. If the hematocrit is elevated or x-ray shows aspiration or pulmonary edema, plasma should be given until the hematocrit is normal. Positive-pressure breathing is stopped only when the lung fields are clear and the hematocrit is normal. For patients known to have aspirated, antibiotic therapy should be considered, and the lungs should be examined frequently for several days.

Mouth-to-mouth breathing also is carried out in cases of fresh-water submersion if breathing movements are absent. Positive pressure ventilation with 100% oxygen should be substituted as soon as possible. After the first successful lung inflation, the carotid artery pulse is checked and, if it is not palpable, closed chest cardiac massage must be carried out by sternal compression 4 or 5 times after each lung inflation (Fig. 47). If a spontaneous pulse is not palpable after the patient is admitted to the hospital, 1 ml. of 1:1000 epinephrine is injected into a cardiac ventricle. If the ECG shows fibrillation, external electric defibrillation should be performed. After spontaneous circulation is restored, the plasma

Fig. 16 (top). Resuscitation of a victim of sea water submersion.
Fig. 17 (bottom). Resuscitation of a victim of fresh water submersion.
(Courtesy of Redding, J. S., and Pearson, J. W.: GP 29:100-104, June, 1964.)

and urine are checked for hemolysis. If a serious degree of hemolysis has occurred, partial exchange transfusion must be considered. Fluid intake must be carefully regulated to promote urinary output, and the patient must be observed closely for complications of aspiration and pulmonary edema.

► It is essential not to waste time by attempting to drain the lungs. In sea water drowning the edema fluid reaccumulates faster than it can be removed. In fresh water drowning, the lungs will not contain water unless the circulation is arrested. This may occur immediately from ventricular fibrillation due to the rapid hemodilution. Hence the emphasis on closed chest cardiac massage until electric defibrillation is available. - Ed.]

**Management of Underwater Accidents** is discussed by John B. Wecth (Ochsner Clinic, New Orleans). The growing popularity of underwater swimming has led to an increasing

incidence of underwater accidents. Any physician living near water more than 30 ft. deep may suddenly be faced with the problem of diagnosis and management of an underwater accident. Those with responsibility for underwater swimmers should acquire a copy of the *US Navy Diving Manual*

There are five general types of underwater accidents due to gas and pressure exposure. Underwater suction injury or "squeeze" results from inequality of pressure. Middle-ear pressure must be equalized rapidly during descent or massive middle-ear hemorrhage will occur. Drowning is possible if enough vestibular stimulation is produced to cause vomiting or whirling loss of orientation. Hemoptysis and pulmonary edema may occur if a surface diver descends too deeply. Faulty breathing regulators with very high inspiratory resistance may create a pulmonary intermittent suction situation as the diver tries to suck air. Should an air hose to the surface blow loose or pressure fail suddenly and the face mask not be equipped with a proper nonreturn valve, the diver's face will be pulled up into a giant suction cup. If a diving suit is worn, folds of skin may be forced into the creases, resulting in serpentine ridges of bruising. In underwater blast victims, one must look for pulmonary and gastrointestinal hemorrhage and rupture of abdominal hollow viscera.

Air embolism is most likely to occur when the victim surfaces rapidly and does not vent expanding air from his lungs properly. The accident usually occurs at the moment of surfacing. If a victim survives the initial episode, he must be immediately repressurized. Air embolism can be prevented by thorough training and familiarity with equipment.

Decompression sickness occurs when a diver stays deep enough and long enough to force nitrogen from the air into physical solution in his blood and body tissues and then surfaces too rapidly. The best treatment for bubble formation is prevention. When prevention fails, the patient should be taken to the nearest recompression chamber and treated according to the Navy treatment tables. Results in patients treated for decompression sickness at this institution are shown in the table. Supportive therapy during recompression treatment must include copious fluids to replace the tremendous body losses of perspiration. Sedatives are occasionally needed.

The effect of pressure will augment the toxicity of certain

MANAGEMENT OF PATIENTS WITH DECOMPRESSION SICKNESS AT THE OCHSNER MEDICAL CENTER, 1960-64

| Predominating Symptoms | Number of Patients | Recompression Therapy: Navy | Recompression Therapy: Guesswork | Recompression Therapy: None | Results |
|---|---|---|---|---|---|
| Pain | 17 | 10 | 4 | 3 | 2 with recurrences in chamber<br>2 with hip necroses |
| Paralysis | 9 | 4 | 4 | 1 | 8 with residual spinal damage |
| Pain and cyanosis | 2 | 2 | 0 | 0 | Good results |
| Pain and convulsion | 1 | 1 | 0 | 0 | Good results |
| Pain and dizziness | 1 | 1 | 0 | 0 | Good results |
| Pain during ascent | 1 | 1 | 0 | 0 | Good results |
| Hemiplegia | 1 | 0 | 0 | 1 | Spontaneous recovery |
| Complete aphasia | 1 | 0 | 0 | 1 | Spontaneous recovery |
| Totals | 33 | 19 | 8 | 6 | 10 with permanent damage |

gases and cause concentrations innocuous at surface pressures to become toxic. Nitrogen narcosis may have a serious intoxicating effect, especially on a novice, at 200 ft. Oxygen toxicity is dangerous because a grand mal seizure may result without warning. Oxygen rich mixtures or pure oxygen should not be used for underwater swimming.

Pain in the chest and joints, numbness and other symptoms of decompression sickness may be simulated by emotional or organic medical problems. Someone swimming vigorously for a number of hours can have a myocardial infarction or other medical disaster. Exhaustion, fatigue and other emotional reactions are common.

➢ [The treatment problems here are more complex, but similarly as for the victims of drowning (see preceding article), the physician must know what to do in an emergency. Most physicians have not the advantage of experience but must depend on instructive articles such as these to prepare themselves for the unexpected but not unlikely circumstance of being involved in the management of these casualties.—Ed.]

## AIRCRAFT AND SUBMARINES

**Air Transportation of Patients with Pulmonary Disease** is discussed by Earl T. Carter and Matthew B. Divertie.[6] At sea level, the oxygen tension of the inspired air is more than 142 mm. Hg and arterial oxygen saturation at normal tempera-

(6) Ill. Clin. North America 45:857-868, July, 1964.

ture and pH is over 95%, corresponding to an arterial oxygen tension of 95 mm. Hg. At 6,000 ft. above sea level, the barometric pressure is 600 mm. Hg and the inspiratory oxygen tension is reduced to 116 mm Hg With normal alveolar $CO_2$ tension and a respiratory quotient of 1, the alveolar oxygen tension is 76 mm. Hg, which is sufficient to insure near-normal arterial oxygen saturation at rest. Under similar conditions at 10,000 ft., the alveolar oxygen tension is about 60 mm. Hg and the peripheral arterial saturation is about 88% In a decompression chamber at a simulated altitude of 6,000 ft , subjects showed a decline in arterial oxygen saturation subsequent to exercise, an effect not observed at sea level The ventilation was greater than that necessary to eliminate the metabolically produced $CO_2$ alone, and a state of hypocapnia resulted. With increased perfusion of tissues, oxygen extraction per unit volume of blood decreases, attenuating the fall in partial pressure of oxygen of the blood as it traverses the capillaries and helping to lessen the need for lowering of the tissue partial pressure of oxygen.

Application of the Fick principle shows that the metabolic rate can be expressed in terms of the cardiac output and the arterial-venous difference of oxyhemoglobin. The fact that this difference under basal conditions is normally 5 vol % does not imply that adequate oxygen extraction by the tissues can be accomplished so long as the arterial oxyhemoglobin is greater than 5 vol.%. The mixed venous oxyhemoglobin is a function of the venous oxygen tension, which depends on the tissue oxygen tension. For internal respiration to continue, the tissue oxygen tension must be maintained at a minimal value. As a practical guide, 13 vol.% may be accepted as the minimal permissible mixed venous oxyhemoglobin for prolonged exposure to altitude, corresponding to a partial pressure of oxygen of about 34 mm. Hg and an oxyhemoglobin saturation of 65%. If the arterial oxyhemoglobin falls below 18 vol.%, a rise in cardiac output will be required for support of normal oxygen extraction by the tissues. The minimal acceptable conditions are found in the average healthy person at an altitude of about 10,000 ft. while breathing air. The cardiac output of 25 L./minute which the 70% saturation at 18,000 ft. makes necessary for maintenance of the basal state of metabolism is a severe demand. Experimental observations have shown that it is

RELATIONSHIP BETWEEN CARDIAC OUTPUT AND ARTERIAL OXYHEMOGLOBIN CONCENTRATION REQUIRED FOR ADEQUATE MIXED VENOUS OXYHEMOGLOBIN AND BASAL METABOLIC RATE

| APPROXIMATE ALTITUDE (FT.) | ARTERIAL OXYHEMOGLOBIN CONCENTRATION (VOL. %) | SATURATION (%) | CARDIAC OUTPUT (L./MIN.) |
|---|---|---|---|
| 10,000 | 18 | 88 | 5.0 |
| 14,000 | 17 | 80 | 6.3 |
| 16,000 | 15 | 75 | 12.5 |
| 18,000 | 14 | 70 | 25.0 |

not met; the partial pressure of oxygen in the tissue and in the mixed venous blood falls below tolerable levels, with resultant serious impairment of body function. The data in the table are applicable for the basal state only.

The decrease in air density at high altitudes interferes with the cough mechanism by leading to a reduction in the expiratory pressure and flow rate that can be developed at the time of the expulsive cough. The lesser density, however, reduces the work of breathing, which is an advantage to patients with increased airway resistance. The mean values for maximal breathing capacity increase as the air pressure lessens with increase of altitude. Trapped gases expand as altitude increases and outside pressure falls. In the thorax, expansion of air in a cyst or pneumothorax or closed in after lobectomy or pneumonectomy may have serious consequences. For air transport of patients with such conditions, it is important that a trained nurse or a physician be present throughout the journey in case unusual attention should be necessary. The presence of pulmonary tuberculosis in an active stage or of any other infectious disease is a contraindication to air travel with other passengers. Pulmonary suppurative disease need not prevent transport in a suitably equipped private plane or in an air ambulance.

A patient with pulmonary emphysema and an arterial oxygen saturation of 88% is physiologically at an altitude of 10,000 ft. even when resting at sea level. For him, ascent to 8,000 ft. in a pressurized airliner cabin is equivalent to ascent above 10,000 ft. for a person with normal lungs. No patient with major cardiopulmonary disease should be exposed to a cabin altitude greater than 8,000 ft. The presence of cyanosis imposes a ceiling of 6,000 ft., and acidosis com-

plicating emphysema should limit the patient to a maximal altitude of 4,000 ft. in a pressurized cabin or in a nonpressurized plane. Cor pulmonale imposes a similar restriction, and markedly reduced respiratory reserve accompanied by tachycardia at ground level is an unfavorable prognostic index for even short-term exposure to moderate cabin altitudes.

► [The authors mention that the experience of the Military Air Transport Service has shown that with proper facilities available most patients who can be transported by any route may be transported with equal safety and greater comfort by air

Doctors Carter and Diverlie here provide useful guide-lines for the physician relative to travel in current jet aircraft

The next paper introduces some of the problems of supersonic air transport, which will soon be upon us —Ed ]

**Ozone in High-Altitude Aircraft Cabins** is discussed by L. S. Jaffe and H. D. Estes[7] (USPHS, Div. Air Pollution, Washington, D. C.). Ozone is found in relatively high concentrations in the atmosphere at high altitudes. Such ambient air supplied to an aircraft cabin at near ground-level pressures could have potentially harmful effects on man and some aircraft materials. A question arose as to whether or not ozone presents an environmental health problem to personnel flying in current jet aircraft at altitudes of 40,000 ft. and above.

The ambient ozone concentration varies with geographic

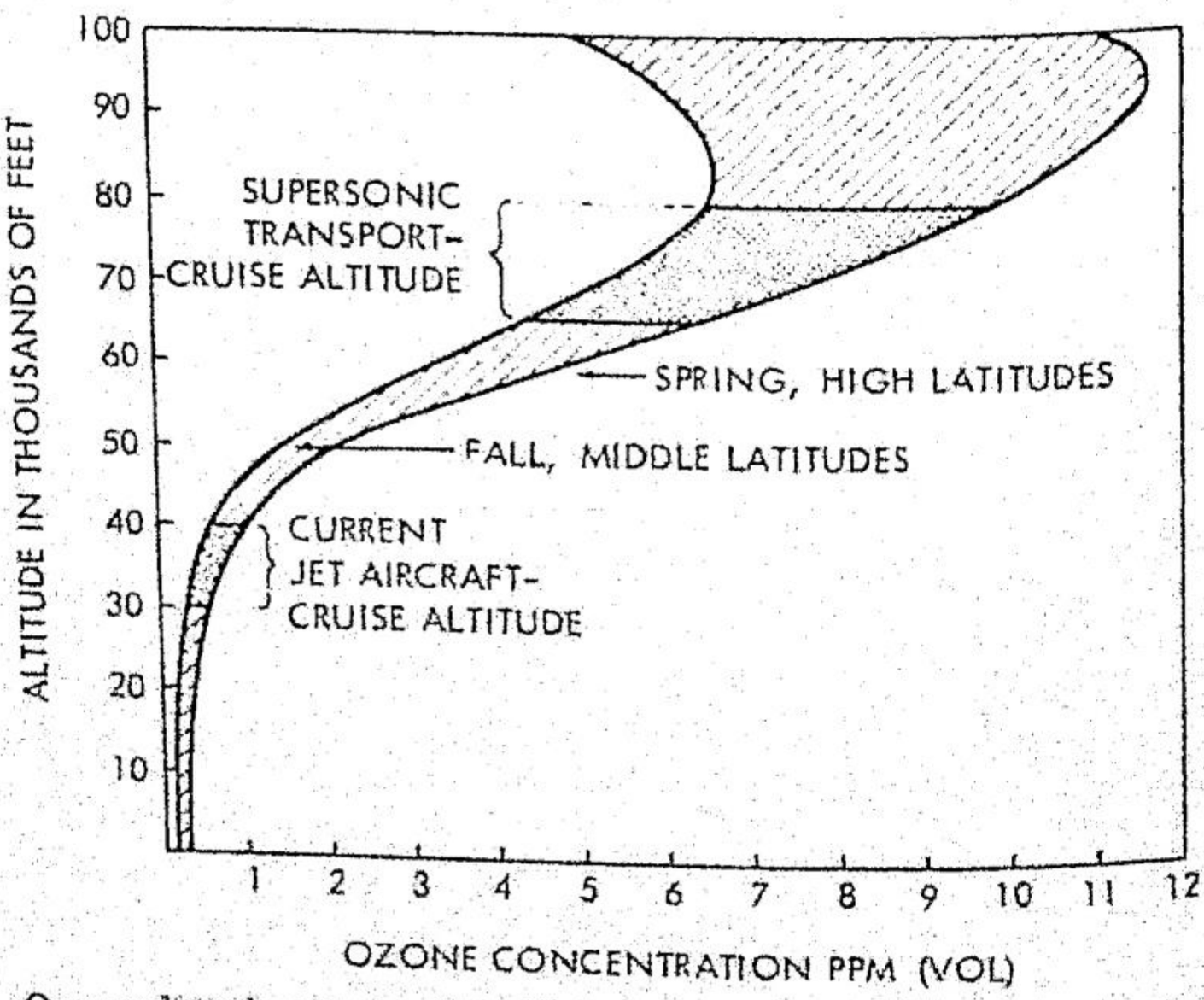


Fig. 48.—Ozone distribution in the northern hemisphere. (Courtesy of Jaffe, L. S., and Estes, H. D.: Arch. Environ. Health 9:61-71, July, 1964.)

(7) Arch. Environ. Health 9:61-71, July, 1964.

latitude, season of the year and meteorologic factors (Fig. 48) High ambient ozone concentrations of 5-10 ppm. are found at altitudes of 65,000-80,000 ft. through which the planned supersonic air transport will cruise. Air used for cabin pressurization passes through the compressors too quickly for all ozone present to be destroyed by adiabatic heating. Unacceptable concentrations of ozone will be present in the cabin environment of the supersonic transport unless devices, such as catalytic filters, or engineering technics are used to delay or increase the dwell time of the ambient air intake through the compressors long enough for adiabatic heating to destroy or reduce the ozone content below 0 2-0 3 ppm.

It is recommended that further research be carried out in the area of time-temperature relationships of air compressors of turbojet, turboramjet and/or other proposed types of supersonic transport propulsion to develop adequate technics of ozone destruction

**Environmental Physiology of Submarines and Spacecraft: Atmospheric Requirements of Confined Spaces** are discussed by K. E. Schaefer (Med. Res. Lab., U.S. Naval Submarine Base, Groton, Conn.) Habitability in nuclear powered submarines during prolonged submergence and selection of a suitable space cabin have posed considerable problems for environmental medicine. Acute tolerance limits to most environmental factors are well known, but little is known of ranges of adaptation to gaseous components, interaction of environmental stressors and threshold limit values for continuous exposure.

When 21 subjects were confined in a submarine and exposed to 1.5% $CO_2$ over 42 days with 9 day control periods before and after exposure, there were no significant changes in performance or in basic physiologic parameters, such as blood pressure, pulse rate, weight and body temperature. However, some remarkable adaptive changes occured. A phase of uncompensated respiratory acidosis lasted 23 days and was followed by a phase of compensated respiratory acidosis from days 24 to 42 of exposure. The respiratory minute volume was increased 38 and 34%, respectively, during the two phases of exposure, and decreased on return to air. Alveolar $CO_2$ tension was elevated about 3 mm. Hg throughout the exposure and during the 9-day recovery period.

(6) Arch. Environ. Health 8:320-331, September, 1964.

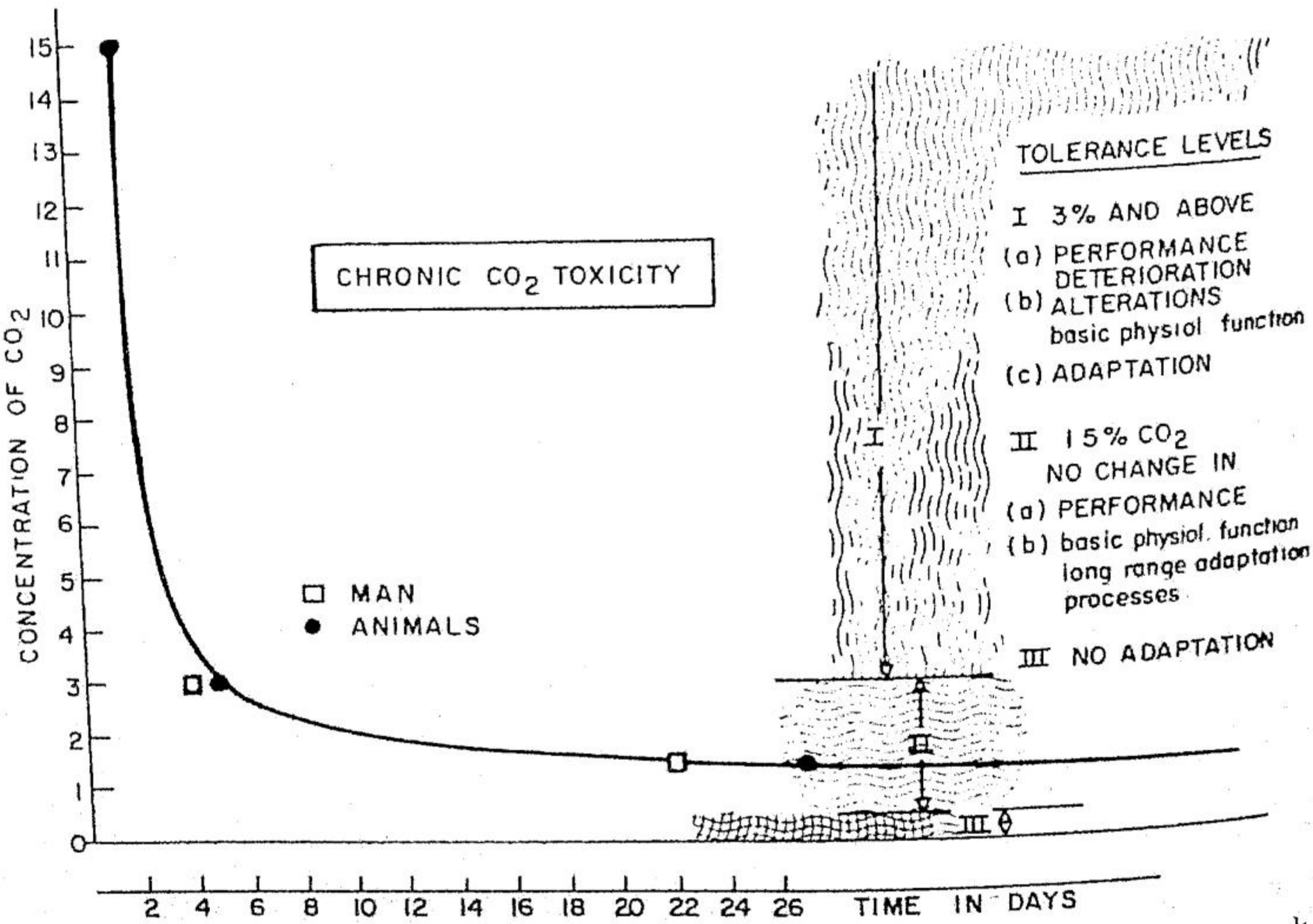


Fig 49 – Time concentration relationship in adaptation to increased carbon dioxide concentration on the basis of human and animal experiments and tolerance limits for chronic carbon dioxide toxicity at three different levels of activity. Adaptation is defined as the time to reach compensation of respiratory acidosis. (Courtesy of Schaefer, K. E.: Arch. Environ. Health 9: 320-331, September, 1964.)

Two peaks of pulmonary $CO_2$ excretion occurred on the 1st and 8th to 9th days of recovery and a peak of urinary $CO_2$ excretion on the 2d day of recovery. The long period of $CO_2$ retention apparently was related to slow equilibration of the bone $CO_2$ store. Kidney regulation of acid-base balance becomes increasingly more important during exposure to high concentrations of $CO_2$.

All dead spaces increased significantly during exposure to $CO_2$. Both the arterial-alveolar $PCO_2$ and $PO_2$ gradients rose. The red cells showed increased sodium and about equal reduction of potassium after 35-41 days of exposure, lasting 8-9 days after the subjects returned to normal breathing atmosphere. Plasma calcium mirrored the pH changes; phosphorus was increased during exposure. There are indications that the changes in calcium and phosphorus metabolism can lead to histopathologic alteration. Calcification of the kidneys has been observed in guinea pigs. Reduction in cardiovascular capacity and increase in ketosteroid excretion

seemed predominantly affected by the increased $CO_2$, independent of pH changes

The data on chronic $CO_2$ toxicity were summarized and a time concentration curve for adaptation to $CO_2$ was established (Fig 49) At a $CO_2$ level of 3% or higher, there is performance deterioration, alterations in basic physiologic functions and pathologic changes Slow adaptive changes occur at a level of 1 5% which might induce pathophysiologic states on greatly prolonged exposure No significant physiologic, psychologic or adaptive changes occur at levels of 0.5-0 8% $CO_2$

If the oxygen content of the atmosphere is lower than normal and the $CO_2$ content is increased, rate of formation of carbon monoxide is increased In a sealed atmosphere, interaction of toxic compounds possibly may result in formation of new toxic reaction products. In a space cabin, the limited power available for atmosphere control, reduced cabin pressure, lower volume per man and zero gravity conditions might impair performance of filtering systems and could possibly affect respiration in man A surprisingly large number of organic compounds was found in a submarine atmosphere; these were generated chiefly from "mineral spirits" used for cleaning purposes and from oil base paints The high aerosol content in submerged submarines is caused mainly by smoking. A 10-20 fold rise in condensation nuclei and in number of positive and negative ions has been found in the air of conventional fleet-type submarines during submergence. The concentration in submerged nuclear-powered submarines is about 0.4 mg./L in about 100 hours. Uncharged aerosol particles can be of biologic significance.

Critical oxygen levels below which mental deterioration and loss of consciousness occur are 55-60% arterial oxygen saturation and an alveolar $PO_2$ of 33 mm. Hg The ceiling for permanent adaptation to altitude is probably about 18,000 ft. A total of 50% oxygen in nitrogen appears to be the threshold concentration for eliciting cardiopulmonary effects. Decreasing the alveolar oxygen tension below 300 mm. Hg increases the sensitivity to $CO_2$. Transitory subsegmental atelectasis in aviators breathing increased concentrations of oxygen while flying high-performance jet aircraft seems to be related to acceleration, use of 100% oxygen or increased

oxygen concentration and elevation of the diaphragm and restricted chest cage expansion from use of a g-suit. Similar conditions exist for an astronaut in an orbital flight. Other hazards of space flight include the bends, fire, and micrometeoroid penetration.

► [Doctor Schaefer is Head of the Physiology Branch of the Medical Research Laboratory at the Submarine Base, but his interest in environmental physiology extends to problems of aircraft and spacecraft. In this paper, which is subtitled "Atmospheric Requirements of Confined Spaces," he elucidates a variety of environmental factors which are unfamiliar to most internists, and outside their usual experience, but which have broader medical significance than merely for the solution of practical problems in the habitability of submarines and space cabins. Doctor Schaefer, indeed, points out a need for new conceptualization in environmental biology and medicine, and he quotes René Dubos to the effect that the classic methods of molecular chemistry and biology are not, as presently pursued, adequately providing systematic knowledge of the responses of living organisms to changing environments. However this may be, Doctor Schaefer's review of certain studies relating to environmental adaptation and tolerance is conceptually sufficiently orthodox to provide most interesting reading for the physician. — Ed.]

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## MISCELLANEOUS

**Pathologic Features of Altitude Sickness** are discussed by N. C. Nayak, S. Roy and T. K. Narayanan[9] (New Delhi, India), who reviewed autopsy findings in 13 men in whom acute respiratory distress developed at altitudes above 8,000 ft., followed by death shortly afterward. Most patients were aged 25-35, and all were healthy before onset of symptoms. Several had come to high altitude for the first time and had stayed a few days before symptoms developed. In most cases, there was a history of exercise. Presenting symptoms were dyspnea, mild fever, cough, cyanosis, chest pain, frothy sputum, edema of the hands and feet, headache, nausea, vomiting and unconsciousness, in order of frequency. In 2 cases, the sputum was bloodstained. Examination showed signs of pulmonary edema in most cases. Treatment with antibiotics had no apparent effect, and oxygen, given only to 2 patients in the terminal stage, failed to bring improvement. Eight patients died within 48 hours after onset of symptoms.

The lungs often weighed over 1,200 Gm. together and were markedly congested, as was the tracheal and bronchial mu-

(9) Am J Path 45 381 391, September 1964

PULMONARY ABNORMALITY IN 13 CASES OF ALTITUDE SICKNESS

| | Grading* | | | | |
|---|---|---|---|---|---|
| | — | ± | + | ++ | +++ |
| Alveolar congestion | 0 | 0 | 1 | 6 | 6 |
| Edema | 1 | 0 | 3 | 5 | 4 |
| Intra-alveolar fibrin | 1 | 4 | 4 | 2 | 2 |
| Hyaline membrane | 6 | 2 | 2 | 3 | 0 |
| Capillary thrombi | 7 | 0 | 0 | 5 | 1 |
| Intra alveolar hemorrhage | 1 | 3 | 3 | 0 | 2 |
| Bronchiolitis and bronchopneumonia | 3 | 4 | 4 | 2 | 2 |
| Atelectasis | 6 | 4 | 4 | 2 | 0 |

*—, absent; ±, minimal; +, mild; ++, moderate; +++, severe.

cosa. The lumens often contained frothy, mucoid or blood-stained fluid. In several cases, the cut lung surfaces showed patchy hemorrhagic areas and noncrepitant solid areas simulating pneumonia. Significant microscopic findings are shown in the table. Small focal areas of myocardiolysis were observed in 2 cases. The liver showed mild to moderate centrilobular congestion in 10 cases and mild fatty change in 8. The spleen showed congestion of the red pulp. In 1 case, multiple fibrin thrombi were found in the kidney, plugging the glomerular and several peritubular capillaries; similar thrombi were found in the sinusoids of the liver, and there were small areas of focal liver cell necrosis.

There is little doubt that hypoxia is responsible for the lung changes in these cases. Prompt administration of oxygen or rapid descent to low altitudes dramatically reverses the condition. Capillary damage due to a factor or factors operating at high altitude combined with excessive physical exercise may very well be the primary mechanism.

► [It is not stated over how many years this extraordinarily large number of autopsies was assembled of this uncommon, and still more uncommonly fatal, condition. One gathers, from a footnote stating that Col. Narayanan is Chief of the Command Laboratory, Military Hospital, Lucknow, that at least some of the casualties were in military personnel. Autopsies in two cases were recently reported from Peru (see the 1964-65 YEAR BOOK, p. 125). The present authors cite these and only 2 others from the literature as cases in which the anatomic findings are well documented. Hyaline membranes were present in all of these 4, but in only 7 of the 13 cases here reported. The present authors agree with most others that the acute pulmonary edema in this condition is not caused by heart failure and that hypoxia initiates the disturbance in some other way.—Ed.]

**Spontaneous Elimination of Inhaled Grass Inflorescences through Lung and Chest Wall** is reported in 2 cases by C. Cheremis, S. Theodorou, Th. Athanasiades and H. Katerelos[1] (Univ. of Athens).

[1] Arch. Dis. Childhood 39:404-408, August, 1964.

Gnl, 3, was hospitalized with pyrexia 40 days after probably swallowing a piece of wood She had been admitted to a hospital with diffuse abdominal pains, diarrhea and pyrexia 6 days after this incident and treated with chloramphenicol for 2 weeks, after which the symptoms subsided The day after discharge, fever recurred At examination, there was dullness over the left chest, diminished air entry and scant rales, particularly throughout the left lower lobe A chest x-ray showed density of the left lower lobe and obliteration of the left costophrenic sinus Despite treatment with penicillin, streptomycin and chloramphenicol, the temperature remained at 102 2-104 F Two days later, nasal catarrh, redness of the conjunctivas and cough developed, and in the next 3 days, the typical rash of measles appeared The white cell count was 12,000/cu mm and the sedimentation rate 50 mm in the 1st hour and 90 in the 2d A hard, immobile, deep-seated nodule about the size of a large pea appeared at the level of the 7th rib 2 cm. from the posterior axillary line 7 days after admission. The axillary lymph nodes became enlarged in the next few days Aspiration of the nodule was negative The swelling enlarged, became inflamed and eventually showed a yellow spot at its apex. A foreign body was removed through a small incision and proved to be a 2-cm long stem of a wheat grass inflorescence. Symptoms and signs subsided rapidly, and chest x-rays showed gradual improvement.

In both cases, the inhaled grass inflorescences migrated through the bronchi, lung and chest wall and reached the skin. Migration required about 2 months in 1 case and only 10 days in the other. In the latter case, the arrangement of the spikelets and the elasticity of the stem gave to the inflorescence (Hordeum murinum) a particularly fast propulsive ability. When a positive history of inhalation of a grass inflorescence exists, and in the presence of clinical and radiologic symptoms from the chest attributed to pneumonitis, it is preferable to control infection and wait instead of advising surgery.

► [Doctor Choremis and his associates record that only 45 cases of grass inflorescences as foreign bodies in the respiratory tract have been reported In the majority they eventually penetrated the chest wall and protruded under the skin —Ed ]

**Complete Resolution of Massive Pulmonary Thromboembolism.** R. D. Sautter, F. W. Fletcher, D. A. Emanuel, B. R. Lawton and T. G. Olsen[2] (Marshfield, Wis., Clinic) encountered 8 patients with massive pulmonary thromboembolism in the last 3 years. Pulmonary embolectomy was performed or attempted in 6 patients, 2 of whom survived. In 2 cases, the clinical condition was such that embolectomy was not indicated. Pulmonary arteriography confirmed the diagnosis

(2) J A M A 189 948 949 Sept 21 1964

in each case. The patients were restudied at 25 and 128 days, respectively.

Man, 62, was injured in an auto accident and admitted with fractures of the 6th, 7th and 8th ribs posteriorly on the left and extensive fractures about the left acetabulum. The acetabulum was treated with skin traction on the left leg On the 13th hospital day, there was sudden onset of dyspnea, with a pulse of 130 but a stable blood pressure. An ECG showed acute strain of the right heart. A pulmonary angiogram confirmed the diagnosis of massive pulmonary thromboembolism. Inferior vena caval ligation was performed. Convalescence was smooth. Heparin sodium was begun at 24 hours. After it was apparent that pulmonary embolectomy would not be required, anticoagulation was continued with warfarin sodium until discharge An arteriogram taken 25 days after embolism showed a normal pulmonary artery with no suggestion of residual thrombi or clots

The 2 cases show that complete resolution does occur in massive, nonfatal pulmonary thromboembolism. The efficacy of any thrombolytic drug used in treatment of this disease will be difficult, if not impossible, to assess. A further implication is that prophylactic pulmonary embolectomy is not indicated in massive thromboembolism that does not immediately threaten life; however, further embolization must be prevented, preferably by inferior vena caval ligation Embolectomy is still considered a life-saving procedure and will be necessary in most cases.

► [The authors suggest that the principal factor leading to resolution of the thromboemboli in these 2 cases was the patients' own fibrinolytic systems and that the only effect and purpose of the administered anticoagulants was to prevent further thromboembolism from occurring as a complication of the inferior vena caval ligations They cite as the basis for their belief (1) observations of Houk *et al* (Am J Med 35 269, 1963) that lysis of thromboembolism does not occur in all cases and (2) observations of Hume (New England J Med 264 471, 1961) that neither urokinase, streptokinase-streptodornase nor plasmins A, B and C produced thrombolysis in every instance One may readily agree that the efficacy of thrombolytic drugs in this situation will be difficult to assess, as they remark, but the evidence presented scarcely justifies any more far-reaching conclusion in this regard – Ed ]

**Pulmonary Alveolar Proteinosis: Case with Improvement after Short Course of Endobronchial Instillations of Heparin** is reported by John Jeffrey Nicholas, J. Howland Auchincloss, Jr , and Lionel Rudolph[3] (State Univ. of New York Upstate Med. Center)

Man, 48, was admitted because of progressive dyspnea on exertion for 4 months He had had jaundice about 30 years previously, and hypertension had been found about 3 years before admission, when evidence of left ventricular enlargement was obtained He had been treated for 2 years with guanethidine, pentaerythritol tetranitrate

and chlordiazepoxide hydrochloride Accompanying the dyspnea were a productive cough and rare night sweats Fine inspiratory rales were heard over the left posterior lung field, and there was a grade II VI apical systolic murmur The patient had smoked 1½ packages cigarettes daily since age 18 The hematocrit was 52% and the white blood cell count 11,300/cu mm The urine contained 4+ protein. The cold agglutinin test was positive at a 1.8 dilution Chest x-rays showed diffuse, bilateral, linear and finely nodular densities A scalene node biopsy showed chronic lymphadenitis Pulmonary function studies showed reduction in total lung capacity, vital capacity, residual volume, maximal ventilatory capacity, maximal midexpiratory flow rate and diffusing capacity Arterial oxygen saturation was 88% at rest and after exercise. The lactic acid dehydrogenase was 465 units Lung biopsy revealed pulmonary alveolar proteinosis

Treatment was with racemic epinephrine hydrochloride, acetylcysteine and aqueous heparin via intermittent positive-pressure breathing nebulizer. Intratracheal instillation of 100 mg aqueous heparin in 100 ml. normal saline produced green sputum containing flecks or chunks of gray-tan material. Some clearing was seen on chest x-ray study, and maximal ventilatory capacity had improved After 7 days of treatment with 65 mg. parenteral heparin every 8 hours and 400 mg. aqueous heparin by nebulizer 4 times daily, there was no apparent x-ray change. Dyspnea decreased subsequently and vital capacity rose, but diffusing capacity did not improve significantly The chest x-ray became entirely clear in the next several months and diffusing capacity improved The latter eventually became normal, and oxygen saturation was normal at rest and after exercise. The patient is working after a remission of 16 months

The change in the course of illness in this patient that followed treatment suggests a response to therapy, and improvement was more rapid than has been reported in spontaneous remissions. Ramirez reported remissions in 2 patients given heparin therapy, and all 3 cases are suggestive enough to prompt further trials and controlled studies on endobronchial heparin instillation.

► [The treatment of alveolar proteinosis with heparin by endobronchial instillation was developed by Ramirez R and his associates (see the 1963 64 YEAR BOOK, p 200), who also reported their technic of endobronchial infusion to be useful diagnostically – Ed ]

**Metabolic Effects of Mechanical Ventilation and Respiratory Alkalosis in Postoperative Patients.** The occurrence of cardiac arrhythmias suggestive of hypokalemia and/or digitalis intoxication in a recent postoperative patient maintained on a mechanical ventilator prompted Robert J. Flemma and W. Glenn Young, Jr.[4] (Duke Univ.) to study the possible role of respiratory alkalosis as an etiologic factor.

(4) Surgery 56 36 43 July, 1964

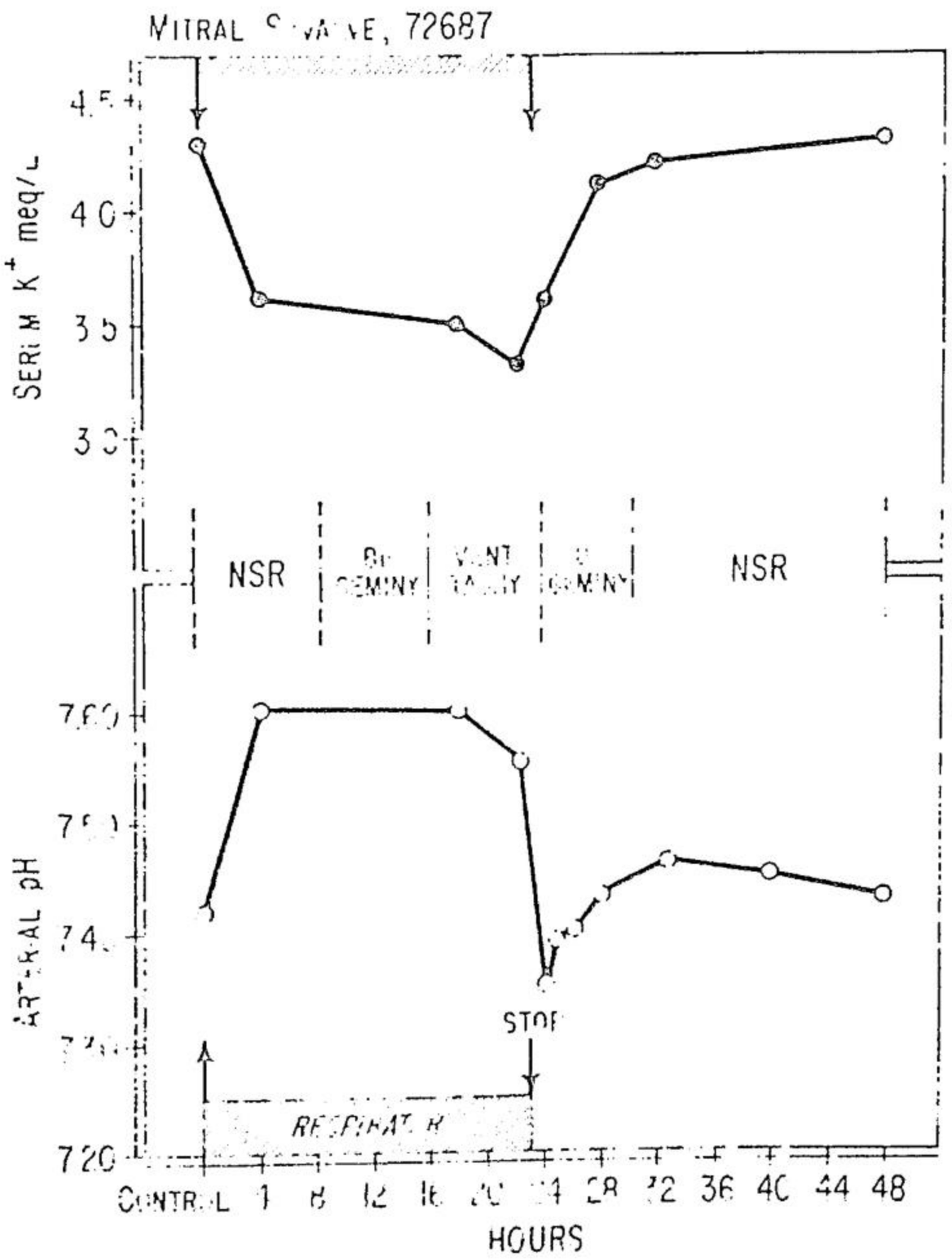


Fig. 80.—Blood changes in a patient during mechanical ventilation after mitral valve replacement. (Courtesy of Flemma, R. J., and Young, W. C., Jr.: Surgery 56:36-43, July, 1964.)

Preliminary studies were conducted by placing 5 anesthetized dogs on prolonged hyperventilation for 3½ hours. Clinical data were obtained primarily from 30 patients who underwent cardiac surgery. One patient underwent thymectomy for myasthenia gravis. Eleven patients, the controls, had no mechanical ventilation after operation. Ten patients had mechanical ventilation for 1-7 days postoperatively, and respiratory alkalosis developed. Nine patients had ventilation for a similar period, but respiratory alkalosis did not develop. The Engström respirator was used for 24-48 hours, and then a Bird or Bennett respirator was often used. The ventilatory rate and minute volume were adjusted so as to induce apnea by removing carbon dioxide and then maintaining a rate sufficient to insure "controlled ventilation."

During hyperventilation, the animals showed a rise in arterial pH to an average of 7.72, and each had a drop in

carboxyhemoglobin occurs at a partial pressure of only 0.12 mm Hg. Even an apparently adequate amount of circulating oxyhemoglobin cannot unload oxygen to the tissues until a dangerously low tension of oxygen exists in these tissues. Although oxygen combines with hemoglobin 10 times faster than does carbon monoxide, the latter dissociates about 250 times more slowly. The time of this dissociation can be speeded up by altering the partial pressures of the reactant gases. Thus, increasing the partial pressure of oxygen in the blood by breathing this gas at 2 atmospheres absolute will increase the rate of dissociation of carboxyhemoglobin. A similar effect can be postulated for other body constituents which bind with carbon monoxide, the most important probably being myoglobin, especially of the heart muscle. These processes require time even at 2 atmospheres absolute.

In 1961, 23 of 32 patients having carbon monoxide poisoning were treated with oxygen at 2 atmospheres absolute, and all survived. Since then, a total of 70 patients have been so treated, and 2 died, both of whom were gassed slowly over at least 8 hours. The success obtained was due in no small part to an excellent alert system and radio-controlled ambulance-to-chamber service run round the clock. Some form of small chamber should be fitted in ambulances, so that treatment could be started at the site of the accident and continued during transport to the hospital.

► [These excellent results appear to establish hyperbaric oxygen therapy beyond question as the treatment of choice in carbon monoxide poisoning.—Ed.]

# THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R. HARRISON, M.D.