LUNG CHANGES DURING HEXAMETHONIUM THERAPY FOR HYPERTENSION

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During the course of treating 54 severely hypertensive patients with parenteral hexamethonium bromide, we have observed the development of unexpected pulmonary dyspnea and associated radiographic changes in the lungs in three cases after 7, 9, and 12 months' therapy respectively. Two of these came to autopsy; the third has recovered. The object of this paper is to record the clinical, radiological, and pathological aspects of these pulmonary changes.

Complications such as disabling headaches, cardiac enlargement, or renal damage were present in all cases in this series, and in seventeen the disease was in an acute malignant or pre-malignant phase. The dose of hexamethonium required varied from 50 mg. to over 600 mg. three times daily. The blood pressure was controlled at levels 30–90 mm. Hg systolic and 10–40 mm. Hg diastolic below the pre-treatment averages. The three patients here recorded all required large doses of hexamethonium, but others who received as much or more of the drug for periods up to 27 months have shown no lung changes.

CASE RECORDS

Case 1. F.T., a man, aged 39, had acute nephritis in 1940. He was admitted to hospital in March, 1951, with Grade 4 retinal changes (Keith et. al., 1939), blood pressure 230/140, heavy albuminuria, and blood urea 70 mg. per 100 ml. The chest radiograph showed slight left ventricular enlargement and clear lung fields. Parenteral hexamethonium therapy produced steady improvement and he returned to work after three months. For the next year the blood pressure was well controlled (Fig. 1); the eyesight returned to

![Graphs showing blood pressure control](image)

**Fig. 1.—**The degree of blood pressure control by hexamethonium in the three cases. The thick lines indicate the range of standing pressures before treatment or after discontinuance of the drug, and the thin lines show the range of pressures on test days. The arrows indicate the dates of the X-rays. The dose of hexamethonium was given three times daily.
normal but the blood urea was unchanged. In March, 1952, he complained of shortness of breath on exertion and the chest radiograph showed bilateral apical shadows. They were rather soft and mottled and suggestive of tuberculosis (Fig. 2A). There was, however, no clinical or bacteriological confirmation of this. Control of blood pressure was inadequate at this time and the dose of hexamethonium was increased to ensure an average blood pressure of 120/90 for the next few weeks. In spite of this, the patient was unwell and easily fatigued and suffered from increasing shortness of breath. Over-ventilation was apparent on slight exertion and was relieved by lying down. There was very slight cough and a little mucoid sputum.

By June, 1952, opacities were visible also in the middle and upper zones of both lungs, not strictly of lobar distribution but limited to the central portions of the lungs and leaving the periphery relatively clear (Fig. 2B). All lobes appeared to be affected to varying degrees. The patient was given streptomycin with PAS and later isoniazid for four months, during which time blood pressure control was maintained (except for one month when hexamethonium was temporarily stopped) (Fig. 1). His general health improved considerably and there was a gradual fading of the opacities, particularly at the apices. Streptomycin and hexamethonium therapy were then discontinued and the patient was discharged from hospital. The blood pressure soon rose, and after six weeks, hexamethonium treatment was resumed with good response. The radiological changes in the lungs showed continued improvement. In March, 1953, the patient returned to work; he had little shortness of breath, a blood urea of 87 mg. per 100 ml. and an average blood pressure of 145/100. The radiological opacities had cleared except for some rather hard residual shadows in the mid zones, indicating the site of demarcation of the original lesions (Fig. 2C). There was, also, evidence of a fine interstitial fibrosis in the mid zones.

Case 2. A.W., a man, aged 45, was admitted in March, 1952 with Grade 4 retinal changes, cardiac enlargement, and early congestive failure, blood urea 76 mg. per 100 ml. and blood pressure 200–230/110–130. He was treated with parenteral hexamethonium and made good progress for six months; his vision was much improved, the blood urea became normal, the blood pressure was well controlled (Fig. 1), and he returned to an active life. A chest radiograph in July, 1952, showed clear lung fields and a diminution of left ventricular enlargement. In August, because of an unsatisfactory blood pressure response, the dose of hexamethonium was raised. During the next month he complained of dyspnea on effort and had several alarming attacks of severe shortness of breath, all brought on by effort and relieved by rest. On examination he looked ill and slight effort produced obvious hyperventilation accompanied by cyanosis. There was no stridor or cough and no adventitiae were heard in the lungs. He was greatly relieved by rest and preferred
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the recumbent position. There were no physical signs of congestive heart failure. An X-ray of the chest on October 7 showed extensive soft shadows with slight mottling in both mid zones, spreading from the hila towards the periphery of the lung and leaving the bases and apices clear (Fig. 3). The distribution and appearances of these shadows suggested acute pulmonary oedema, but they were not absolutely confluent and there were extensive aerated spaces present within the solid lung. In the belief that hexamethonium was in some way responsible for these lung changes the drug was discontinued and the patient treated by bed rest only. The blood pressure rose rapidly in the next week and he developed a fatal cerebral haemorrhage.

**Fig. 3**

Case 2. (Ward unit A.P. film—October, 1952). Extensive soft mottled shadows in the central portions of both lungs, leaving the periphery clear—pulmonary oedema. Along the left mediastinal border there is a thin-walled cavity, representing a large emphysematous bulla.

**Fig. 4**


**Necropsy.** The main findings were a massive haemorrhage into the left cerebral hemisphere, gross hypertrophy of the left ventricle (heart 560 g.), and marked ischaemic atrophy of the outer cortex of both kidneys. Sections of the kidneys showed arterial and arteriolar elastosis. Necroses in the glomeruli and afferent arterioles, typical of malignant hypertension, were present but had been collagenized.

Both lungs were enlarged; the pleural spaces were dry and free from adhesions. The left lung weighed 800 g. (normal 350), the right was used for radio-opaque injection. Striking nodular rubbbery density was felt in the more central portions of both lungs. These solid areas were sharply demarcated from the unaffected peripheral parenchyma, were grey mottled with clumps of pigment, slightly glassy, but by no means entirely airless; the condition could be described as a diffuse irregular carnification. This change extended from the hilum to the periphery of the left upper and lower lobes but the apices, anterior fringes, and bases were free. The right lung showed a similar distribution. The lymphatics of the visceral pleura were dilated and prominent. The pleura overlying solid lung presented a nodular contour due to tethering down of interlobular septa by deep fibrosis. The mediastinal lymph-nodes were not enlarged. Radiographs of the injected right lung showed a normal pulmonary arterial tree.

Microscopy showed the solid zones to consist of discrete and confluent sharply demarcated small patches of recent fibrosis (Fig. 4), often abutting upon but showing no constant relationship to interlobular septa.
The fibrous tissue was made up of reticulin and fine collagen fibres quite rich in fibroblast and fibrocyte nuclei (Fig. 5). Capillaries in the fibrosed area were moderate in number and there were present very occasional scattered lymphocytes and plasma cells. The connective tissue fibres were arranged in thin bands and in small whorls. Elastic stains showed that the fibrosis was both interalveolar and intra-alveolar (Fig. 6). Enclosed within the fibrous tissue were both small and emphysematous surviving alveoli, greatly diminished in number, mostly lined by plump cuboidal "endothelium" (Fig. 5). There were in addition widespread patches of albuminous oedema, congestion, and terminal bronchopneumonia. The sections stained for elastic fibres showed an underlying fairly good preservation of alveolar pattern in the fibrous areas (Fig. 6).

Although there was slight condensation and distortion of elastic fibres in the walls of the alveoli and alveolar ducts. There was no evidence of any old or recent arteritis.

Case 3, F.B., a man, aged 50, presented in January, 1952, with hypertension of 10 years' duration, much cardiac enlargement, nocturnal dyspnoea, Grade 3 retinopathy and blood urea of 39 mg per 100 ml. The blood pressure range was 220–260/130–170. He was treated with hexamethonium bromide and the blood pressure was lowered considerably (Fig. 1). In March, 1952, he discontinued his treatment and was re-admitted in May with acute left ventricular failure, orthopnoea, and blood pressure 210/160. Hexamethonium was again administered with fair control of blood pressure (Fig. 1) and complete clearing of the congestive changes on the chest radiograph. He subsequently returned to work. In September he developed
shortness of breath on effort with several mild attacks of dyspnea at night. There were crepitations in the lungs and X-ray revealed ill-defined soft shadows at both apices and in the lower zones (Fig. 7A). These changes persisted until October, 1952, and thereafter cleared only slowly at the apices but more rapidly at the bases (Fig. 7B). Hexamethonium was discontinued in September and the patient treated with bed rest and digitalis, later supplemented by cortisone. He improved steadily but the blood pressure rose to 250/145 and hexamethonium treatment was started again after five weeks with no ill effects. By December the opacities had virtually cleared, leaving some fine linear shadows at the apices and at the right base, indicating interstitial fibrosis. During December and January he had several attacks of severe pain in the left side of the chest accompanied by a very high blood pressure (290/180), and without electrocardiographic evidence of myocardial infarction. A radiograph in January, 1953, showed no change in the pulmonary appearances but the aortic arch had widened (Fig. 7C). Three weeks later he became very breathless, had further severe chest pain, and died in coma.

**Necropsy.** The main findings were gross hypertrophy of the left ventricle (heart 600 g.), very recent myocardial infarction, two unruptured dissecting aneurysms of the thoracic aorta and one of the abdominal aorta, and moderate ischemic atrophy of the cortex of the kidneys.

The lungs were fixed by arterial perfusion with 15 per cent formol saline. Palpation revealed a striking rubbery firm consolidation of the superior portions of all lobes. Examination of the cut surfaces of the lungs showed this consolidation to be due to zones of grey translucent fibrosis, mostly peripheral in distribution, varying in extent from one to a few centimetres; these zones appeared airless. The remaining lung tissue was moderately oedematous and showed small irregularly distributed patches of fibrosis. The visceral pleura of the left lung was puckered by the underlying fibrosis.

Microscopy confirmed the presence of fibrosis in the periphery of the superior portions of all lobes (Fig. 8). The fibrous tissue was oedematous and made up of delicate collagen fibrils, poor in nuclei, which had replaced most of the alveolar air spaces. Scattered mixed small and grossly distended alveoli much reduced in number, many of them lined by a prominent "endothelium" were present in the fibrous tissue (Fig. 8). Elastic stains showed fairly good preservation of the walls of obliterated alveoli. Sections of the periphery of the mid portion of the right lower lobe showed plugs in the lumina of alveolar ducts and alveoli of young well nucleated vascular fibrous tissue (Fig. 9). A number of these plugs contained central condensed fibrin. In many places these structures were seen to traverse alveolar walls through interalveolar pores (Fig. 9). In the left lower lobe there was an area of fibrosis intermediate in age between the picture just described and the older fibrosis, consisting of massive confluent intra-alveolar fibrosis by well nucleated collagen (Fig. 10). There was no evidence of any recent infection nor of any old or recent arteritis.
Comment on Pathological Findings

The changes in the lungs—a mixed intra-alveolar and interstitial fibrosis associated with preservation of the normal alveolar elastic pattern—are typical of carnification (Kaufmann, 1929). Study of the alveolar elastic tissue is essential for the differentiation from other types of fibrosis (Mallory, 1948). Collapse is associated with a regular condensation of contiguous alveolar walls. In healed infarcts the elastic fibrils are condensed and irregularly matted together, and following destructive pneumonitis they are mostly absent. The chief immediate established cause of carnification in general is the presence within the alveolar ducts and the alveoli of an unresolved fibrinous exudate, which becomes organized and converted into fibrous tissue. It is thought that the intra-alveolar vascularized fibrous tissue is chiefly derived from the connective tissue sheath which surrounds the alveolar ducts (Kaufmann, 1929; Policard, 1949). This proliferates locally and also grows into the air spaces, and the newly formed intra-alveolar fibrous tissue is frequently joined to that in the neighbouring alveoli through the interalveolar pores. In young and small foci of carnification the intra-alveolar plugs of fibrous tissue are often retracted from the alveolar walls.
and covered by "endothelium." In older and larger foci the fibrosis is diffuse in the lung parenchyma (Kaufmann, 1929). The latter picture predominated in the lung sections of Case 2 and in many areas in Case 3, but in addition, in Case 3, foci of varying ages and stages were seen including alveoli in which intra-alveolar fibrin was still present within a mantle of fibroblasts.

The findings are therefore interpreted as representing in Case 2 the results of widespread outpouring of an intra-alveolar exudate rich in fibrin which was not resolved but was organized. Case 3 is thought to have suffered a number of such episodes, some occurring shortly before death, with a similar outcome. Though the most commonly described cause of carnification is organization of an unresolved pneumonic exudate, there is no evidence of this etiology in our cases. The distribution of the lesions in Case 2 was typical of acute pulmonary œdema. The pathology in both cases is similar to, though mostly more advanced than the subacute organizing fibrinous pulmonary œdema observed in patients dying of heart failure associated with uræmia (Doniach, 1947). To sum up, the pathological findings are interpreted as carnification following one or more bouts of fibrinous pulmonary œdema.

DISCUSSION

The post-mortem findings of an organized fibrinous œdema confirm the radiological diagnosis of pulmonary fibrosis, and the resultant loss of aerated lung could account for the symptoms of pulmonary rather than cardiac dyspnœa. Apart from the pulmonary changes these three patients did not differ from the remainder of the series in any important respect such as type or degree of hypertension. In trying to account for the onset of fibrinous pulmonary œdema we have considered such possibilities as incipient left heart failure and changes in capillary permeability. Although there was no history of typical attacks of acute pulmonary œdema while these patients were under drug control, the presence of organizing fibrinous œdema, makes it difficult to avoid the conclusion that they must have had minor attacks. It is conceivable that they were cut short by treatment, and that survival was sufficiently prolonged to permit the development of organization and carnification. While this seems reasonable in Cases 2 and 3, Case 1 had no objective evidence of left heart strain.
Rabbits receiving 10 mg. per kg. of hexamethonium daily for one month showed no macroscopic or microscopic evidence of pulmonary oedema (Paton and Zaimis, 1949). Additional evidence against the direct production of increased permeability of the pulmonary capillaries by hexamethonium is the fact that only three out of fifty cases were affected, and that resolution of the lesions in Case 1 occurred under continued hexamethonium therapy.

We think it unlikely that the complication described can be attributed directly to the hexamethonium and that it is not a contra-indication to continuation of the drug. Cessation of the treatment in these severely hypertensive patients might well lead to their rapid demise and, in fact, did so in Case 2.

**SUMMARY**

Three out of a series of 54 severely hypertensive patients treated with hexamethonium bromide for a prolonged period developed an unexpected pulmonary type of dyspnea and associated radiographic changes in the lungs. Their clinical and radiological findings are described together with the changes found at necropsy in the two who died. The lung lesion was found to be an organized fibrinous pulmonary oedema. This oedema was attributed to attacks of left heart failure probably modified by intermittent lowering of the blood pressure by hexamethonium. This treatment also prolonged life and thereby made possible the development of carification. The lung lesions were thus not considered to be directly attributable to hexamethonium therapy and were no contra-indication to its continuation.

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**REFERENCES**