PLAINTIFF'S EXHIBIT SA-49

which patients received muscle adenosin phosphoric acid (M.A.P.) intramuscularly and in 4 cases in which patients received adenosin intramuscularly.

Evidence is presented to show that these effects are not the result of vasodilatation but are the result of some direct action on the contracting ischemic muscles.

BIBLIOGRAPHY.

1. Barker, N. W.: J. Am. Med. Assn., 97, 841, 1931.
2. Barker, N. W., Brown, G. E., and Roth, G. M.: Trans. Am. Therap. Soc., 33, 115, 1933.
3. Elliot, A. H., and Nuzum, F. R.: J. Pharmacol. and Exp. Therap., 43, 463, 1931.
4. Frey, E. K.: München. med. Wchnschr., 2, 1951, 1929.
5. Frey, E. K.: Berlin Letter, J. Am. Med. Assn., 95, 676, 1930.
6. Frey, E. K., and Kraut, H.: Ztschr. f. physiol. Chem., 157, 32, 1926.
7. Gley, P., and Kisthinios, N.: Presse méd., 2, 1279, 1929.
8. Roth, G. M., Barker, N. W., and Brown, G. E.: Proc. Staff Meet., The Mayo Clinic, 8, 481, 1933.
9. Schwarzmann, J. S.: München. med. Wchnschr., 2, 1329, 1929.
10. Schwarzmann, M. S.: Ibid., 1, 736, 1930.
11. Wolffe, J. B.: Trans. Am. Therap. Soc., 31, 31, 1931.
12. Wolffe, J. B., Findlay, D., and Dessen, E.: Ann. Int. Med., 5, 625, 1931.

A STUDY OF THE SPUTUM IN PULMONARY ASBESTOSIS.

By Robert C. Page, B.A., B.M.,

RESIDENT PHYSICIAN, PRESBYTERIAN HOSPITAL, PHILADELPHIA, PA.; RECENT RESEARCH ASSISTANT TO PROF. M. J. STEWART, LEEDS, ENGLAND.

PHILADELPHIA, PA.

(From the Department of Pathology and Bacteriology, the University of Leeds.)

So much has been written on pulmonary asbestosis during the few years which have elapsed since its first recognition (Cooke, 1924, 1927; Stuart McDonald, 1927; Merewether, 1930; Lynch and Smith, 1930; Kruger *et al.*, 1931; Ellman, 1933) that only a brief introductory statement is necessary here. The disease is a slowly progressive fibrosis of the lungs due to the inhalation of asbestos dust. The fibrosis is widespread, mainly basal and subpleural in distribution, and leads ultimately to such extensive destruction of the parenchyma that the most serious functional disability results. Death is usually brought about by some intercurrent infection, tuberculosis, influenza, or some form of pneumonia. The length of exposure to dust has varied within wide limits, but it is clear that gross disease may follow even as short an exposure as 18 months, provided the dust concentration has been sufficiently high. A certain interval of time must elapse before the disease seriously manifests itself, possibly a period of 7 years (Merewether, 1933–1934). At a certain stage of its development the disease can be diagnosed with great assurance on clinical and radiological

e adenosin phosphoric acid (M.A.P.)
in which patients received adenosin

v that these effects are not the result
result of some direct action on the

:OGRAPHY.

.ssn., 97, 541, 1931.
:nd Roth, G. M.: Trans. Am. Therap. Soc.,

.: J. Pharmacol. and Exp. Therap., 43, 463,

Wchnschr., 2, 1951, 1929.
Am. Med. Assn., 95, 675, 1930.
:schr. f. physiol. Chem., 157, 32, 1926.
Presse méd., 2, 1279, 1929.
and Brown, G. E.: Proc. Staff Meet., The

. med. Wchnschr., 2, 1329, 1929.
758, 1930.
ap. Soc., 31, 31, 1931.
Dessen, E.: Ann. Int. Med., 5, 625, 1931.

I IN PULMONARY ASBESTOSIS.

. PAGE, B.A., B.M.,

SPITAL, PHILADELPHIA, PA.; RECENT RESEARCH
. STEWART, LEEDS, ENGLAND.
ELPHIA, PA.

and Bacteriology, the University of Leeds.)

on pulmonary asbestosis during the
since its first recognition (Cooke,
, 1927; Merewether, 1930; Lynch
, 1931; Ellman, 1933) that only a
necessary here. The disease is a
he lungs due to the inhalation of
widespread, mainly basal and sub-
ads ultimately to such extensive
that the most serious functional
ally brought about by some inter-
influenza, or some form of pneu-
o dust has varied within wide limits,
nay follow even as short an exposure
concentration has been sufficiently
ne must elapse before the disease
y a period of 7 years (Merewether,
e of its development the disease
urance on clinical and radiological

examination, the more so as a clear industrial history of exposure to asbestos dust is almost invariably available. In the earlier stages of disordered function it may be possible only to suspect that a lesion is developing.

The Asbestos Body. This has attracted much attention since it was first adequately described and its probable significance pointed out by Stuart McDonald (1927). A detailed description is given by Gloyne (1932). The bodies are formed in the lung alveoli by the deposition around individual asbestos fibers of an iron-containing silica gel, derived partly from the fiber, partly from the surrounding fluids. They are highly characteristic in form, while presenting considerable individual variation. The two chief varieties are: (1) a spindle-shaped elongated form, very slender in the center and swelling gradually to bulbous extremities, and (2) a beaded form, with the smallest elements in the center and a gradual increase in size to large terminal knobs. In the latter form, the central core of asbestos fiber can often be made out very clearly, especially if the body has been fractured, as often happens. The bodies, which range in size from a few up to several hundred microns, vary in color from pale green through golden yellow to deep brown, depending mainly on their size. They give the Prussian blue reaction with corresponding grades of intensity.

The bodies were first observed in sections of the lung, where they occur singly, in small groups and in radiating clumps in the alveoli, or embedded in the fibrous tissue of the grossly diseased areas. They were next recovered from lung juice obtained by exploratory puncture of the chest during life (Stewart and Haddow, 1929) and finally these observers were able to demonstrate their presence in the sputum of asbestos workers. Later Stewart, Tattersall and Haddow (1932) recovered clumps of bodies similar to those seen in the lung alveoli postmortem from 2 cases of asbestosis, one advanced and since dead of the disease, the other moderately advanced. They suggested that the presence of such clumps meant disintegration of lung tissue and was of much greater significance than the finding of individual bodies, which merely indicated that there had been exposure to asbestos dust.

Personal Observations. The following observations are based partly on Professor Stewart's collected material, partly on a reinvestigation of the cases which he had previously examined, and partly on a few new cases first seen during the first half of 1934. Thirty-eight individual cases have been studied, and a large number of specimens of sputum examined.

Of these cases 11 have died and in 10 the presence of asbestosis was confirmed postmortem. In 6 cases there was superimposed pulmonary tuberculosis, in 2 a terminal acute bronchitis and in 1 the proximate cause of death was influenza. In 1 case death followed pregnancy and parturition and in 1 (Case 14) an abdominal

operation. In this case no autopsy was obtained. Of the surviving cases, 2 are now acutely ill with pulmonary tuberculosis, 2 are doubtfully tuberculous, while 9 are apparently uncomplicated cases of pulmonary asbestosis of considerable and progressive severity. Four others present evidence of mild asbestosis. Adequate information is lacking in regard to 7 of the remaining 10 cases, while the other 3 are in excellent health. Of these, 2 are office employees and the third was employed in an asbestos factory only after the introduction of modern methods. In consequence she was exposed to a minimum amount of dust.

Detailed examination of these cases has been going on at varying intervals for a period of 5 years. Several have been receiving medical attention for indefinite periods and the sputum has been examined at intervals when conditions permitted. Patients with pulmonary asbestosis are extremely susceptible to chest colds and coughs, particularly so during the damp winter months. It is upon such occasions that the ever-present cough becomes productive and that sputum may be obtained for examination.

The best time to obtain a specimen is in the morning owing to the accumulation of mucus overnight. The type of sputum varies: usually in an uncomplicated case it is very thick and tenacious and when allowed to stand develops a very disagreeable odor. When tuberculosis is associated, pus and streaks of blood are not infrequently present. The consistency in many cases is not uniform; clear, thin, watery mucus, when present, tends to settle out from the underlying thick and stringlike portion.

In conjunction with this work complete clinical and radiologic examinations have been done wherever possible. In the developed disease dyspnea and cough are the ever-present and progressive symptoms. Physical signs are for the most part localized to the region of the lower chest. Roentgen ray examinations invariably confirm the findings on physical examination, and when taken at infrequent intervals illustrate a definite bilateral progressive, mainly basal, fibrosis, with characteristic signs of old pleurisy, hazy diaphragmatic margins, and so on. Complications in the nature of upper respiratory infections, bronchitis, bronchiectasis, empyema, pneumonia and especially tuberculosis, aggravate the symptoms to a notable degree, with greatly increased debilitation of the patient and evidence of right heart failure. In all cases the sputum has been examined for the presence of asbestos bodies (including clumps) and tubercle bacilli, and in a small group of 6 cases a special search for elastic tissue has been made.

Technique for Demonstration of Asbestos Bodies. The method originally suggested by Stewart and Haddow (Stewart, 1929) consisted in adding to selected portions of the sputum an equal quantity of antiformin. Following gentle agitation in a test tube and the addition of 4 or 5 times the volume of water, the mixture is placed in the incubator at 37° C. for some hours.

opsy was obtained. Of the surviving
with *pulmonary tuberculosis*, 2 are
) are apparently uncomplicated cases
onsiderable and progressive severity.
f mild asbestosis. Adequate informa-
of the remaining 10 cases, while the
h. Of these, 2 are office employees
in an asbestos factory only after the
ds. In consequence she was exposed
.

se cases has been going on at varying
years. Several have been receiving
te periods and the sputum has been
conditions permitted. Patients with
remely susceptible to chest colds and
the damp winter months. It is upon
r-present cough becomes productive
ined for examination.

specimen is in the morning owing to
vernight. The type of sputum varies:
case it is very thick and tenacious and
ops a very disagreeable odor. When
s and streaks of blood are not infre-
stency in many cases is not uniform;
hen present, tends to settle out from
nglike portion.

work complete clinical and radiologic
wherever possible. In the developed
are the ever-present and progressive
re for the most part localized to the
Roentgen ray examinations invariably
sical examination, and when taken at
a definite bilateral progressive, mainly
ristic signs of old pleurisy, hazy dia-
on. Complications in the nature of
bronchitis, bronchiectasis, empyema,
berculosis, aggravate the symptoms to
y increased debilitation of the patient
failure. In all cases the sputum has
e of asbestos bodies (including clumps)
small group of 6 cases a special search
de.

of Asbestos Bodies. The method orig-
laddow (Stewart, 1929) consisted in adding
an equal quantity of antiformin. Follow-
and the addition of 4 or 5 times the volume
n the incubator at 37° C. for some hours.

The supernatant fluid is now poured off and the last 10 to 15 cc. centrifuged for 5 or 10 minutes. The supernatant fluid is again poured off and the precipitate, by means of a very fine pipette, is placed on albuminized slides. The films are dried, fixed and washed, and mounted in Canada balsam.

Simson and Strachan (1931) suggested a direct method. Thick films of the mucoid portion of sputum were made and dried in a paraffin oven at 54° C. These were fixed with saturated mercuric chlorid solution and subsequently stained with hematoxylin and eosin. These workers concluded that "it was as easy to demonstrate bodies in the direct film as in the antiformin method" and recommended its use as showing both the cytology of the specimens and the intracellular development of the asbestos bodies.

Gloyne (1931) describes a method in which ammonium sulphate replaces the hematoxylin. After antiformin digestion and centrifugation the antiformin is pipetted off and replaced by 5% ammonium sulphid. The bodies as a result are colored black. The author recommends this method because it allows the minute details of the body to be clearly seen, while the central core of asbestos fiber can readily be observed extending between adjacent segments of the asbestos body.

Dr. Norah Schuster (Ellman, 1930–1931) uses the following simple wet method: The sputum is mixed with an equal quantity of 4% sodium hydroxid and left in the incubator until the mucus is dissolved (about 1 hour usually). Following centrifugation a wet film of the deposit is examined directly without staining.

The method used in the present study (Stewart, 1934) is substantially the same as the original.

Technique for Demonstration of Elastic Tissue. The sputum was prepared for staining by the method of Gentz and Bennet (1931). Three or 4 cc. of selected portions of sputum are placed in a centrifuge tube and 2 or 3 times this volume of 3% caustic potash is added. It is then shaken energetically until the mixture is homogeneous. Heat to the boiling point is now applied. Rapid cooling follows and the mixture is centrifuged for ½ to 1 minute. The supernatant fluid is poured off and the deposit placed on albuminized slides and allowed to dry. After being fixed with heat the films are carefully washed to remove the caustic potash.

Two methods of staining have been used for the demonstration of elastic fibers, one a modification of Barth's method (Calmette, 1928), the other a variant of Rappaport and Ellison's (1928–1929) modification of Weigert's stain. In Method I, Barth's orcein stain is heated to 55° C. and the slides immersed. They are kept at this temperature for from 1 to 2 hours, and are then washed in water, differentiated in acid alcohol (2 to 3% hydrochloric acid in 95% alcohol), washed again in water, dehydrated in absolute alcohol, cleared in xylol and mounted in Canada balsam. The elastic fibers are stained a dark reddish purple.

In Method II, the films are immersed in Weigert's stain, as prepared by Rappaport and Ellison, for a period of 20 minutes, following which they are washed in water, differentiated in acid alcohol (2 to 3% hydrochloric acid in 95% alcohol), washed again in water, dehydrated in absolute alcohol, cleared in xylol and mounted in balsam. Elastic fibers are stained a deep blue-black.

The relative merits of these two methods of staining are as follows: The stain as used in the Barth method is relatively easier to prepare, and once prepared can be used for an unlimited time, while the modified Weigert's stain, besides being far more difficult to prepare, tends to deteriorate much more quickly. On the other hand it stains elastic tissue in 20 minutes, whereas the modified Barth method takes from 1 to 2 hours. The final result is equally efficient and each can be used as best fitted to the individual laboratory.

TABLE 1.—LIST OF CASES.

Case No.	Sex and age (yrs.).	Duration of exposure to dust (yrs.); nature of work.	Interval since leaving employment (yrs.).	Interval since first exposure to dust (yrs.).	Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum. Bacilli.	Sputum. Clumps.	Sputum. Tubercle bacilli.
1	F 25	4 Mattress making	2	6	Always subject to catarrh: Roentgen ray negative for both tuberculosis and asbestosis.	3	−	−	−
					No definite Roentgen ray evidence of asbestosis.	4	−	−	−
					Now, 2 years later, apparently in excellent health.				
2	M 34	3 Spinner	3	6	Very mild fibrosis; continuous dry hacking cough.	3	+	−	−
3	M 36	7 Office worker	Still empl.	7	Excellent health; no cough.	3	+	−	−
4	M 28	10 Office worker	Still empl.	10	Excellent health; no cough.	5	+	−	−
					Now, 3 years later, still in excellent health.				
5	F 27	10 Spinner	Still empl.	10	Cold; cough; gastritis; thought to be due to asbestos dust; definite jaundice.	5	−	−	−
					Pulmonary asbestosis.	10	+	−	−*
6	F 27	6 Teaser and carder	4	10	Definite progressive basal fibrosis.	9	+	−	−
7	M 30	9 Every dept.	½	10	Pulmonary tuberculosis superimposed on asbestosis. Confirmed postmortem 7 months later.	9½	++	+	+
8	M 45	9	4	13	Bilateral asbestosis with associated tuberculosis. Confirmed postmortem 1 year later.	12	++	+	−
9	M 37	13½ Associated with much dust	Still empl. clerk	14	Bilateral pulmonary asbestosis with suspected superadded tuberculous infiltration of upper zone of right lung.	14	++	+	−
10	M 46	12 White dust	3	15	No data.	12	++	−	−
					Died of pulmonary asbestosis with superimposed tuberculosis 3 years later; confirmed postmortem.				
11	F 31	11 Mattress maker	3	16	Advanced pulmonary asbestosis, bronchitis and cardiac failure; confirmed postmortem.	16	++	+	−
12	F 31	15 Mattress maker	1	16	Progressive pulmonary asbestosis of moderate severity.	15	+++	+	−
					Similar state.	16	++	−	−
13	F 44	1	16	17	Bronchitis.	17	+	−	−
14	M 55	15 Spinner	1	16	Emphysema with dyspnœa, cough and pain in abdomen.	12	+++	−	−
					Very ill; cirrhosis of liver(?). Later laparotomy was done; death followed.	15	+++	−	−
15	M 36	13 Foreman mattress maker	½	16	Pulmonary tuberculosis and asbestosis. Confirmed by postmortem 1 year later.	17	++	−	+
16	M 43	6	12	18	Pulmonary asbestosis complicated by tuberculosis.	18	++	+	+*
17	M (?)	20 Spinner	..	..	(?) Tuberculosis plus asbestosis.	..	+	−	−
18	F 35	18 Mattress maker	3	21	Progressive pulmonary asbestosis with cardiac involvement.	20+	+	−	−
					Died 1 year later following pregnancy and parturition.				
19	F 35	6 Mattress maker	16	22	Right-sided basal pleural thickening; dyspnœa, cough; tubercle suspected; tuberculosis confirmed.	20	+++	+	+
					Primary pulmonary asbestosis with superimposed active tuberculosis.	22	+++	+	+
20	M 47	17 Mattress maker	2	22	Pulmonary asbestosis.	19	++	−	−
					Progressive pulmonary asbestosis.	22	++	+	−*
21	F 45	6 Mattress maker	15	23	Cerebral softening; acute bronchitis and broncho-pneumonia with associated asbestosis. Confirmed later, postmortem.	23	+	+	−
22	F 41	19 Mattress maker	4	23	Cough, dyspnœa; evidence of basal fibrosis by Roentgen ray examination.	21	+	−	−
					Death from acute influenza 2 years later.				

* Elastic tissue present (Cases 5, 16, 20).

—List of Cases.

Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum. Bodies.	Cilumps.	Tubercle bacilli.
...to catarrh; Roentgen ray negative ...rculosis and asbestosis.	3	–	–	–
...ntgen ray evidence of asbestosis.	4	–	–	–
...later, apparently in excellent health.				
...sis; continuous dry hacking cough.	2	+	–	–
...h; no cough.	2	+	–	–
...h; no cough.	5	+	–	–
...ater, still in excellent health.				
...sorder; thought to be due to asbestos ...jaundice.	5	–	–	–
...estosis.	10	+	–	–*
...ssive basal fibrosis.	9	+	–	–
...erculosis superimposed on asbestosis. ...-mortem 7 months later.	9½	++	+	+
...tosis with associated tuberculosis. ...mortem 1 year later.	12	++	+	–
...onary asbestosis with suggested ...tuberculous infiltration of upper zone	14	++	+	–
...onary asbestosis with superimposed ...3 years later; confirmed postmortem.	12	++	–	–
...monary asbestosis, bronchitis and ...; confirmed postmortem.	16	++	+	–
...ulmonary asbestosis of moderate	13	+++	+	–
	16	++	–	–
	17	+	–	–
...with dyspnea, cough and pain in	12	+++	–	–
...osis of liver(?). Later laparotomy ...ath followed.	15	+++	–	–
...erculosis and asbestosis. ...postmortem 1 year later.	17	++	–	+
...estosis complicated by tuberculosis.	18	++	+	+*
...is plus asbestosis.	..	+	–	–
...ulmonary asbestosis with cardiac	20+	+	–	–
...ter following pregnancy and parturi-				
...basal pleural thickening; dyspnea, ...cle suspected; tuberculosis confirmed.	20	+++	+	+
...onary asbestosis with superimposed ...uiosis.	22	+++	+	+
...estosis.	19	++	–	–
...monary asbestosis.	22	++	+	–*
...ning; acute bronchitis and broncho- ...ith associated asbestosis. ...n postmortem.	23	+	+	–
...sis; evidence of basal fibrosis by ...examination.	21	+	–	–
...ute influenza 2 years later.				

Table 1.—List of Cases—*Continued.*

Case No.	Sex and age (yrs.).	Duration of exposure to dust (yrs.); nature of work.	Interval since leaving employment (yrs.).	Interval since first exposure to dust (yrs.).	Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum. Bodies.	Cilumps.	Tubercle bacilli.
23	F 40	22 Mattress maker	2	24	Mild pulmonary fibrosis. Progressive pulmonary asbestosis.	18 24	–† –	– –	– –
24	F 37	4 Spinner	14	24	Pulmonary asbestosis with tuberculosis. Asbestosis with extensive phthisis confirmed by postmortem 1 year later.	23	++	–	+
25	F 44	16 Mattress maker	9	25	Suggestion of pleural effusion. Progressive pulmonary asbestosis. Two years later, advanced asbestosis, dry cough.	23‡ 23	+† +	– –	– –
26	F 39	13 Mattress maker	10	26	Pulmonary asbestosis. Uncomplicated pulmonary asbestosis of pronounced severity.	21 26‡	+ +	– –	– –
27	F 46	21 Mattress maker	2	29	Progressive pulmonary asbestosis. Uncomplicated pulmonary asbestosis.	27 29‡	++ ++	+ +	– –
28	M 63	30 Cashier	Still empl.	30	Very severe cough, dyspnea; *mild pulmonary asbestosis.* Pulmonary asbestosis and tuberculosis confirmed later postmortem.	25 30	++ ++	– –	– ++
29	M 53	35 Warehouseman	Still empl.	35	General condition fairly good.	35	++	–	–
30	F 67	31 Mattress maker	4	35	Fairly advanced fibrosis (Roentgen ray examination). Progressive uncomplicated pulmonary asbestosis.	26 31‡	++ ++	– –	– –
31	M 63	50 Fiber rope dept.	..	50	Advanced pulmonary fibrosis.	50	+++	–	–

† Lung juice.
‡ Elastic tissue not present on repeated examinations (Cases 26, 27, 30).

Analysis of Cases. The present study includes 38 cases of asbestos workers of whom 31, where full details are available, are recorded in the preceding table. The cases have been arranged in accordance with the period of time that has passed since they first became exposed to asbestos dust, which in several cases is not equivalent to the actual duration of exposure plus the interval since leaving employment, since some were employed irregularly or were absent from work on account of childbirth, service overseas, etc.

Twenty-one of the cases are males and 17 females. The age at which they began working in an asbestos factory ranges from 13 to 39, average 21, but 17 of the 31 recorded in the table began work before the age of 21. The average duration of exposure is 15 years, with a range from as low as 1 up to 50 years. Tuberculosis was present in 8 cases, and in this group the average period of exposure was 9.2 years, as contrasted with 16 years in the non-tuberculous group. Case 28 is exceptional in that he was not really a worker in asbestos and he is therefore not included in the averages given.

Sputum Examination. *Asbestos bodies* have been present in every case with the exception of Case 1, a woman, aged 25, who was in contact with a minimum amount of dust as a mattress maker for

4 years, the whole period being subsequent to the abolition of the dry method of manufacture. She has always been subject to respiratory tract catarrh, which may have been a factor in preventing entry of dust to the lung alveoli. With two exceptions (Cases 1 and 5) bodies were demonstrated at every examination. In Case 5 the sputum was negative after 5 years' exposure but positive (a solitary body only) when examined after 10 years' exposure.

The number and type of bodies were most variable. Generally the large beaded or "weathered" type of bodies, deep brown in color and strongly iron-reacting, were most prevalent in cases where the interval since the onset of exposure had been long, including those where a long interval had elapsed since they were last employed in asbestos. Bodies recovered from those who had only been in this employment for a few years were smaller in size, paler in color and less strongly iron-reacting. It is clear that asbestos bodies in the lung slowly increase in size with the passage of time and become in consequence both darker in color and more strongly iron-reacting.

Clumps or groups of bodies were present in 10 of the cases. Five of these had tuberculosis, of whom 3 have died and the other 2 are critically ill. One of the remaining 5 cases is doubtfully tuberculous, 1 has died of pulmonary asbestosis with associated cardiac failure, while the remaining 3 are apparently cases of progressive uncomplicated asbestosis.

In 6 cases (Nos. 5, 16, 20, 26, 27 and 30) the sputum was examined for *elastic tissue* by the methods described and a positive result obtained in 3. In Case 5 a solitary "weather-beaten" asbestos body was discovered after 10 years' exposure, yet elastic tissue was present (Fig. 1). In Cases 26 and 30, bodies had been found on several former occasions but neither clumps nor tubercle bacilli; elastic tissue was absent from both. In Cases 20 and 27 clumps as well as single bodies had been found previously but no tubercle

---

LEGENDS FOR FIGS. 1 TO 7.

FIG. 1.—Case 5. F., age 25. Elastic tissue in sputum of asbestos worker. Ten years' exposure to asbestos dust. Only one "weather-beaten" body found, no clumps, no tubercle bacilli. × 300.

FIG. 2.—Case 20. M., age 47. Elastic tissue in sputum of asbestos worker. Twenty-two years since onset of exposure (duration 17 years). Asbestos bodies and clumps present, but no tubercle bacilli. × 300.

FIG. 3.—Case 16. M., age 43. Elastic tissue in case of asbestosis with tuberculosis. Eighteen years since onset of exposure (duration 6 years). Elastic fibers, asbestos bodies and clumps (Fig. 7) and tubercle bacilli all present. × 300.

FIG. 4.—Elastic tissue in sputum of a pure case of pulmonary tuberculosis. × 300.

FIGS. 5 and 6.—Case 28. M., age 65. Elastic tissue in caseous material in a phthisical cavity. Case of pulmonary tuberculosis superimposed upon asbestosis. Interval since onset of exposure 30 years. × 300.

FIG. 7.—Case 16. Small clump of asbestos bodies in sputum, from same case as Fig. 3. × 300.

ng subsequent to the abolition of the
She has always been subject to respir-
ay have been a factor in preventing
eoli. With two exceptions (Cases 1
ted at every examination. In Case 5
er 5 years' exposure but positive (a
ined after 10 years' exposure.
odies were most variable. Generally
red" type of bodies, deep brown in
g, were most prevalent in cases where
of exposure had been long, including
ad elapsed since they were last em-
recovered from those who had only
a few years were smaller in size, paler
n-reacting. It is clear that asbestos
ease in size with the passage of time
oth darker in color and more strongly

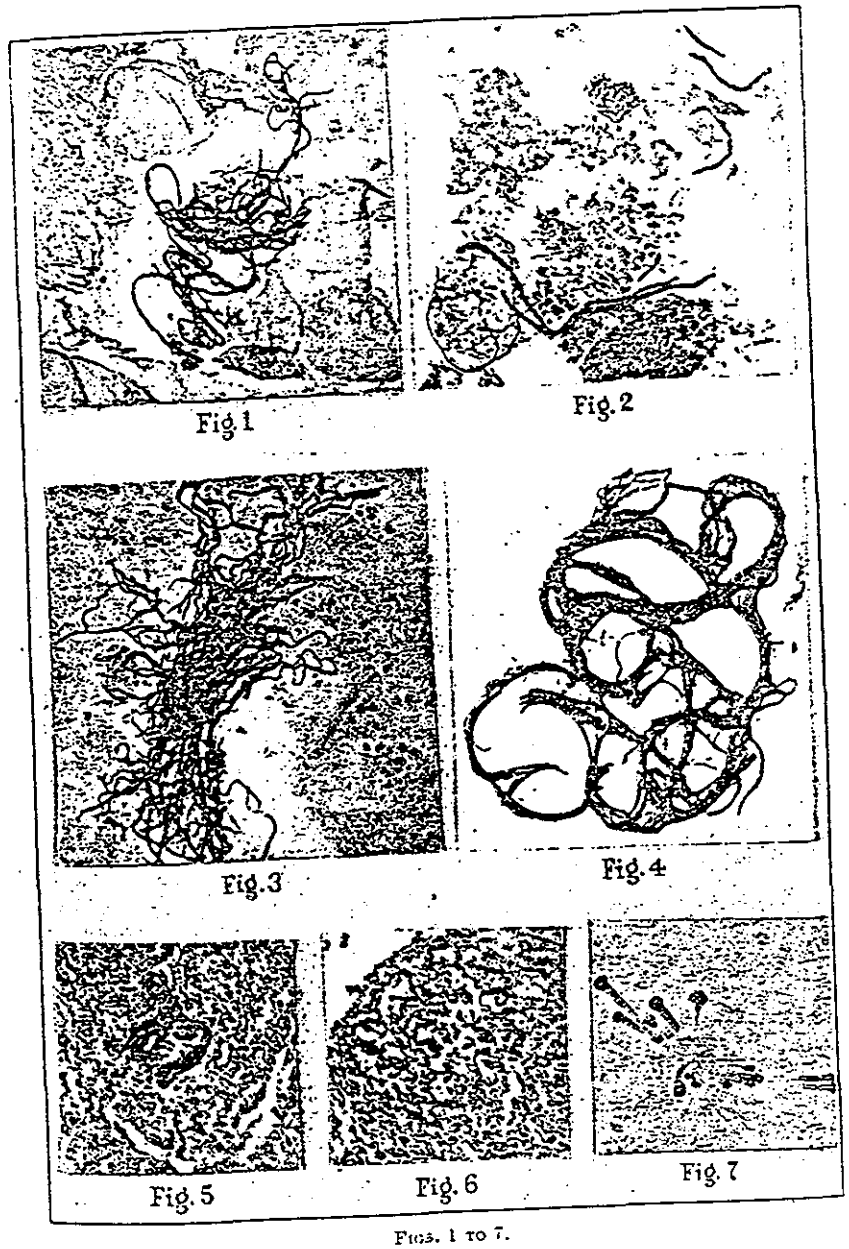
were present in 10 of the cases. Five
whom 3 have died and the other 2 are
naining 5 cases is doubtfully tuber-
ary asbestosis with associated cardiac
3 are apparently cases of progressive

27 and 30) the sputum was examined
hods described and a positive result
a solitary "weather-beaten" asbestos
years' exposure, yet elastic tissue was
6 and 30, bodies had been found on
neither clumps nor tubercle bacilli;
both. In Cases 20 and 27 clumps as
n found previously but no tubercle

FOR FIGS. 1 TO 7.

tic tissue in sputum of asbestos worker. Ten
one "weather-beaten" body found, no clumps,

lastic tissue in sputum of asbestos worker.
sure (duration 17 years). Asbestos bodies and
li. × 300.
astic tissue in case of asbestosis with tuber-
exposure (duration 6 years). Elastic fibers,
d tubercle bacilli all present. × 300.
a pure case of pulmonary tuberculosis. × 300.
Elastic tissue in caseous material in a phthisi-
losis superimposed upon asbestosis. Interval
300.
asbestos bodies in sputum, from same case as



FIGS. 1 TO 7.

bacilli; elastic tissue was demonstrated in Case 20 (Fig. 2). In Case 16, clumps, tubercle bacilli and elastic tissue were all present (Figs. 3 and 7). These results are summarized in Table 2.

TABLE 2.—CASES EXAMINED FOR ELASTIC TISSUE.

Case No.	Asbestos bodies.	Clumps.	Elastic tissue.	Tubercle bacilli.
5	+ (1)	−	+	−
16	+	+	+	+
20	+	−	+	−
26	+	−	−	−
27	+	+	−	−
30	+	−	−	−

Discussion. The findings here reported are for the most part in accordance with those of other workers and show that the mere presence of asbestos bodies in the sputum of an individual denotes nothing more than that he has at some time been in contact with asbestos dust. The actual number of bodies is likewise of little significance. If, however, they are consistently present in considerable numbers the possibilities are that either the individual has been in contact with large quantities of dust over a long period or there is some underlying pathologic condition of the lung, leading to gradual liberation of accumulated bodies. This is illustrated in Cases 14 and 19. In the former the sputum upon repeated examination showed large numbers of bodies, the individual in question having been associated at the time of examination and for 15 years previously with large quantities of dust. Case 19, on the other hand, also with numerous bodies on repeated examination, had only been directly exposed for a period of 6 years and had not been in contact with dust for 16 years at the time of examination. Clinically there was an associated tuberculosis.

The type of body present is of considerably greater significance than the number. The formation of asbestos bodies in the lung takes but a short time. They were found by Simson (1929) in the lungs of a patient who had been exposed for 2 months only, and by Stewart (1930) in a guinea pig after 3 months' exposure in an asbestos factory. Once formed, they can remain in the lung for an indefinite period. In a patient of Ellman's (1933) exposure was for 10 weeks only, and 5 years later bodies were recovered from the sputum. In Case 13 of this series, the patient had worked in asbestos for 1 year, and 17 years later bodies were still present in small numbers.

Reference has already been made to the "growth" or increase in size of these bodies, presumably by slow diffusion out of silicates from the central fiber and their interaction with constituents of the surrounding body fluids. It follows that bodies of large size in the sputum indicate that these have formed around fibers inhaled many years before. On the other hand, small, thin bodies, though doubtless of recent formation, are no indication that their central fibers have been recently inhaled. "Young" bodies may be encountered in sputum from persons who have had no opportunity

strated in Case 20 (Fig. 2). In and elastic tissue were all present summarized in Table 2.

NED FOR ELASTIC TISSUE.

Clumps.	Elastic tissue.	Tubercle bacilli.
−	+	−
+	+	+
+	+	−
−	−	−
+	−	−
−	−	−

reported are for the most part in workers and show that the mere e sputum of an individual denotes t some time been in contact with ber of bodies is likewise of little e consistently present in consider- re that either the individual has ities of dust over a long period or gic condition of the lung, leading ated bodies. This is illustrated in he sputum upon repeated examina- odies, the individual in question e of examination and for 15 years of dust. Case 19, on the other es on repeated examination, had period of 6 years and had not been t the time of examination. Clinic- culosis.

f considerably greater significance on of asbestos bodies in the lung re found by Simson (1929) in the xposed for 2 months only, and by er 3 months' exposure in an asbes- n remain in the lung for an indefin- an's (1933) exposure was for 10 s were recovered from the sputum. tient had worked in asbestos for ere still present in small numbers. le to the "growth" or increase in by slow diffusion out of silicates teraction with constituents of the ws that bodies of large size in the e formed around fibers inhaled hand, small, thin bodies, though e no indication that their central l. "Young" bodies may be en- s who have had no opportunity

of inhaling dust for many years, and it is known that asbestos fibers may remain in the lung for long periods without necessarily becoming converted into "bodies" at all.

Another point of great importance is the so-called "weathering" of the asbestos body. Many of the old large bodies present a distinctly ragged or weather-beaten aspect, often consisting, as it were, of widely separated irregularly shaped beads strung on the fibrous core. There can be little doubt that this process is associated with solution and disintegration of "body" substance and accounts, in my opinion, for the interesting finding of Fowweather that the silica content of the fibrotic portion of the asbestos lung is much less in workers who have been away from dust for many years than in those recently or still in employment, even where the length of exposure has been the same. "Weathering" is probably a constant process in these cases, but may be accelerated by the occurrence of caseous or suppurative change.

The clump-like arrangement of bodies within the lung alveoli was observed from the very outset of detailed histologic studies (Stuart McDonald, 1927). When the presence of clumps in the sputum was first reported by Stewart, Tattersall and Haddow (1932) it was suggested that this finding was a clear indication of disintegration of lung tissue, whether by a process of simple suppurative bronchopneumonia or as a result of a secondary tuberculous infection. In either case it was regarded as being virtually diagnostic of an underlying asbestosis. In the present study, 10 cases in which clumps were present in the sputum tend to substantiate this view. Four of them suffered from superimposed tuberculosis. Two of these have died and the remaining 2 are now critically ill. One other patient in whose sputum a clump was demonstrated is considered as a probable case of superimposed pulmonary tuberculosis. Of the remaining 5 cases, 2 have died, 1 of cerebral softening, acute bronchitis and bronchopneumonia, the other of bronchitis and cardiac failure, both with underlying asbestosis. The remaining 3 are suffering with definite progressive pulmonary asbestosis, fully confirmed by clinical and radiologic examination.

While the presence of asbestos clumps in the sputum is probably indicative of lung destruction, the converse is by no means true, that is, the absence of asbestos clumps affords no assurance of pulmonary integrity. There are many cases in the present series in which there has been definite disintegration of the lung and yet no clumps have been demonstrated in the sputum. Other possible fallacies exist. More prolonged and more careful examination might have yielded a positive result, or roughness in handling may have caused the clumps to break up. Lastly and perhaps most important, the underlying pathologic condition in the lung may have led to chemical or physical dissolution of the clumplike arrangement so that when expectorated in the midst of caseous material or pus, the clumps may have disintegrated into their individual fibers.

Gardner and Cummings (1931) state that in guinea pigs tuberculous caseation causes the asbestos bodies present to lose their golden-yellow color; they also fail to give a Prussian blue reaction and later are apparently so completely disintegrated that not even a supporting fiber remains.

Elastic tissue in the sputum, irrespective of the underlying pathologic condition, has long been accepted as unequivocal evidence of lung disintegration. Rappaport (1929–1930) mentions that elastic tissue may appear in the sputum of patients who present only very mild signs of clinical activity. He refers to Durand, a French worker, who demonstrated elastic fibers in the sputum of tuberculous patients, both before and after the appearance of tubercle bacilli. The 3 cases of the present series in which elastic tissue has been demonstrated in the sputum illustrate several points of interest. In Case 5, the presence of the elastic fibers is difficult to explain. She had been exposed to asbestos dust, it is true, for the last 10 years, and during this time it is quite possible for a progressive pulmonary asbestosis to have developed. Yet only a solitary asbestos body was found on one occasion. There was no definite evidence of tuberculosis, but the possibility that this disease existed in an abacillary or prebacillary stage could not be excluded. In Case 20, the presence of elastic fibers is associated with a rapidly progressive form of uncomplicated pulmonary asbestosis. In Case 16, the presence of elastic tissue is associated with active tuberculosis and clearly indicates a state of definite disintegration. The underlying pulmonary lesion here is probably illustrated by Case 28, from which Figures 6 and 7 were obtained. These show, in sections of the lung, elastic tissue in the midst of caseous tuberculous material, in a similar form to that expectorated in Case 16.

A careful search for tubercle bacilli has been carried out in every sample of sputum obtained. Positive findings were present in 6 out of 8 cases of proven tuberculosis. The incidence of tuberculosis in this series is therefore 21%, exactly the same as that recorded by Wood and Gloyne (1931), but less than figure given by Ellman (1930–1931), 6 out of 17 cases. Bridge (1931) reports an incidence of 31.5% in fatal cases.

Conclusions. 1. The presence of asbestos bodies in the sputum is indicative merely of exposure to asbestos dust. If they are of large size it means that a long interval has elapsed since the onset of exposure.

2. The number of bodies in any given specimen is insignificant, but the presence of old and weathered bodies on repeated examinations strongly suggests that a definite pathologic process is in existence.

3. Clumps in the sputum are definite evidence of lung disintegration, but their absence does not mean that disintegration is not in process.

4. Elastic fibers are probably indicative of rapid lung destruction.

1931) state that in guinea pigs tuber-
asbestos bodies present to lose their
so fail to give a Prussian blue reaction
completely disintegrated that not even

m, irrespective of the underlying patho-
en accepted as unequivocal evidence of
port (1929–1930) mentions that elastic
trum of patients who present only very
ity. He refers to Durand, a French
elastic fibers in the sputum of tubercu-
and after the appearance of tubercle
present series in which elastic tissue has
trum illustrate several points of interest.
the elastic fibers is difficult to explain.
sbestos dust, it is true, for the last 10
it is quite possible for a progressive
ave developed. Yet only a solitary
n one occasion. There was no definite
the possibility that this disease existed
llary stage could not be excluded. In
astic fibers is associated with a rapidly
dicated pulmonary asbestosis. In Case
issue is associated with active tubercu-
state of definite disintegration. The
here is probably illustrated by Case 28,
were obtained. These show, in sections
the midst of caseous tuberculous mate-
t expectorated in Case 16.
cle bacilli has been carried out in every
.. Positive findings were present in 6
erculosis. The incidence of tuberculosis
%, exactly the same as that recorded
), but less than figure given by Ellman
es. Bridge (1931) reports an incidence

ence of asbestos bodies in the sputum
sure to asbestos dust. If they are of
g interval has elapsed since the onset of

in any given specimen is insignificant,
weathered bodies on repeated examina-
a definite pathologic process is in exist-

are definite evidence of lung disintegra-
not mean that disintegration is not in

ly indicative of rapid lung destruction.

5. Elastic fibers may be present in the sputum in pure pulmonary asbestosis both with and without clumps, or in asbestosis with associated tuberculosis.

6. The routine examination of the sputum in cases of suspected pulmonary asbestosis is essential, as it plays a significant rôle in the clinical diagnosis.

I wish to express my sincere appreciation to Professor M. J. Stewart for the use of his personally collected material, his friendly criticism and able advice, under whose guidance this paper has been written, and to the British Medical Research Council for financial assistance.

I am also indebted to Dr. A. C. Haddow and Dr. N. Tattersall for the use of their clinical and radiological material, and to Mr. Lawson for his technical assistance.

REFERENCES.

Bridge, C.: Ann. Rep., Senior Med. Inspector of Factories, p. 74, 1931.
Calmette, A.: L'infection bacillaire et la tuberculose, 3r ed., Masson, Paris, p. 499, 1928.
Cooke, W. E.: Brit. Med. J., 2, 147, 1924; Ibid., 2, 1024, 1927.
Ellman, P.: Proc. Roy. Soc. Med., 24, 526, 541, and 699, 1930–1931; J. Indust. Hygiene, 15, 165, 1933.
Fowweather, F. S.: Personal communication, 1934.
Gardner, L. U., and Cummings, D. E.: J. Indust. Hygiene, 13, 65 and 97, 1931.
Gentz, C., and Bennet, K.: Acta Med. Scandinav., 75, 424, 1931.
Gloyne, S. R.: J. Indust. Hygiene, 13, 85, 1931; Lancet, 1, 1351, 1932.
Kruger, E., Rostoski, O., and Saupe, E.: Arch. f. Gewerbepath. u. Gewerbehyg., 2, 558, 1931.
Lynch, K. M., and Smith, W. A.: J. Am. Med. Assn., 95, 659, 1930.
McDonald, S.: Brit. Med. J., 2, 1025, 1925.
Merewether, E. R. A.: J. Indust. Hygiene, 12, 198, 1930; Tubercle, 15, 69, 109 and 152, 1933–1934.
Rappaport, I.: J. Lab. and Clin. Med., 15, 1, 1929–1930.
Rappaport, I., and Ellison, R. T.: Ibid., 14, 261, 1928–1929.
Simson, F. W.: Ann. Rep. So. African Instit. Med. Res., p. 64, 1929.
Simson, F. W., and Strachan, A. S.: J. Path. and Bact., 34, 1, 1931.
Stewart, M. J.: Brit. Med., J. 2, 581, 1929; J. Path. and Bact., 33, 848, 1930; J. Tech. Methods and Bull. Internat. Assn. Med. Museums, 13, 70, 1934.
Stewart, M. J., and Haddow, A. C.: J. Path. and Bact., 32, 172, 1929.
Stewart, M. J., Tattersall, N., and Haddow, A. C.: Ibid., 35, 324, 1932.
Wood, W. B., and Gloyne, S. R.: Ibid., 2, 954, 1931.

ACETYL-β-METHYLCHOLIN (MECHOLIN). OBSERVATIONS CONCERNING ITS ACTION ON THE BLOOD PRESSURE, SKIN TEMPERATURE AND THE HEART, AS EXHIBITED BY THE ELECTROCARDIOGRAM OF HYPERTENSIVE PATIENTS.

By Irvine H. Page, M.D.,
Associate in Medicine, Hospital of the Rockefeller Institute for Medical Research, New York, N. Y.

Hunt and Taveau[1] were the first to prepare and determine many of the pharmacologic properties of acetyl-β-methylcholin. Major and Cline[2] have synthetized it ("mecholin") by a process which has made it available in quantity. Recently studies of its pharmacology