EXTENSIVE CALCIFICATION OF THE LUNGS AS A DISTINCT DISEASE *

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Calcareous deposits, especially local, are of frequent occurrence in degenerated and necrotic tissue, old inflammatory exudates, and other dead material such as thrombi. Calcification in the media and intima of the arteries in old persons, in pleural and pericardial exudates where large calcareous plates may form, the concretions in the apices of the lungs and in the bronchial lymph nodes as the result of tuberculosis, are all familiar examples. Wherever tissue degenerates, deposits of calcium salts may take place, usually in the stroma, but also, although rarely, in the cells themselves, as, for instance, in the renal epithelium in toxic necrosis, in ganglion cells, in muscle fibers. Deposition of calcium salts also occurs on a larger scale, when it may give rise to peculiar conditions and even distinct diseases. The cause of such deposits is in general assumed to be a supersaturation, so to speak, of the blood and tissue fluids with calcium salts. If the normal elimination of calcium by way of the intestinal tract and the kidneys is disturbed as, for instance, on account of nephritis, calcareous deposits occur more readily. Added to this we have the facts that certain organs and tissues are predisposed to calcareous infiltration, namely, the lungs, the endocardium of the left ventricle, the pulmonary veins, the gastro-intestinal mucous membrane and the kidneys, as shown in 1885 by Virchow, who described calcareous infiltrations of these organs in diseases of bones in the course of which calcium salts are set free, more particularly in bone tumors, either primary or secondary, but also in osteomalacia and in leukemic conditions. Virchow called this process lime or calcium metastasis. It is believed that a lowered acidity of the blood in these organs and tissues may account for their predisposition to calcific deposits. According to Wells,¹ some thirty-six cases of extensive, and, as a rule, multiple, calcareous "metastasis" had been described up to 1915; since then some additional cases have been reported. Still different are the cases in which deposition of lime salts takes place primarily in certain tissues or organs in persons who do

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1. Wells, H. G.: Classification and Ossification. *THE ARCHIVES INT. MED.*, 1911, **7**, 721. Metastatic Calcification, *Ibid.*, 1915, **15**, 514. These articles contain references to the literature.

not appear to suffer from any other disease except such peculiar deposits. A form of this condition is infiltration of calcium salts in bursae, tendon sheaths, etc., which may occur as an independent process and cause more or less severe disturbances of function. A number of cases of this kind have been described recently in Norway by Paus and Natvig (subacromial bursa), and by Sinding-Larson and Kjerschow (subepichondral bursa). In these cases there was found in the bursae white, chalky masses or a milky fluid with smaller, hard concretions and incrustation of the surrounding tissues, the masses consisting principally of carbonates and phosphates of calcium. In the tissues were chronic inflammatory changes with indefinite giant cells, enclosing small calcareous masses, but no demonstrable primary necrosis; on the inner wall of the bursae were small papillomatous outgrowths. A rare but also more serious condition is "calcinosis universalis," cases of which have been described recently, which is a chronic affection, especially of young persons, sometimes of several children of the same family, but also of older persons. Phosphates and carbonates of calcium are deposited as nodular or band-like formations, or as softer, crumbling or even confluent material, especially in the subcutaneous tissue as well as in bursae, tendons, muscles, about nerves, and often in symmetrical form. As a rule the internal organs are not involved and the joints and bones appear to be normal. Over affected parts the skin may be pigmented and hard. Various vasomotor changes have been observed. The upper as well as the lower extremities and also the trunk may be affected. Muscular atrophy takes place and invalidism in different grades results. External irritation, injury or rheumatic attacks may hasten the depositions, which also may take place in paroxysms with fever, swelling, redness and tenderness of the parts involved. As a rule, however, the process is gradual. If a softening takes place, with secondary infection, death may result from septicopyemia. There appears to be no primary degeneration in the connective tissue or elastic elements, which are especially affected, and it seems reasonable to assume that it concerns a metabolic anomaly of an unknown nature.

The following case under the care of Dr. Winge is an illustration:

A woman, 63 years old, suffered many years until the hands and fingers became greatly deformed and enlarged on account of extensive deposits around all the joints; there was a fluctuating swelling on one buttock as large as half a hen's egg, which on incision was found to contain a liquid and semisolid, clumpy, white material, extending along the subcutaneous tissue through fascia and muscles clear to the bone, so that it was not possible to make a complete removal. A clump 4.5 by 7.5 cm., white as chalk and irregular, was removed and found to contain carbonate, phosphate and a little oxalate of calcium.

Morbid infiltration with calcium salts without evident cause may take place also in internal organs, and I have examined a remarkable

case of most extensive calcareous deposition in the lungs, which it is my special purpose to report:

History.—The patient was a woman, 41 years old, a workingman's wife, admitted to the service of Prof. P. F. Holst, Feb. 10, 1917. The family history was good; no children. While a child and also three years prior to admission, she had acute rheumatism, the last attack being rather mild; for some time she had had dyspeptic symptoms, pain in the region of the stomach, and during the previous three years several rather large hemorrhages from the stomach; occasionally she would have severe nose bleed, and once it was very extensive; menstrual bleeding was also severe. During the previous ten years she would get out of breath easily, and recently dyspnea would come on readily at the same time that the face seemed to become blue. In the summer and fall of

Fig. 1.—Roentgenograms of sections of the same thickness of normal lung (a) and calcified lung (b).

1916 the legs became edematous; at Christmas time the edema returned, and at the same time the abdomen became large, the urine small in amount and deeply colored, and from then on dyspnea forced her to sit up in bed at night.

Examination.—On admission the face was cyanotic, there was anasarca, the finger tips were club-shaped; pulse 104, respirations 34; prolonged expiration, especially over the left lung; at the base of the lungs, fine crepitation; heart somewhat enlarged, especially to the right; loud systolic murmur, most marked at the apex, with accentuation of the second pulmonary sound; blood pressure 110; liver enlarged; ascites; urine of specific gravity of 1.032, no albumin, blood or sugar.

A few days later the blood showed 8,448,000 red corpuscles and 11,600 leukocytes.

Under treatment with digitalis and theobromin sodium salicylate the edema diminished and the urine increased in amount, but before long the edema again increased, also the cyanosis, the heart action became irregular, and the patient died suddenly, March 3.

Necropsy.—The postmortem showed cyanosis and edema of the legs. The heart was enlarged, weighing 400 gm., the enlargement involving practically exclusively the right side; the heart muscle was normal; valves normal, and the coronary arteries only a little sclerotic and not narrow; the aorta was normal, without calcareous deposits.

There was no fluid in the pleural cavities; a few fibrous bands were present over the left lung and general adhesions over the right; the lungs were large, as in croupous pneumonia, solid and heavy, feeling like stones and sinking in water; the right lung weighed 2,750 gm., the left 2,130, in all 4,880 gm. Placed on the base, the lungs stood by themselves; in consistency the substance was almost like wood, but not uniformly so, being apparently full of small, solid particles, and under the pleura here and there were small, white, flat masses of mineral nature. The substance could be cut only with difficulty and felt like porous bone. Passing the finger over the surface felt like rubbing it over sandpaper, and here and there were round or irregular concretions. The distribution of mineral matter was about the same in both lungs, perhaps a little more marked in the left. The cut surface was peculiar, reddish-brown, with numerous small holes in an extensive stroma; bloody, frothy fluid exuded. The first impression that the lungs were free of air and compact was not correct; air was present everywhere, but the air-containing tissue was less in amount than the interstitial tissue with the mineral deposits. Areas in the anterior border of the right lung and the anterior surface of the upper lobe contained more air than other parts of the lungs. After drying a small slice of lung substance it had a peculiar yellow red color and a porous surface which felt like sandpaper and from which small calcareous granules would fall out. In both apices, at the hilus of the lungs and in the lymph nodes in the neck, were small, old caseous foci. The pulmonary arteries were sclerotic but not calcified or dilated; the pulmonary veins were normal. No calcification was present in the larger bronchi, trachea, or larynx.

Mouth, pharynx and esophagus were normal.

The thyroid gland was rather large; weight 29 gm.; parathyroid glands not enlarged; no traces of the thymus.

The peritoneal cavity contained 900 c.c. clear yellow fluid; lining smooth.

Spleen, liver and kidneys were passively congested.

Microscopic Examination.—Microscopically there were no changes in the kidneys, except that the glomeruli were quite cellular and that under the capsule were occasional linear infiltrations of round cells.

In the surface of the left adrenal was a small concretion.

The ovaries were small and fibrous; tubes tuberculous, containing caseous material and tubercles in the mucosa.

No ulcers or definite scars were found in the stomach, the mucosa of which was normal under the microscope.

The hypophysis, which was large and weighed 1.1 gm., appeared normal on microscopic section.

The spinal column, ribs, femur, sternum and cranial bones were normal so far as could be determined on careful gross and microscopic examination.

Frozen sections of the lungs showed numerous round and oval concretions in the interstitial tissue, and compression of the alveoli. In decalcified section the concretions have a lamellated structure, concentric, there being no needle shaped crystals or larger masses; the clumps lie in the interalveolar tissue and encroach on the alveolar spaces (Fig. 2). The stroma is increased in amount, in places sclerotic, also anthracotic and infiltrated with round cells. The veins and capillaries in the septa are dilated and there are hemorrhagic infiltrations

into the septa as well as into alveoli and small bronchi. In places the alveoli appear as narrow clefts; in other places as small spaces with swollen desquamated cells, and then again as large spaces, the lungs being not totally solid anywhere. The larger vessels and the bronchi appear normal. There were no signs anywhere of old diffuse inflammatory processes, such as chronic bronchitis or pneumonia. On addition of sulphuric acid to frozen sections, typical gypsum crystals formed; of hydrochloric acid, gas bubbles. Chemical analysis (H. Siebke) gave 78.05 per cent. ash, of which 18.3 per cent. consisted of calcium carbonate and about 80 per cent. of calcium phosphate, as well as small quantities of iron, magnesium, etc.

The extensive lime deposits in the lung in this case, so extensive that it seems quite remarkable that life lasted as long as it did, do not appear to be duplicated by any reports in the literature either of genuine "metastatic" deposits or of the few cases in which there was no definite cause. It is noteworthy that the lungs weighed nearly six times as

Fig. 2.—Photomicrograph of decalcified section of calcareous lung: between the large alveolar spaces numerous round, concentrically constructed calcareous clumps are seen.

much as normal and that on first impression they appeared to be almost entirely airless; the deposits were diffuse and evenly distributed throughout the lungs, showing that they were independent of local changes such as thrombi or infarcts.

For purposes of comparison I wish to mention briefly certain cases of calcification of the lung which I have found in the literature. These may be divided into two groups, (1) the metastatic, dependent on bone destruction, and (2) cases like the one I have described in which there were no indications of bone disease.

1. In addition to a number of cases of metastatic calcification, some of moderate degree only, described by Virchow, Kockel, Askanazy and others, I would mention especially the following cases: The case described by Tschistowisch and Kollesnikoff of extensive calcium

metastases in the lungs and other organs associated with multiple myeloma; the lungs were large, very heavy, hard, dry, the surface grayish-white and rough, due to deposits in the walls of the alveoli and around the blood vessels. Pari's case in a patient who died from cancer of the uterus with bone metastases, in which there was general calcification of the lungs, the surface was coarsely porous, dry, grayish-white and rough, there being also present larger, more completely calcified areas. And in the instance described by Wells, who mentions the cases just cited, of extensive calcification in the heart and lungs in a case of myelogenous leukemia, the lungs were heavy, solid and felt sandy.

In this group probably belongs the following case, the facts in regard to which I obtained through the courtesy of Professor Quensel in Upsala and Dr. Hellman:

The patient was a woman, 65 years old, who died with symptoms of intestinal obstruction and marasmus. The lungs were enlarged, grayish-red and looked as if powdered; on removal they retained their form, were solid and heavy but floated in water; finger depressions remained. The cut surface seemed as if dusted with fine sand and a grayish-red frothy fluid could be pressed out. The heart, kidneys, liver and spleen seemed normal. The mucous membrane of the stomach was dark red and showed numerous small depressions surrounded by narrow, less deeply colored elevations, but whether this was due to calcification was not determined. The intestines were normal; there was coprostasis. The cranium was normal in form and thickness but very soft, consisting mostly of diploe, and both the surfaces showed irregular dark-red and grayish-white spots. The brain and its membranes were normal.

There was here a diffuse and extensive calcification of the lungs and possibly also of the stomach, due most likely to a primary disease of the bone, as indicated by the appearance of the cranium; but the exact nature of this disease we do not know.

As examples of the second group, I would mention the case in which Virchow found grayish-white incrustated nodes as large as nuts in one lobe in a woman, 43 years old, with chronic pleuritis and nephritis, but no disease of the bones; Chiari's case in a woman, 27 years old, with gastric ulcer and general marasmus, half of the right lung being hard, grayish-white, grating on section; microscopically, there were calcareous deposits in the wall of the alveoli and in the vessels; there were also a few calcareous foci in the left lung and calcification in both kidneys; bones normal. Hlava also found calcification in spongy form, of the right upper lobe, especially, in a person who died with circulatory disturbances. Kockel described microscopic calcification in the lungs in a number of cases in some of which there was heart disease; while Kischensky found advanced calcification in part of one lung in a woman with chronic nephritis, amyloid disease, but with no changes in the bones. Here belongs also the case described by Stade, who found an extensive deposit of calcium salts in the lungs of a man,

44 years old, who died with pneumonia and who had no changes in the bone system. The substance of the lung was rough like sandpaper, solid, and microscopically the calcification was extensive.

We see that in no case of either group was there so extensive and complete a calcification of the lungs as in the one I have described. Usually the calcification seems to have been rather limited, sometimes strictly local, but there are cases in which it was diffuse, as, for example, in the case described by Virchow as follows: "Lungs mostly grayish-white, resistant, especially at the borders of the lobules, calcified; cut surface porous like a sponge, with small holes, dry, rough; alveoli everywhere, large and wide." The cases described by Pari, Stade and Wells are also characterized by extensive deposits.

In regard to the cause of calcification in the lungs, it appears that in most cases it may be regarded as metastatic in Virchow's sense, that is, as secondary to some form of destructive bone disease, with solution of the calcium salts in the bone and secondary deposition in other tissues. In some cases the evidence of bone destruction is not definite. In a small group, however, there is not the slightest evidence of any bone destruction; this would seem to be especially true in my case, in which several bones were carefully examined with this point in view. In my case the kidneys were also normal, so that there is no reason to believe that there was any interference with calcium elimination by way of the urine. Neither were there any extensive changes in the stomach or intestines, the most important places of calcium elimination; so that we are without any indications that in this case diminished calcium excretion was the reason of the calcification in the lungs. The question arises whether there were peculiar degenerative or dystrophic conditions in the lungs which would induce precipitation of calcium salt, as is believed is the fact in necrotic and degenerated tissue. In this case such changes would have had to be diffuse, and there is no evidence that such changes were present. The dyspnea and cyanosis, which were noticed for many years, may have been the result of the calcification; possibly calcification might result from chronic stasis and secondary nutritive changes in the walls of the alveoli, but there is no way to account for any primary stasis in this case, as the condition of the heart clearly was secondary and there was no sign of previous disease in the lung, such as interstitial pneumonia, on the basis of which calcification might have taken place. The possibility that some organ with internal secretion was at fault must be considered — the parathyroid glands, the thyroid, the hypophysis, the thymus, and the ovaries. There is evidence that the parathyroid glands influence calcium metabolism; removal of these glands increases elimination of calcium and disturbances of ossification. In osteomalacia, rickets and senile osteo-

porosis, tumors and other changes have been found in the parathyroid glands. In my case, however, there were no changes in the parathyroids, the thyroid, thymus, or hypophysis. Whether any significance is to be placed on the fibrous condition of the ovaries in this case is indeed a question. We know but little of the influence of the ovaries in calcium metabolism. The ovaries are frequently fibrous in young women in whom there are no demonstrable disturbances of calcium elimination or metabolism. Taking it all in all, there are in this case no changes in the internal organs to explain the calcification in the lung. It would seem, then, that one is driven to assume that in such cases as I have described there is a "constitutional anomaly" or metabolic disturbance of unknown nature, in consequence of which calcium salts are deposited from the blood in apparently normal tissues, and especially in the lungs, perhaps on account of the low acidity of the blood as it gives up carbon dioxid.