and subsequent investigations may prove it untenable. Indeed, already Grenell and Kabat[26] feel that the degree of vascularity of a certain region is no index of its susceptibility to anoxia.

Finally, I would like to add that limitations of space preclude any discussion of the central nervous system changes in "irreversible hypoglycæmia" beyond their mere mention. In reviewing reported studies of this state,[28 to 32] one is struck by the similarity of the histopathological picture it presents to that detailed above. This is not surprising when one considers that the disturbance in hypoglycæmia is essentially an intracellular anoxia with inability to use oxygen due to lack of available substrate, glucose. By broadening our concept of "histotoxic anoxia" somewhat, insulin in excess might be regarded as a toxin.

SUMMARY

The histopathological changes occurring in the brain of a man deprived of oxygen for a period of between five and ten minutes are described. The most severe changes were found in the cerebral cortex, particularly in the motor and visual areas, in the putamen and in the cerebellum. In both the precentral and visual cortex, a striking band of softening containing compound granular corpuscles was found. Here and elsewhere nerve cell and blood vessel changes of varying degrees of severity were seen. The entire pathological picture supports a concept of variation in the susceptibility of different areas of the brain to oxygen lack. The possible significance of this variation is discussed and a portion of the pertinent literature is reviewed.

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ESSENTIAL BROWN INDURATION OF THE LUNGS

(Idiopathic Pulmonary Hæmosiderosis)

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ESSENTIAL brown induration of the lungs (idiopathic pulmonary hæmosiderosis) has recently been reviewed by Wyllie[1] and his colleagues at Great Ormond Street, London. The condition was first described in 1931 and the reviewers present 17 cases from the world literature and a series of 7 of their own. Only two of the cases quoted are from the North American continent. While admittedly a rare condition, it is noteworthy that, of the 24 recorded cases, 16 are the work of five groups of authors. Accordingly one could justifiably assume that the diagnosis is usually missed. The condition is not familial and has been encountered in children from a few months to 16 years of age. It is characterized by periodic attacks of tachycardia, pyrexia, pallor, fatigue, cyanosis, increasing dyspnœa, signs of congestive cardiac failure, severe anæmia with signs of active blood regeneration, and hæmoptysis. Pulmonary findings in life are usually more conspicuous radiologically than clinically. Between attacks the subject may remain well but commonly there is chronic ill-health. The condition ends fatally

and autopsy findings are remarkable for the advanced degree of brown induration of the lungs and the absence of conspicuous abnormality in other organs. The case presented here is classical in all respects.

CASE HISTORY

The child, a boy, was born in March, 1944, at full term and weighed 8½ pounds. He was described as being difficult to rear and vomiting of feedings proved troublesome. The mother noticed that at one year old the child easily became tired and appeared bluish on exertion. He walked at fourteen months but was often found lying on the lawn resting. Early in life he developed the habit of "head butting" and would bump his head against the side of his cot or into his pillow until he fell off to sleep. This trait remained with him until he died. He fractured a leg in December, 1945, and seemed to get worse after this. His father, mother and sister were all alive and well.

While mental development appeared normal the child was always pale and easily tired. At one time (in Alberta) he was diagnosed as having leukæmia and showed improvement on receiving several blood transfusions. Later his condition was labelled "severe anæmia". He had measles and otitis media which followed a stormy course.

The parents moved from Alberta to Saskatchewan in 1947 and the child came under the care of Dr. Bradley, Regina. He noted that the child was weedy, very pale, and was failing to gain weight. There was marked clubbing of the fingers and breathlessness and cyanosis developed on exertion. The heart was of normal size radiologically and physical examination failed to reveal evidence of congenital heart disease, coarctation of the aorta, or pulmonary disease. Hæmatological examination showed a normochromic anæmia which responded to iron preparations and vitamins. Radiological examination revealed no obvious abnormality of the lungs.

In September, 1947, the child was admitted to Regina General Hospital in a condition of collapse associated with severe dyspnœa and deep cyanosis. There was pyrexia (104.5° F.), tachycardia (140/minute) and dyspnœa (40-50/minute). Physical examination revealed bilateral consolidation of the lungs. The condition was diagnosed as pneumonia and treated with oxygen inhalation, penicillin, and sulfonamides. It was noted that oxygen gave symptomatic relief and the cyanosis diminished, while, if withdrawn, the general condition became worse and cyanosis deepened. The temperature chart revealed a "spiking" intermittency ranging from 105.2 to 102° F. over a period of four days. All abnormal physical signs gradually subsided and by the tenth day the temperature was normal, the pulse rate was maintained at 100 to 110 beats per minute and respiration was constant at 30/minute. The pulse rate remained rather high (90-100/minute) over a period of eight weeks while the respiratory rate became normal and there was no sign of cyanosis.

Laboratory examination revealed a normochromic anæmia (hæmoglobin 71% where 100% = 15.6 gm. per 100 c.c.); within six weeks the hæmoglobin rose to 96% under hæmatinics and vitamins. The white cell count on admission was 7,850 with neutrophil polymorphonuclear cells 61% and rhabdocytes 20%. The relatively high proportion of leucocytes fell to normal within six days. The sedimentation rate was 2 mm. in 15 minutes, 13.5 mm. in 45 minutes, which is within normal limits on correction for anæmia. The urine was normal. Blood culture was sterile. No sputum was available for examination. Throat swabs did not yield a pathogen.

On admission radiological examination of the lungs showed a diffuse bilateral infiltration presenting as a coarsely mottled appearance against a general background of increased density. This involved almost all of the lung area. The cardiac shadow was enlarged chiefly towards the right. The abnormal appearances diminished during the following three weeks when, by November 25, there only remained a fine stippling together with a slight general enlargement of the cardiac shadow. This gave the impression of cardiac insufficiency with passive pulmonary congestion.

Shortly after discharge from hospital the patient was again admitted in January, 1948, with an acute attack. The condition was similar in all respects to the previous attack and followed a similar course on the same treatment, with the following variations. On admission the white cell count was 13,800 with neutrophil polymorphonuclear cells 71% and rhabdocytes 17%. Within five days the count was down to 8,000 with a normal differential picture. Slight normochromic anæmia (hæmoglobin 86%) was present on admission; streptomycin was given in addition to penicillin and sulfonamides. The clinical course was the same as in the previous attack.

The patient was investigated by Dr. Bennett of the anti-tuberculosis service. The tuberculin test was positive. While he did not consider that the condition was tuberculous he had the patient removed to a sanatorium (Fort San) for investigation.

On admission he weighed 35 pounds. Repeated physical, laboratory and radiological examinations revealed only tachycardia and no evidence of tuberculosis. Tachycardia was constantly present (120-124 occasionally falling to 90). Radiological examination of the lungs showed little change from time to time, mostly presenting as a moderate coalescent mottling throughout both lung fields, increasing and decreasing a little from time to time, but never returning to the fine stippling presented on two occasions while at Regina General Hospital. No other abnormality was detected. He was given bed rest, cod liver oil and heliotherapy.

The patient was shown at a number of clinical conferences and was ultimately diagnosed as a case of congenital cystic disease of the lung. This diagnosis was made on the clinical history and by the inference that the pathological and radiological findings had mainly been of value in excluding other conditions. The patient was discharged in May, 1948. He remained poorly nourished.

In August, 1948, an acute attack of dyspnœa and cyanosis similar to the previous ones but with the addition of hæmoptysis developed suddenly. The boy died shortly after admission to Regina General Hospital. He was then 4 years and 5 months of age.

AUTOPSY REPORT

The important post mortem findings were as follows: There was slight cyanosis, and clubbing of the fingers. The trachea and bronchi contained blood-stained mucus. There was no blockage of the air passages. Both pleural cavities contained a small amount of straw-coloured fluid. There was no adhesion of the pleuræ, no thickening and no signs of inflammation.

The lungs presented a striking appearance. They were both uniformly consolidated. Inspection of the pleural surface of the lungs showed no abnormal markings. Section of the lungs showed a liver-like appearance. The lungs were semi-solid and had a firm, rubbery consistency. The cut surface was a uniform brownish-red colour showing no sign of the

granularity of inflammatory processes, the cut-surface being relatively smooth. On pressure a copious blood-stained frothy fluid was exuded. Smears of this fluid showed red cells and large numbers of macrophages which contained hæmosiderin granules. There was no evidence of bronchiectasis or of diffuse fibrosis.

The hilar glands were enlarged, one at the bifurcation of the trachea being at least 2 cm. in diameter. The capsules were not thickened and they were of soft consistency and a uniform café-au-lait colour. The blood vessels of the lungs showed no abnormality. The great vessels were normal. The heart showed slight hypertrophy of the right ventricle. The liver was of normal size; section showed no unusual features, in particular, it was not the nutmeg pattern that one might expect from long-standing heart failure. The spleen, of normal size, showed the Malpighian bodies to be more prominent than usual, the pulp consisting mainly of Malpighian tissue. The other organs were normal.

EXAMINATION OF LUNGS

The lungs were cut into serial thin slices using a bacon-slicing machine. Inspection of the slices showed normal bronchial and vascular systems, and a normal pleura. The normal lobular pattern was accentuated by œdema of fibrous septæ and by œdema and slight fibrous thickening of sub-pleural lymphatics. The walls of the air sacs were uniformly thickened. Air sacs immediately under the pleura and abutting on septæ were larger than the remainder and appeared cystic. Comparison, however, with lungs from children of the same age has shown the size of the air sacs to be within normal limits, except for an occasional subpleural air sac which was ballooned out to about twice the average size. Histological examination showed the alveolar thickening to be due to dilatation and tortuosity of capillaries with great thickening of capillary and alveolar basement membranes, prominence of connective tissue cells, and a generalized interstitial œdema. The œdema fluid

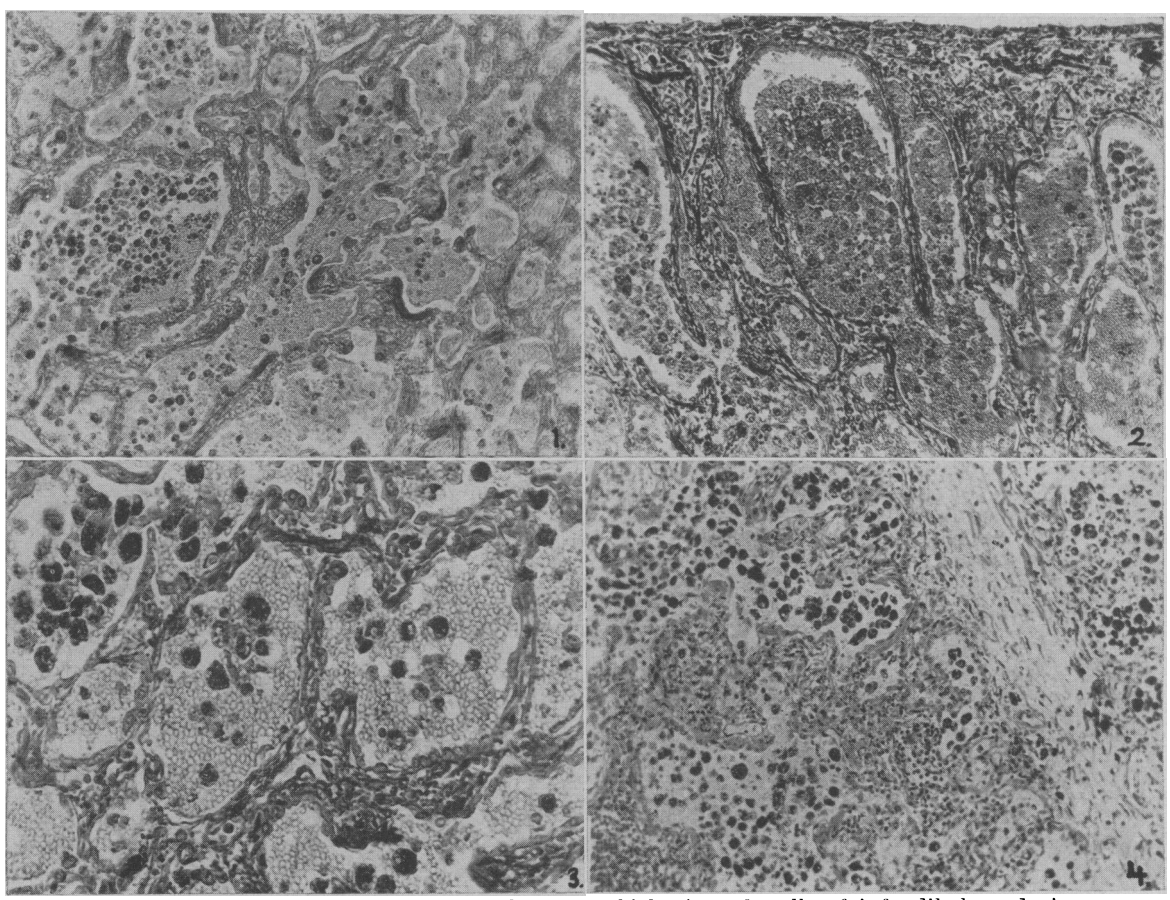

Fig. 1.—Section of lung. Note the great thickening of walls of infundibula and air sacs and the general consolidation (x 100). **Fig. 2.**—Note the large size of air sacs abutting on the pleura (x 125). **Fig. 3.**—The section shows air sacs filled with lysed (ghost) red blood cells and macrophages laden with hæmosiderin. The respiratory epithelium is prominent and there is generalized thickening of basement membranes (x 275). **Fig. 4.**—Section of lungs showing œdema of septum. This œdema spreads out into the interstitial tissue but can only be appreciated in thick frozen sections (x 125).

contained macrophages, and there was a slight generalized interstitial increase of reticulin and fine collagenous fibrils. The elastica in the lung was grossly deficient, being almost completely absent in the alveolar walls and septa, though almost normal in the infundibula and normal in all other structures. In the majority of air sacs the respiratory epithelium was prominent to cubical in form. The consolidation of the lungs was seen to be due to filling of the alveoli with red blood cells, many of them lysed (ghost) forms, and macrophages laden with hæmosiderin. There was no evidence of rupture of blood vessels (Figs 1 to 4).

OTHER HISTOLOGICAL EXAMINATION

The hilar glands showed simple hyperplasia and sinus catarrh. The spleen showed lymphoid hyperplasia while the sinusoids were stuffed with blood. The kidneys were normal. The liver was normal and there was no evidence of centro-lobular fatty change. The pancreas showed no evidence of cystic disease. Smears of the bone marrow showed no conspicuous abnormality.

DISCUSSION

It is patent that in the case described we have to relate to a condition of anoxic anoxæmia a conspicuous degree of brown induration of the lungs, a paucity of findings elsewhere, and periodic, acute and severe episodes of anoxæmia accompanied by a pulmonary consolidation unique in that it resulted from a massive and universal diapedesis of red blood cells from the pulmonary capillary vessels. To this complex the name idiopathic brown induration of the lungs has been given and our case is classical. For completeness we have only to add the following additional information from the review by Wyllie *et al.* In acute attacks one may find reticulocytosis, presence of nucleated red cells in the circulating blood, slight jaundice, slight increased urinary urobilinogen, and cold agglutinins in the serum. These are all manifestations of either lysis of the intra-alveolar hæmorrhage or of the marrow reaction to the hæmorrhage. With increasing chronicity hæmosiderin is deposited in the pulmonary interstitium (idiopathic pulmonary hæmosiderosis). The x-ray appearances are often grossly abnormal.

> "The commonest features are mottled shadows most noticeable in the hilar areas, and a diffuse speckling throughout the lung fields. These abnormal shadows become accentuated in an attack. Evidence of a partial lobar collapse is often visible. The x-ray appearances of the lung frequently have a superficial resemblance to those of miliary tuberculosis, but, in the place of miliary dots, one can usually distinguish small, clear circular spaces surrounded by thickened opaque walls giving a pumice-stone appearance. There is much similarity in the picture to that presented either by sarcoidosis or Gaucher's lipoidosis involving the lungs. The degree of hilar mottling attained during an attack has been likened to the root-shadows seen in cases of mitral stenosis. The cardiac shadow is enlarged chiefly towards the right, and the pulmonary conus may be prominent."

Hepatosplenomegaly is sometimes found in the acute attack.

In their analysis Wyllie *et al.* are indefinite as to the true nature of the condition. They mention the question of a primary structural abnormality of the lungs but conclude that "changes are confined to, or maximal in, the lesser circulation". We consider that the findings warrant a closer interpretation. In analyzing the morbid pulmonary features we consider that almost all of the findings can be considered as changes secondary to anoxæmia. Accordingly it will aid our argument to relate how far the clinical and pathological findings could follow from a primary (unknown) lung condition producing defective aeration of the circulating blood.

1. The anoxæmia produced cyanosis and breathlessness, aggravated by exercise, relieved by rest. We regard the tachycardia as a compensatory mechanism to overcome the pulmonary defect.

2. In severe attacks of anoxæmia, the lung capillaries dilated and became stuffed with blood, flowing slowly—the common response to anoxic anoxæmia.

3. Diapedesis of red cells took place from the dilated capillaries and this was massive leading to pulmonary consolidation in the three acute attacks.

4. Recovery from acute attacks was possible with rest and oxygen by absorption of the alveolar hæmorrhage.

5. The fever in the acute attacks was a reaction to mass lysis of red cells in the alveoli. The white count, which early in the acute attacks showed a relative or slight absolute leucocytosis, was also related to the alveolar hæmorrhage as opposed to the marked leucocytosis (25,000 to 40,000) which would be expected with the same degree of pulmonary consolidation of pyogenic origin. The transient normochromic anæmia paralleled the severe pulmonary hæmorrhage.

6. The "induration" of the lung can be explained as being secondary to long-standing anoxæmia as can the cuboidal condition of the respiratory epithelium. These changes would render the aeration of the circulating blood still more defective.

7. The interstitial and lymphatic pulmonary œdema, the hilar lymphadenopathy, and the lymphoid hyperplasia in the spleen were manifestations of local and systemic reactions to the phagocytosis of the massive lung hæmorrhage.

The above offers a rational clinico-pathological correlation of the findings in our case but leaves an unknown primary lung condition productive of anoxic anoxæmia. Wyllie *et al.* and others have mentioned the possibility of the primary abnormality being structural for, like us, they have no rational scheme to include the hypoplasia of the elastica as an effect rather than a cause. Thus the child may have been born with relatively rigid inelastic lungs and the anoxæmia followed from defective pulmonary ventilation; a condition which would lead to a vicious cycle in regard to pulmonary fibrosis. It can hardly be doubted that forced inspirations acting on an inelastic lung produced the pseudo-cystic appearance of the sub-pleural and juxta-septal air sacs and that this appearance represented an accentuation of the normal architecture. A theory based on a primary structural abnormality appears to us to be weak in certain respects. Thus permanent structural defect hardly explains the striking periodicity of the severe attacks. Progressive fibrosis and inelasticity hardly tally with a history where the breathlessness, fatigue and cyanosis of effort became, as far as we can ascertain, less noticeable after the second year of life. Again one might have expected primary inelasticity of the lungs to be associated with a reduced pulmonary capillary bed and with chronic right heart failure. Neither of the latter obtain. We thus return to the capillary vessels and stress the gross and extensive nature of the diapedesis which must have demanded massive and universal dilatation of the capillary vessels. As far as we can ascertain from the clinical history this dilatation must have been of relatively sudden onset and moreover it is unlike the findings in other fatal pulmonary conditions where one finds gross diapedesis in that the dilatation and stuffing of the vessels with blood have passed off, for, although some are dilated, on the whole the post-mortem is of tortuous, thick-walled, wide-bore capillaries which are largely collapsed. We cannot conceive of this capillary dilatation being secondary to defective pulmonary aeration alone since we consider that the asphyxial condition, becoming much worse with the pulmonary consolidation, would lead to still further capillary dilatation and engorgement when, in fact, it has passed off.

Accordingly we consider that one has to turn to the mechanism of capillary tone itself to find a solution and with the evidence available assume that the primary abnormality is one of defective vasomotor control. Such a hypothesis admits of periodicity, of variation in degree, of massive capillary dilatation abrupt in onset and termination, of development at any age (though generally found in the young the condition need not necessarily start in the first years of life), and of not necessarily always being universal in the pulmonary circulation (Wyllie *et al.* mention progressive involvement of the lungs).

SUMMARY

A case of essential brown induration of the lungs is described and discussed. The condition is characterized pathologically by an extreme degree of brown induration of the lungs and a complete lack of primary pathological change outside the lungs. There are periodic attacks of severe anoxic anoxæmia associated with massive intra-alveolar diapedesis of red cells. The attacks give rise to a characteristic clinical condition referable to symptoms and signs associated with massive blood lysis, defective pulmonary aeration, and right heart failure. Symptoms arise in children from months to 16 years of age. Between attacks there may be signs of deficient pulmonary aeration. The essential nature of the disease is unknown. Attention is drawn to two possible primary conditions—(1) inelasticity of the lungs due to hypoplasia of the elastica; (2) a vasomotor abnormality of the lesser circulation.

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