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Arterio-venous fistula of the lung

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INTRODUCTION

The disease entity known by a multitude of names but which will be referred to in this paper as arterio-venous fistula of the lung is not as rare a lesion as was once thought. In the past few years the number of these cases reported has increased tremendously, and the understanding of the disease becomes important accordingly. This paper is designed to present the prime points of importance concerning this lesion and to review the literature on the subject. It is impossible to present in detail each of the almost 50 cases now reported but a summary of the symptoms, diagnosis, physical and laboratory findings, and radiological determinations can be included. In addition the theory of the etiology of the lesion can be stressed as this appears more and more important with the increasing number of cases described in the literature. The pathology and physiology of the disease and their relationship to the symptomology will also be considered, as will the treatment and its effectiveness. The treatment has been so efficacious that the diagnosis and understanding of the lesion with all its sequellae becomes of primary importance.

There are many names given the lesion. Among these are angioma of the lung, cavernous hemangioma of the lung, arterio-venous varix, arterio-venous aneurysm, and arterio-venous fistula.

As the variety of names implies, the lesion comprises some vascular abnormality in the lungs with abnormal arterio-venous communications. Anatomically the lesion is a hemangioma, but physiologically it is an arterio-venous fistula (4, 52). The signs and symptoms of the disease are determined chiefly by the physiological aspects of the lesion, and, hence, I will refer to it as an arterio-venous fistula of the lung. Later in the course of this paper I will show the pathological relations in the lesion and discuss the physiological sequellae. These lesions are probably all benign, and there are some hereditary factors involved in transmission. This paper will also present some of the hereditary principles involved and the relationship of arterio-venous fistula of the lung to the already well-known syndrome of Rendu-Osler-Weber's disease.

HISTORY

The discovery of the lesion is a relatively recent one. The first description of the disease was at autopsy by Churton in 1897 (9). The case was a 12 year old boy with a loud roaring pulmonary systolic bruit and a highly accentuated second sound during life as well as hemoptysis, epistaxis and dropsy. The findings showed four of the secondary vascular branches in one lung, and three in the other, led into aneurysms as large as walnuts, filled with blood clot. This case was confused, however, as the heart showed several wart-like growths that were firm and smooth on the tricuspid valve and the endocardium near it.

This suggestion of a heart lesion may have been a factor in the failure of recognition of the pulmonary lesion as being one of prime importance. It was not until 1917 when G. D. Wilkens described another case of multiple pulmonary aneurysms (35). C. de Lange and de Vries Robles described another similar lesion at autopsy in 1923 (11). This latter case was in an infant, age two and one-half months, whose lungs at post mortem examination showed 2 pulmonary hemangiomata. These diagnoses were not suspected ante-mortem and up to that time the clinical picture of the disease had never been described. In 1932 Reading described the case of a four year old colored girl who at autopsy showed an arterio-venous communication in the lung with a branch of the pulmonary artery entering and communicating with a venous plexus. The patient in life had shown a murmur, clubbing of the fingers and toes, and cyanosis. This diagnostic triad was to be considered in a few years as important in the clinical diagnosis of the lesion. Laboratory work on the patient showed an increased red blood count and hemoglobin. There was also evident growth retardation. The picture was clinically suggestive of a congenital heart lesion of some kind. The patient died of an unrelated brain abscess, and the autopsy then showed the pulmonary lesion without any heart findings (28). The first case of hemangioma of the lung complicated by a secondary polycythemia was reported by Rodes in 1938 in a 25 year old male. The diagnosis was made post-mortem following death from a pulmonary hemorrhage. The patient had

shown cyspnea, cyanosis, clubbing and epileptiform seizures. He showed jaundice and small hemangiomas on the lips. There was no heart murmur and the lungs were apparently clear. The blood pressure was within normal limits. The hemoglobin was 118 per cent and the red blood count was 7,540,000. There was a normal white blood count and the urine was clear. The patient was fine when five months after he was first seen he was suddenly seized by severe pain below the sternum and in the upper abdomen follow- immediately by hemorrhage from the lungs. He recovered from this attack and died in a subsequent attack one week later. The autopsy was negative except for the lung findings. There was a dark blue saccular mass 2 cm. in diameter in the lower anterior right lung. A similar mass 6 cm. in diameter was found in the posterior portion of the right median lobe. Still another mass, 6 x 3 x 2 cm. was found in the midportion of the upper lobe of the left lung. These were multilocular and filled with blood, and the lining of each of these cystic masses was smooth and thin. The final diagnosis was, of course, multiple hemangioma of the lung with rupture into the bronchus (30). This case once more presented the picture of clubbing, cyanosis, dyspnea, and polycythemia, and was an important contribution to the possibility of making clinical diagnoses. This was similar to Reading's case in 1932 and to one noted by Bowers in 1936 (6). He reported a case of a baby boy well after a normal delivery until the second day when he suddenly became very dyspneic and expired within a few minutes. The autopsy

performed showed a rupture of one of multiple lesions in the lungs with a resulting massive left hemothorax.

The first to make the diagnosis clinically were Smith and Horton in 1939 (32). Their patient was a 40 year old man who had been blue since birth. He had marked clubbing of the extremities and dilatation of the peripheral veins. A bruit was audible over the posterolateral aspect of the thorax in the region of the eighth and ninth ribs. They employed the first use of the contrast-medium X-Ray in diagnosis of this disease and noted a shadow in the right lung. It was over this shadow that the bruit was heard. The laboratory findings in this patient again showed a secondary polycythemia. The red blood count was 6,470,000 and the hematocrit was 66 per cent. Blood volume was 6068 cc (121cc/kilo) as compared to a normal of 85 cc per kilo. The treatment used here was venesection at frequent intervals. Their idea of the lesion was that it was anatomically a hemangioma but physiologically an A-V fistula. They described the hemangioma as an irregular lesion with intercommunicating blood spaces surrounded by fibrillary connective tissue and smooth muscle. The lesions may vary in size from microscopic to several pounds with bruits in the larger ones such as the one in their case.

In 1942 Hepburn and Dauphinee reported a case of a 25 year old woman who had polycythemia, clubbing, cyanosis, and a 70 percent arterial oxygen saturation as well as a shadow in the right middle and lower lobes (18). Their great contribution was

in treatment, however, as they were the first to attempt a pneumonectomy on a patient with this lesion, and they achieved disappearance of her cyanosis, polycythemia, and clubbing. Goldman presented a case of arterio-venous fistula of the lung in each of two brothers. (14). The first was reported in 1943 as a cavernous hemangioma of the lung. The case was successfully treated with a pneumonectomy. This case in two members of the same family became important in the understanding of the etiology of this disease and indicated the importance of heredity in its transmission. This will be discussed at greater length elsewhere in this paper. Janes reported a case of arterio-venous fistula of the lung in 1943 in a 30 year old white female (21). This patient had only cyanosis as a specific finding and some hemangiomas on the lips. Radiological examination showed two shadows in the right lung and 1 or 2 in the left lung. Treatment in this case was prompted by hemorrhage and consisted of local resection of the tumors. Adams, Thornton, and Eichelberger presented a truly "classic" case in 1944 (1). The patient was a 24 year old white female with extreme cyanosis, hemangiomas on the lips, and clubbing. The laboratory reported a red blood cell count of 7,200,000 and a hemoglobin of 23 grams. Blood volume was 12,750 cc of which plasma volume was 2,420 cc and cell volumne 10,330 cc. The treatment here was pneumonectomy. The specimens reported showed a multi-loculated smooth-lined cavity 3 x 4 cm. communicating with the pulmonary artery via a vessel 4 to 5 mm in diameter and with the

inferior pulmonary vein through a channel 1 cm. in diameter. Microscopically these cavities were lined by mesothelial cells on a fibrous connective tissue wall. There was no evidence of any hemangiomatous tissue outside of the cavities. These gentlemen maintained that the lesions were not just cavernous hemangiomas but actually arterio-venous fistulas. Jones and Thompson did a pneumonectomy on a 24 year old white female in 1944 and achieved a disappearance of cyanosis in a few hours (22). This patient was cyanotic since birth. Clubbing of the extremities began at age 9. There was a soft systolic murmur audible over the right lung area; the murmur was continuous but greatly increased on full inspiration and almost disappeared on full expiration. At first a pneumothorax was tried, but it did not close off the fistula. Sisson, Murphy, Newman reported a case of arterio-venous fistula of the lung in a 45 year old colored female (31). The patient showed polycythemia, clubbing, cyanosis, and a lesion in the left lung over which a to-and-fro murmur could be heard. She died shortly after injection of diodrast, and post-mortem examination showed arterio-venous aneurysms in both lungs. In 1946 Makler, Todd, and Zion reported a case in a 17 year old white female (26). This patient was not cyanotic since birth. Her cyanosis and dyspnea came on years later along with clubbing of the extremities. There were also occasional nosebleeds and headaches and a complaint of easy fatiguability. Physical examination showed a murmur in the fourth interspace 5 cm. to the

left of the midline. There were small telangiectases behind one ear. In 1947 Bisgarde reported another case of the same type, this one being in a 20 year old man who presented cyanosis, headaches, blurring of vision, chronic fatigue, and exertional dyspnea (4). There was slight clubbing of the fingers and toes and multiple small hemangiomata of the lips. Laboratory work in this patient showed a polycythemia and a high hematocrit accordingly. A lobe resection was performed and 2 cavernous hemangiomas, 2 x 4 cm. and 1 x 2 cm., were found in the resected specimen. Whitaker reported a case in 1947 also (35). Since that time there have been about 30 new cases added in the literature. In 1949 Yater, Finnegan, and Giffin reported 2 cases of the lesion (38). In that same year Beddard reported a case in a 36 year old man with no clubbing, cyanosis or abnormal physical signs (2). There was a systolic murmur in the right axilla that was faintly heard. The radiological examination showed an abnormal lesion in the lung with no evidence of telangiectases elsewhere. Laboratory reports showed a polycythemia. Since the patient was symptomless, he would not resort to surgical intervention. Another recently reported case was that of Carswell who reported the lesion in a 20 year old male (8). The patient's chief complaints were recurrent mild shooting pains in the interscapular region. The pain lasted several minutes recurring at intervals of a few days to weeks and were not incapacitating. They were unrelated to exercise, emotions, eating or breathing.

A chest film showed an area of increased density in the right lower lobe. This area was about 5 x 4 cm. in measurements on the film and was circumscribed. Bronchograms and bronchoscopy were negative. The patient had mild clubbing and no murmur in the chest. The hemoglobin was somewhat high and there was a normal red blood count to a mildly polycythemic one. Thoracotomy and lobectomy was performed and the lesion was shown to be an arterio-venous fistula of the lung. A review of the literature shows that 48 cases have now been reported. Moyer and Ackerman in 1948 reported a case of pulmonary arterio-venous fistula in two members of a family (27). Drusenberg and Ansmendi reported a case in 1949 in a 26 year old male with four severe hemorrhages in eighteen days. The only characteristic clinical features were hemoptysis and mild polycythemia. Angiography aided the diagnosis (12).

ETIOLOGY

The disease is probably a congenital inherited anomaly and is much more frequent than originally thought. Some of the cases are part of the syndrome known as hereditary hemorrhagic telangiectasia, a well known and relatively common inherited vascular disease. Others have only the lung lesion without any other evidence of multiple telangiectasia (14). Reid states that the embryological explanation for the occurrence of other types of arterio-venous fistula is that the arteries and veins develop

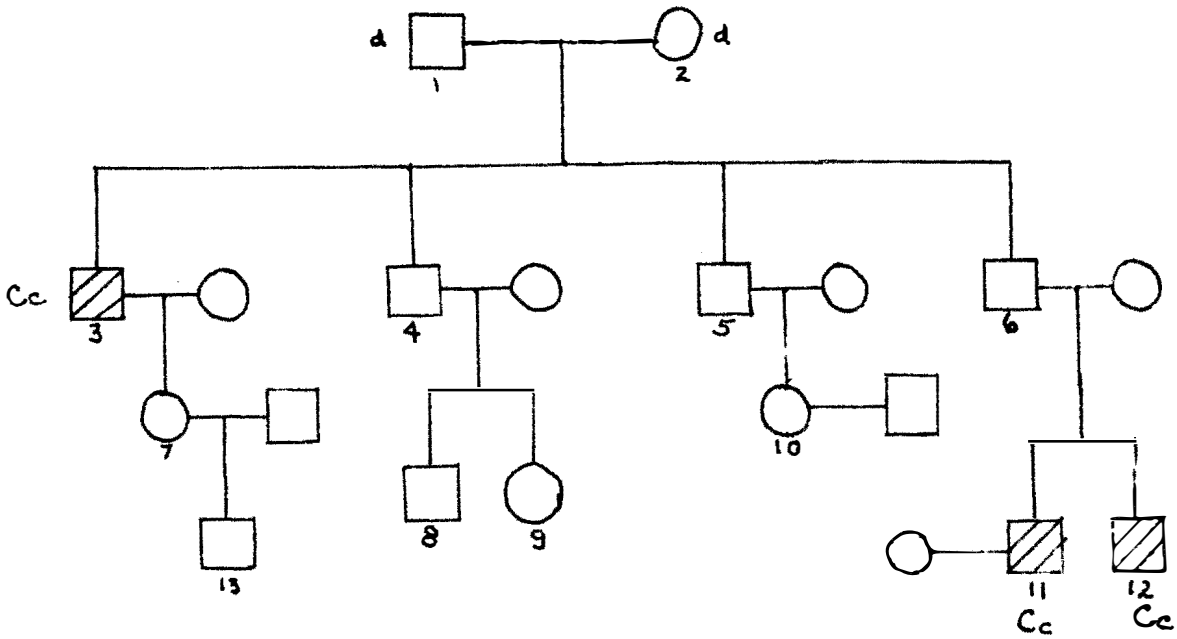
out of a common capillary plexus, so that opportunities for persistent connections are always present (29). Hereditary hemorrhagic telangiectasia was recognized by Rendu in 1896. It was first described by Osler in 1901. Weber noted it later and the disease was then known as Rendu-Osler-Weber's disease. This disease is characterized by typical localized dilatations of small vessels to form telangiectases, angiomata or small ruby points with a tendency to bleed. They occur most commonly on the skin of the face and neck, and on the buccal and naso-pharyngeal mucous membranes. It is inherited -- transmitted as a simple dominant characteristic. (14). Moyer and Ackerman state that there are now over 1000 cases of hereditary hemorrhagic telangectasia. They also feel that the vascular defect is transmitted as a dominant characteristic and that it affects both sexes but more frequently the female. They further have determined that in families with the disease about one-third are affected. The congenital defect is in development of the terminal loops of the capillaries with hemorrhage due to fragility of the small vessels. Coagulation time, bleeding time, platelet count and fragility tests are all normal. Abnormal vessels usually appear between 20 and 30 and are fully developed in the 4th decade, but the age of onset varies from 3 months to 67 years. (27). Epistaxis is the commonest symptom early, but this does not appear before puberty usually. Telangiectasia may be in any organ so that gastro-intestinal bleeding, hemoptysis, hematuria,

melena, and cerebro-vascular bleeding may occur. Goldman has worked out a proposed genetic scheme for the inheritance of the lesion (14). This was correlated to his report of the presence of pulmonary arterio-venous fistulae in 2 brothers in 1945. The C gene is said to be a dominant gene with incomplete penetrance; that is, it may act in a single dose in Cc persons and produce the disease or it may be present in the germ plasm without expressing itself in the soma. An individual with the genotype CC, born of parents each of whom carried the C gene, would probably not survive. This is exemplified by a case report of Snyder and Doan in 1944 wherein a case of death in an 11 week old infant is reported (38). This infant had hereditary hemorrhagic telangiectasia with multiple lesions over the entire skin and in all internal organs. Both parents had the disease. This is the first recorded case of a homozygous form of the disease and the men reporting it feel that the gene for multiple telangiectases is lethal when homozygous.

The scheme of inheritance in Goldman's listed family is:-

C - - dominant gene -- carried the hemorrhagic telangiectasis factor.
c - - normal and recessive.

Cc ⇌ cc



Numbers 1 and 2 are probably Cc and cc - no stigmata of the disease.
Number 3 died at 46 of "flu" - cyanotic all his life with marked clubbing of his extremities and yet worked till time of death. Probably an arterio-venous lesion.
Numbers 4 and 5 - had negative X-rays.
Number 6 (father of the 2 cases) showed no clinical evidence of the disease but X-ray shows definite widening of the right hilar region strongly suggesting dilated pulmonary vessels. May be a silent arterio-venous fistula.
Numbers 11 and 12 are the two reported cases.
Number 13 died at age 9 supposedly of complication following a birth injury.

Fitz-Hugh maintains that the hereditary factor is constant and that where it cannot be demonstrated, the failure is due to atavism (15). One generation may be spared the lesion, but it will appear in the next. Teahan supported the hereditary phase of the disease by tracing hemorrhagic telangiectasia through six generations of one family (34).

The importance of this genetic study is obvious when one realizes that many of the reported cases of arterio-venous fistula of the lung also show some telangiectatic lesions elsewhere. For example, the cases reported by Bisgard, Adams et al, and Janes showed the presence of hemangiomata on the lip as well as the pulmonary lesions (4, 1, 21). In total the finding of telangiectases elsewhere in the body in association with hemangioma of the lung suggests that the pulmonary lesion is another telangiectatic manifestation. This is present in about half of the cases of pulmonary arterio-venous fistula. In the other half, no extrapulmonary telangiectases are present. (14). Cappon reported a case of hereditary hemorrhagic telangiectasia in a thirty-one year old female whose chief complaint was repeated epistaxis since age ten (7). She had evident multiple telangiectasiae, and a report of her family history showed that there were four generations in the family with similar vascular lesions. When she was free of attacks of bleeding she developed polycythemia with a red count up to 6,250,000 and a hemoglobin of 112 per cent. Cappon attributed this to an overcompensation

device, and although no mention was made of the lungs, the polycythemia was probably due to an arterio-venous fistula of the lung present in this patient. Another example of the hereditary aspects of the problem is Goldstein's case in 1921 (15). This case was in a 52 year old woman with a history of nose bleeds, multiple telangiectasia, dyspnea on exertion, clubbing of the extremities, and cyanosis. There was no evidence of any cardiac abnormality, and here too a check into the family history showed others with telangiectasis. All these case reports and the coexistence of telangiectases and arterio-venous fistula of the lung show some definite relation between the disease and the older disease known as Rendu-Osler-Weber's disease. Basically there is a genetic background for the vascular lesions, and the location of the lesions may be varied and multiple. The existence of a pulmonary arterio-venous fistula apparently is one manifestation of the disease, or at least a disease with a similar heredofamilial background.

PATHOLOGY AND PHYSIOLOGY

The pathology and physiology of the disease must be considered together because of the close correlation of the two to each other, and because of the definite relationship of both to the symptomatology. Basically the reports of the lesion discovered in all the reported cases are similar. The usual pulmonary arterio-venous fistula is composed of a distended thin-walled

afferent artery, distended efferent veins, and an intervening loculated vascular sac or labyrinth of distended vessels. All these vascular components gradually become more dilated, and degenerative changes may occur. This degenerative type change causes more inter-communications to form and may lead to rupture with hemorrhage into the pulmonary parenchyma or pleural sac (38). Moyer and Ackerman feel that the communications are not through capillary beds at all but always through distended vessels. Their theory of the pathogenesis is that there has probably been a gross deviation of capillary formation (27). The small cutaneous and mucocutaneous telangiectases or angiomas are characterized by disseminated abnormalities of capillaries, small venules, and small arterioles. They vary from typical spider nevi to pea-size hemangiomata. They may involve any organ - including the lung - and they may rupture easily. In patients with these lesions one should be aware of not only the existence of other vascular lesions elsewhere in the body, but also of the possibility of other congenital anomalies. As far as the lung is concerned, the general agreement is with the statement of Moyer and Ackerman. Makler and Zion feel that the lesion consists of a knot of blood vessels connected by feeder vessels with both the pulmonary arterial and venous systems (26). This becomes important in understanding the right-to-left shunt established and the symptoms secondary to this. Lindgren also feels that there is no capillary communication at all, but that the blood passing between the artery and the vein or veins

flows through one or more malformed branch vessels in a direct route. This again illustrates the principle of the right-to-left shunt or as Lindgren terms it, "a short circuit". (24). Smith and Horton, and Bisgarde both note the pulmonary lesion to be a hemangioma anatomically but an arterio-venous fistula physiologically (4, 32). Hemangiomas are irregular, intercommunicating blood spaces surrounded by fibrillar connective tissue and smooth muscle as Smith and Horton describe them. They may vary in size from microscopic to several pounds. Bruits are evident only in the larger ones. Additional facts concerning the gross characteristics are that over 50 per cent are multiple (38). As has been previously mentioned Moyer and Ackerman feel that the age of onset may vary from 3 months to 67 years but the abnormal vessels usually appear between 20 and 30 years of age and are fully developed in the fourth decade of life (27). The cases reported substantiated this idea. Microscopically the cavities may be seen to be lined by mesothelial cells on a thin layer of connective tissue, fibrous in nature (27).

Carswell illustrated the lesion in the case he reported earlier this year. His drawing shows a typical lesion. There was a thin pleural lining on this cyst-like affair with the lobe outside of the lesion normal (8). This is the reported drawing:-

A - pulmonary artery branch.

B - bronchus.

V - pulmonary vein branch.

A-V - arterio-venous fistula.

Malignant hemangioma of the lung may occur and there have been a few cases reported. Hall reported a case in a 40 year old married white female (16). Here there were multiple metastases. The type cell was an endothelial cell similar to the type which forms blood vascular spaces, and which did form these vascular spaces in the tumor nodules. Wollstein reported a case in an infant, age 4 months and 20 days (37). This was diagnosed as a malignant hemangioma - a sarcoma. There were metastases from the right lung to bronchi, small intestine, pancreas, suprarenal gland, adipose tissue, abdominal sympathetic ganglion, scalp, and lip. There have been no cases reported of malignancy in the arterio-venous fistulae as discussed in this paper.

These pathological studies are directly concerned with the symptoms of the lesion because of the physiological sequellae to the fistula. Basically an arterio-venous fistula not caused by trauma, infection, or degenerative changes in the walls of blood vessels is a form of cavernous hemangioma. The size of the vascular channels varies considerably, and with this variation comes a difference in physical findings and symptomology. When large arteries and veins are present, a free communication between the arterial and venous systems may be established. The result of this is a shunt of a lot of venous blood from the pulmonary artery to the pulmonary vein and the left auricle. Since the blood passing through the shunt does not go through the capillaries of the lung, it is not oxygenated in the normal manner.

Because the lung has a dual blood supply from the pulmonary and bronchial systems, one or more branches of both systems may join with the cavernous hemangioma. A large communication between the pulmonary artery and vein means a tremendous right-to-left flow of blood and the sequellae, of that in the form of cyanosis, clubbing, and a secondary polycythemia (25). Bisgarde feels that at least 25 per cent of the blood must be shunted before cyanosis can occur. He also notes that the direction of the blood flow in the pulmonary fistula is opposite to that in a systemic shunt. This means that much of the blood leaving the left ventricle is venous and not saturated with oxygen so that some degree of cyanosis is constant. The same constancy is true of secondary polycythemia. The degree of both the cyanosis and the polycythemia depends on the size of the fistula (4). In other words, it may take years for the fistula to get large enough to produce the evident signs and symptoms. The important thing to note is that the lesion in some measure is compensated for by a secondary polycythemia, but that all the sequellae are due to the anoxemia primarily. The two factors of importance in determining the presence and the degree of symptoms are the size of the fistula and the duration of the lesion. With large fistulae the bone marrow is stimulated to form more red blood cells (10). The blood volume is, therefore, increased with most of the increase being due to the greater number of erythrocytes. It is evident then that the hemoglobin and the hematocrit must increase also (38).

There have been cases reported in which there has been no cyanosis and polycythemia, but where the diagnosis of arteriovenous fistula of the lung has been suggested on physical examination by a loud murmur over the involved part of the lung. Maier et al feel that here the lesion involves the bronchial arteries rather than the pulmonary system. The bronchial arteries would bring the blood to the fistula and under greater pressure than were the pulmonary vessels alone involved. The chief danger here is hemorrhage because of the increased pressure in the hemangioma (25).

SYMPTOMATOLOGY AND PHYSICAL FINDINGS.

The pathology of the lesion as well as the circulatory dynamics have already been discussed. This brings to a sharper focus now the understanding of the symptomatology and the physical findings. The chief patho-physiological basis for symptoms is anoxemia. This will give us a secondary polycythemia with all its manifestations as well as the clubbing of the extremities and cyanosis. Occasionally a pulmonary hypertrophic osteoarthropathy has been seen. Other manifestations of the disease are dyspnea on exertion, weakness, precordial pain, convulsions, unconsciousness, dizziness, diplopia, cerebro-vascular accidents, numbness, faintness, palpitation, headache, thick speech, and emesis. Many of these are due to the compensatory polycythemia. Yater, Finnegan, and Giffin reported two new cases in 1949 and also summarized the 45 cases reported up to that time including

theirs (38). Their statistical report is extremely interesting and informative, and none of the few cases reported since then have changed the material perceptibly. Their list is as follows:-

SYMPTOMS	PRESENT	ABSENT	NOT STATED
Cyanosis	53	3	9
Clubbing	51	3	11
Bruit	26	3	16
Dyspnea	23	2	20
Epistaxis	14	2	29
Weakness	13	3	29
Cardiac Abnormalities	9	24	12
Convulsions	9	4	32
Hemoptysis	8	2	35
Chest Pain	8	3	34
Unconsciousness	8	3	34
Dizziness	7	4	34
Cerebrovascular accidents	4	0	41
Numbness	5	0	40
Splenomegaly	3	4	38
Vomiting	3	4	38
Faintness	3	3	39

This list is a good summary of the physical findings and symptoms of the disease. There have been a few variations in the more recently reported cases. Beddard reported a case with no clubbing or cyanosis (2). Carswell reported a case with the chief complaint

of mild shooting pains in the interscapular region lasting several minutes at a time and recurring at irregular intervals of a few days to a few weeks (8). Drusenberg and Ansmendi reported a case where only a mild polycythemia existed and there was some hemoptysis (12). The presenting features in any given patient may be the results of the polycythemia such as thrombotic episodes or may be massive hemorrhage from the fistula rupturing - especially where there is a connection with the bronchial artery. A murmur is often heard over the lesion itself and is usually continuous. There is often a systolic accentuation. It is usually most intense on deep inspiration and may even fade on expiration. Occasionally the murmur is entirely diastolic and increased on inspiration. The heart is usually not enlarged because the strain on the right ventricle is slight since the pressure in the pulmonary circulation is low. In the table listed cardiac abnormalities are not noted to be a constant finding. The heart output stays normal. Many of these facts are important in differentiating the disease from a congenital heart as the symptoms may be very similar. The actual differential diagnosis will be discussed later in this paper. Venous pressure is usually within normal limits. Arterial oxygen saturation is decreased and so may the vital capacity be decreased. Splenomegaly is only an occasional feature. Basically, then the cyanosis, clubbing and polycythemia are the highlights of the presence of a pulmonary vascular fistula. It is interesting to

note that there are different physiclogical effects in pulmonary shunts than in peripheral shunts and the symptoms are consequently considerably different. In a peripheral fistula the increased blood volume is a result of a fairly proportional increase in plasma and red blood cells, and the heart may be enlarged, the oxyhemoglobin saturation is normal, and the cardiac output is increased. Cyanosis and clubbing do not result, therefore, from a peripheral fistula (20). The difference in response to treatment is striking also, as the results in pulmonary fistulas are excellent, but peripheral fistula excision may leave a limb with chronic vascular insufficiency since the collateral circulation may be adequate when the tissue is at rest but not when it is active (5).

DIAGNOSIS

It has already been noted that there are very definite clinical findings that are highly suggestive of the presence of a pulmonary fistula. The importance of family history is obvious with the apparent relation of this lesion to hereditary hemorrhagic telangiectasia. The establishment of a diagnosis must depend on two other means, however, and these are the laboratory and the X-ray. The laboratory findings are rather uniform and hence significant. In the Yater survey the chief laboratory reports were not included in all the cases. The more recently reported cases do list laboratory findings and would bear out the fact that the red blood count is elevated to the polycythemic level,

the oxygen saturation is down below 90 per cent, the hemoglobin is increased, the hematocrit is greater than normal, and that the blood volume is increased. Yater's summary is included here since it does illustrate the importance and incidence of these findings in the case reports in which they were included (38).

	Present	Absent	Not Stated
Polycythemia	28	5	12
Oxygen saturation (less than 90 per cent)	12	0	33
RBC (5 million)	above 28	below 4	13
Hemoglobin (15G is 100 per cent)	above 25	below 5	15
Hematocrit (50 mm)	above 10	below 3	32
Blood volume	increased 9	0	36

The lowest oxygen saturation in this series was 63 per cent. The highest red blood cell count was 11,450,000. The highest hemoglobin was 24.9 grams and, on the basis of 15 grams being 100 per cent, this represents 155 per cent. The highest hematocrit was 82, and the greatest blood volume was 12,900 cc or 161 cc per kilogram of body weight. It is apparent than that a routine blood count, hemoglobin, and hematocrit should be done in every suspected case. If the evidence shows some polycythemic trend, a blood volume study and an oxygen saturation measure would be of aid. Landowne has shown that tests used to support the diagnosis of right-to-left shunt in congenital heart disease are also good for diagnosing pulmonary arterio-venous fistula.

Intravenous ether is injected and one would expect peripheral manifestations of the ether or possibly a reduction in the arm-to-tongue circulation time depending on the size of the shunt and the amount of the material used for the test (25). Benenson and Hitzig also note the value of doing ether circulation time tests in diagnosing a vascular shunt, and what is of greater importance is that it is useful only in a right-to-left shunt as only then can the ether be manifest peripherally (3). Electrocardiograms will usually be normal in this type of disease as the heart is rarely affected, but occasionally one may note some right or left axis deviation. Nodal tachycardia and premature beats have been noted during operative intervention, but this is of no aid in diagnosis since any change in the heart clinically is absent or minimal. Biochemical determinations are normal except for the fact that the CO_2 combining power or alkaline reserve of the blood may be slightly depressed.

The value of radiological studies is now well established. The X-ray picture is characteristic of the lesion. The lesion is visible on plain film but angiocardiograms are pathognomonic. On a routine film a lobulated opacity is seen with bandlike linear or sinuous opacities connecting with the hilus. These are seen in angiocardiography very clearly, the bandlike connecting densities being the afferent and efferent pulmonary vessels. Fluoroscopy may demonstrate pulsations in the lobulated density or in the band-like structures between the density and the hilus. (24).

The band-shaped structures are often seen to communicate with one another in the periphery either through more vascular formations or more rounded ones resembling tumors. The vascular communications with the hilus vary in size according to the pressure conditions in the thorax. Makler and Zion were the first to attempt the Valsalva experiment in aiding radiological diagnosis (26). Here the pressure in the thorax is altered by having the patient try to expire with his mouth closed and nostrils occluded and inspire the same way. First there is a decrease and then an increase in the size of the feeder vessels as the negative pressure is made lower and then increased. Mueller's test is another aid. This consists of deep expiration followed by forcible inspiration against the closed glottis and will cause an increase in vessel size. Pulsation of the vessels may be proved by the use of kymography. In Drusenberg and Ansmendi's case laminagraphs and plain films showed large pulmonary vessels connected with an intrapulmonary mass, but accurate diagnosis could not have been made without the use of angiography and rapid film changing technique. The rapid technique permitted taking a large number of pictures in rapid succession. Rapid films taken 15 to 20 seconds after injection show the afferent artery, the arterio-venous fistula, and the efferent vein. The technique is also valuable in diagnosis of multiple lesions. Lesions hidden behind the dome of the diaphragm or behind the cardiac shadow, or small lesions not demonstrable in ordinary roentgenograms may

be seen by the use of angiocardiography. Although planigraphy is of aid, it is not as specific as angiocardiography (12).

DIFFERENTIAL DIAGNOSIS

This lesion must be differentiated clinically from any others producing similar symptomatology, and from other diseases with similar laboratory or radiological findings. Chief in this group of similar diseases are polycythemia vera, congenital heart disease, emphysema, Ayerza's disease, chronic pulmonary lesions producing polycythemia and clubbing, and lung tumor. Since polycythemia is so constant a finding in pulmonary arterio-venous fistula, the differential diagnosis between the lung lesion with secondary erythrocytosis and polycythemia vera is important. There is no cause evident for true or primary polycythemia. The cyanosis that is present is "reddish" rather than the true blue cyanosis of arterio-venous fistula of the lung. Splenomegaly is usually striking in polycythemia vera whereas it is insignificant or absent in the lung lesion type. Another point of great difference is the great leukocytosis and platelet count increase in polycythemia vera along with the presence of immature cells in the peripheral blood (17). Of course, the physical characteristic of a murmur in the lung fields and the typical X-ray findings should make the arterio-venous fistula obvious. Congenital heart disease may confuse the diagnosis by presenting a very similar clinical picture of clubbing, cyanosis, and a secondary polycythemia. There are often very early signs of

cardiac disease in the congenital heart, whereas the pulmonary lesion may not become evident until much later in life. In addition the electrocardiographic findings may show some heart defect in a true cardiac disease, but none where the primary pathology is pulmonic. The best diagnostic criterion, however, is the X-ray where the picture shows normal lung tissue in congenital heart lesions, or at least will fail to show any evidence of abnormal vascular communications in the lungs. Emphysema is usually seen to produce great dyspnea on mild exertion and has a typical pulmonary picture on roentgenograms - very different from the lesion when a pulmonary hemangioma is present. Ayerza's disease or any other chronic pulmonary disease producing some fibrosis, anoxia, and subsequent cyanosis, clubbing and secondary polycythemia can be noted as different on the basis of lung findings. The chest film will often show marked pulmonary fibrosis and emphysema with cor pulmonale, and enlarged right heart sequellae may be demonstrated clinically. Other tumors of the lungs may be ruled out by history most often, but certainly angiocardiography is the most specific method. In short, the syndrome associated with pulmonary arterio-venous fistula is very characteristic along with the typical laboratory findings and radiology findings. It need not be mistaken for any other disease. The chief differentials to be made are from polycythemia vera and congenital heart disease. It is interesting to note that in true polycythemia the lungs show a typical picture too.

They may show two types of nodular lesions:- one, a conglomerate tubercle which differs in no way from the formation often found without any polycythemia present, and the other a sharply defined nodular lesion which appears to be characterized by multiplicity, homogeneity, and transientness, leaving a residue (19).

COMPLICATIONS

The chief complications of the lesion are those due to the compensatory polycythemia. A continued severe demand upon the bone marrow may lead to an actual exhaustion of the marrow. Although the total blood volume increases, the greatest increase is due to the huge number of red cells in the peripheral blood, and consequently there is an increased blood viscosity. This increase in viscosity increases the load on a heart already having some difficulty because of the anoxemia per se. Eventually heart strain may become evident, and this may be true in those cases showing some right or left axis deviation on electrocardiographic tracings. Many of the difficulties are seen secondary to thrombotic episodes and the thrombosis itself is attributable to the polycythemia. According to Makler and Zion duodenal ulcers are often seen with polycythemia, and these may be due to thrombotic phenomena (26). Cerebral thrombosis is a very serious complication and was noted in 4 of the 45 cases summarized by Yater and his group. The thrombi may hit any organ or system in the body and consequently the number and types of

complications due to them are varied. One major complication is that of hemorrhage from a rupture of the fistula. This may be so massive as to be fatal. Bowers's case, previously mentioned, in an infant boy showed massive and fatal hemorrhage secondary to rupture of one of multiple lesions in the lungs. This danger of hemorrhage is greatest when there is a bronchial artery involved in the vascular lesion as the pressure in the lesion is, therefore, greater. When the fistulas are well within the parenchyma of the lung, the danger of serious hemorrhage is less than when they are subpleural.

TREATMENT AND PROGNOSIS

Treatment of the lesion is definitely surgical, and the results have been excellent. Surgery is indicated even in the absence of many symptoms since the danger of fatal hemorrhage is always present. Removal of the fistula can be done by local excision, lobectomy, or pneumonectomy. Hepburn and Dauphinee in 1942 performed the first pneumonectomy on a patient with the disease and achieved complete disappearance of her symptoms. The lesions tend to be multiple and because of this fact and also the possibility of additional arterio-venous fistulae becoming manifest later, conservation of pulmonary tissue is indicated. If local or segmental resection is feasible, it should be done. Usually, a lobectomy or a pneumonectomy is required. Because of the possibility of associated vascular anomalies, one should

be certain that there are adequate channels left for return of blood to the left heart. Jones and Thompson presented a case with a single pulmonary vein (22). Hepburn and Dauphinee as well as Jones and Thompson first attempted pneumothorax, but this was not successful. Ligations likewise are not satisfactory. Temporary relief of the polycythemia may be obtained by venesection, but this is not a recommended therapeutic measure for a cure. For solitary lesions, lobectomy or partial resection is usually satisfactory. Even solitary lesions, however, when they are massive require at least lobectomy. Because of the danger of fatal hemorrhage, surgery should not be delayed (21). Moyer and Ackerman feel that surgery is indicated only in symptomatic cases; they feel that the rest can be followed with X-ray and blood counts. Bisgarde maintains that symptoms do not have to be noteworthy to warrant surgery as the danger of fatal hemorrhage and thrombotic episodes is great whether symptoms are present or not (4). After removal of the lesion the symptoms usually disappear promptly. Maier reported interesting results in his case post-operatively. There was a high partial pressure of carbon dioxide in the arterial blood. This was still present after two weeks, but the blood showed normal values four months later. Pre-operatively the partial pressure of carbon dioxide in the arterial blood was somewhat elevated because of the mixture of venous blood with arterioal blood via the shunt. After surgery the maintenance of a high arterial carbon dioxide

pressure must have been due to a high alveolar carbon dioxide pressure due in turn to hypoventilation. This finding is probably due to the effect of the change in acid-base relationships on the respiratory center occurring after closure of the shunt (25). No change similar to this occurs in the peripheral-type shunt. In general, the surgical excision treatment is very effective and results have been excellent. The results in the 45 cases reported by Yater et al show that of the 45 cases only 26 were operated. Of these, 17 were cured and 2 showed improvement. Two died post-operatively; four were not reported as to post-operative condition; and only 1 case remained unchanged (38). It is doubtful that a patient could have a normal life expectancy with a symptom-producing arterio-venous fistula of the lung if left untreated. The possibility of other lesions occuring is not known. The prognosis in general is poor if untreated, and excellent if treated by surgical removal of the lesion. In the event of recurrence of the lesion elsewhere, local excision or segmental resection would most certainly be advisable.

CONCLUSION

A pulmonary arterio-venous fistula is not as rare as was once thought. The lesion is anatomically a cavernous hemangioma, but physiologically a fistula. The fact that there is some relation between this lesion and the syndrome known as Rendu-Osler-Weber's disease has been established. There is some

hereditary background associated with the etiology. The size of the shunt and the symptoms are directly related, and the size of the shunt and the degree of oxygen saturation of the blood are inversely related. Basically the lesion produces a right-to-left shunt with an anoxemia and all its sequelae. The commonest symptoms and findings are cyanosis, clubbing of the fingers and toes, and a secondary polycythemia. Most other symptoms are secondary to the polycythemia as are the bulk of the complications. Laboratory tests are invaluable in the diagnosis of this disease. The use of the roentgenogram with special emphasis on the importance of angiocardiography has been discussed. Since over 50 per cent of the lesions are multiple, treatment must be widespread. Treatment is surgical and is either local excision, segmental resection, lobectomy, or pneumonectomy, but at least it is known that the removal of the entire fistula is vital. Those with the lesion have an excellent chance for normal life if the treatment is active and adequate, but the prognosis is poor if the treatment is delayed as the dangers of thrombotic episodes secondary to the polycythemia and fatal hemorrhage by rupture of the fistula are always present. The signs and symptoms of the lesions, the laboratory findings, and the radiological findings are very specific, and the presence of an arterio-venous fistula of the lung need not be overlooked.

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