Specialty Conference

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Pulmonary Arteriovenous Communications in the Lung

JOSEPH CUMMISKEY, MD:* This morning we plan to discuss the management of two patients with Rendu-Osler-Weber syndrome, and also to discuss the use of nuclear isotope scanning in this disease and in estimating pulmonary vascular shunts. A 33-year-old woman, a divorced mother of two, came to the Palo Alto Medical Clinic. When she was 22 years old, left hemiplegia and aphasia developed suddenly, and cleared in three to four days. She was taking birth control pills at that time and this was discontinued. Findings on carotid arteriography were inconclusive. Twelve months later, hemoptysis, blood in the feces, dyspnea, poor vision and dizziness developed. No cause was found, but these manifestations cleared spontaneously. She resumed using birth control pills.

EUGENE D. ROBIN:† A condition that appeared to be thrombotic disease involving the central nervous system developed in this patient and subsequently arteriovenous communications were demonstrated. How should the differential diagnosis be approached? Is it clear that the original episode was cerebral thrombosis related presumably to the use of birth control pills? The cerebral vascular disease in this patient could be related to many disorders which produce focal abnormalities of the central nervous system. A diffuse approach to differential diagnosis becomes almost unmanageable because anything is possible.

To be orderly in one's thinking and given two events that can be connected by a single diagnosis, one should favor the single diagnosis rather than assuming that the two events are unconnected. A philosophical approach which is useful in differential diagnosis is known as Ockham's razor. William of Ockham, a 14th century British philosopher, was a nominalist, that is, a believer in the theory that there are no universal essences in reality. Ockham's razor states that the fewer hypotheses required to explain several phenomena, the more likely it is that a correct one will be selected. That is how the word *razor* comes in—one

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shaves the number of hypotheses. The application of Ockham's razor to medicine dictates that a differential diagnosis should be as tight and economical as possible. The physicians caring for this patient used Ockham's razor as follows: The use of birth control pills leads to local thromboses, causing cerebrovascular disease. This is logical because there is substantial evidence that the use of the pill does lead to localized vascular disease, including vascular disease of the brain. Can an alternative hypothesis be given involving arteriovenous (A-V) fistulae?

GEORGE CAUGHEY:* There may have been a brain hemorrhage because of an A-V malformation in the brain.

DR. ROBIN: The thesis would be that A-V malformations lead to cerebral hemorrhage. These vascular malformations are known to be quite thin walled and often bleed (hence the term hemorrhagic). Cerebral hemorrhage is unlikely; the effects of intracerebral hemorrhage tend to be devastating even when bleeding in minor. She recovered completely in three days. Since this is a pulmonary conference can you think of a hypothesis by which pulmonary A-V fistulae could give rise to cerebrovascular lesions?

GEORGE CAUGHEY: There might have been an embolic event because any thrombus or embolism arising in the right side of the heart could pass through the lung.

DR. ROBIN: Good. With A-V fistulae in the lung, the filter function of the pulmonary capillaries which are about 8 micra in diameter is lost. One possibility is that there were A-V fistulae in the patient's lungs that permitted an embolus arising on the right side to traverse sequentially pulmonary veins, left atrium and the systemic circulation to the brain—so-called paradoxical emboli. This discussion may not be as tangential as it sounds because Dr. Goris is going to tell us that he uses paradoxical *emboli* to detect and quantitate the degree of right-to-left shunting in such patients.

DR. CUMMISKEY: Is there not another cause for a cerebral vascular accident (CVA) in this type of case, thrombus formation from increased blood viscosity secondary to the polycythemia of chronic hypoxia?

DR. ROBIN: Is that an acceptable application of Ockham's razor? This requires several extra hypotheses. You add both hypoxemia and erythrocytosis. Both are possible; however, not all pulmonary A-V fistulae give rise to substantial hypoxia and secondary polycythemia.

MICHAEL GORIS, MD:† There is another consideration which is purely statistical. Here is somebody who at age 24 has had three CVA's, which could be emboli. Without A-V fistulae to transmit pulmonary emboli, many of these might have been asymptomatic. However, with pulmonary A-V fistulae, some of these became clinically apparent as brain emboli.

DR. ROBIN: Your point is a good one, and raises a basic issue. I believe that normal people have pulmonary emboli frequently. Trapping emboli is one of the important functions of the lung. Small pulmonary capillaries trap particulates entering the venous circulation. These pulmonary emboli may account for the 5 percent incidence of perfusion defects in perfectly normal people.[1] I can visualize in our patient, then, small showers of paradoxical emboli, one of which happened to involve a critical area of the brain and became clinically manifest. When everything is known about pulmonary emboli, I believe one of the concepts that will emerge is that pulmonary embolism in a sense is a normal process. Most emboli are relatively small, and do not produce the clinical disorder that we call pulmonary embolism.

DR. CUMMISKEY: The patient began to take birth control pills again and again a left hemiplegia developed. She stopped taking the pills and hemiplegia cleared in a week, and again it was assumed that the vascular disease was related to birth control pills. At that time, she was admitted to the Jewish Hospital in Brooklyn. Hematocrit was 55 percent and hemoglobin was 18 grams per dl. The electrocardiogram was normal. An x-ray study of the chest showed multiple circular lesions in the right lower lobe and left lower lobe and one lesion in the right upper lobe which appeared vascular on tomography. Cardiac catheterization showed normal right heart pressures; cardiac output, 6.7 liters per minute; cardiac index, 3.6. Arteriovenous oxygen difference was 4.1 volume percent; arterial oxygen pressure (Po_2), 59 torr; pH, 7.48; arterial carbon dioxide pressure ($Paco_2$), 30 torr on room air. On pulmonary angiography

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multiple pulmonary A-V fistulae were shown in the left lower lobe and the right middle lobe. In the right lower lobe there were three A-V fistulae and one fistula in the right upper lobe. Resection was carried out at that time, with removal of the left lower lobe fistula. Then the left lingular fistula was removed with a subsegmental resection.

JAMES THEODORE, MD:* Do you think that is a curative procedure when dealing with large A-V fistulae? Do you think that once they have removed some of the fistulae, there will be no more problems?

DR. CUMMISKEY: That is a loaded question. If you knew she had Rendu-Osler-Weber syndrome, the answer would be no.

DR. THEODORE: Let's just stay with A-V fistula.

DR. CUMMISKEY: If it was congenital A-V fistula and you removed all of the fistulae, it might be a curative procedure.

DR. THEODORE: That is hard to say. There are a number of circumstances in which they are multiple. When larger fistulae predominate there is always the possibility that the small ones which were relatively inapparent may become more apparent with time. Although surgical operation is the procedure of choice under such circumstances, there is always the possibility that there will be recurrence.

DR. CUMMISKEY: But looking through the literature on A-V malformation, I have seen more than six reports showing that removal of the A-V malformation is curative.[2]

DR. THEODORE: I am not saying patients are not cured of symptoms at that time. The point I am trying to make is that there is always a possibility that another one may develop later. I cannot give you the actual percentages.

DR. ROBIN: Recur?

DR. THEODORE: They have probably been there all along.

DR. ROBIN: The Rendu-Osler-Weber lesions represent, as far as I know, a congenital malformation. My impression of the disease is—and if I am wrong tell me—that persons with the Rendu-Osler-Weber syndrome are born with a preformed package of A-V communications.

PATRICIA LYNNE-DAVIES, MD:† Are they fully functional though? If in a patient there were two or three which were contributing to a major extent to hypoxemia and which were resected, is it possible that for the next few years some of the remaining communications by redirection of flow might have a more profound effect?

DR. ROBIN: That is an intriguing idea. It appears reasonable to consider that the regulation of flow through A-V fistulae is a dynamic process. Therefore, long-term alterations of pressure-flow relations might alter the contribution of shunts to hypoxemia and might create the impression of formation of new communications.

DR. THEODORE: I did not mean to imply that new ones were forming either in this circumstance or when there are isolated pulmonary AV fistulae.

DR. ROBIN: Let me say that I think that surgical operation, when possible, is by far the best approach for patients who have pulmonary A-V fistulae.

DR. CUMMISKEY: Well, that obviously was the thought in this case, as well. Now the question comes up as to how often reoperation should be considered? There was moderate relief of symptoms with surgical therapy, and there was no further hemoptysis in this patient after the procedure until the age of 28. Then a left CVA developed. This time she was not taking birth control pills, which would argue against your feeling, Dr. Robin, that the birth control pills were contributing to the development of thrombosis.

DR. ROBIN: That was not my conclusion. I suggested that given several possibilities for disease in the brain, I would have picked either A-V communication with hemorrhage or an A-V fistula in the lung with paradoxical emboli. Then Dr. Goris asked if it was possible that there were numerous pulmonary emboli. I answered that this was possible and that birth control pills might have accelerated that process.

S. J. SALFEN, MD:‡ Is it not a fact that the Rendu-Osler-Weber syndrome often presents as a cerebral vascular accident, not for any of those reasons but rather because of a brain abscess from the presumed pre-existing A-V malformation?

DR. ROBIN: The literature I have seen does not

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emphasize the complication of brain abscess as it does in patients with right to left congenital heart disease. I, therefore, thought that the reason there may be infection as a presenting sign, is that the filter function of the lungs is lost, and bacteria in the bloodstream find access to the brain.

ALLAN HANCE, MD:* It must be an infected thrombus.

DR. THEODORE: Without even getting into the specifics of the disease, endarteritis or some kind of infection is always a possibility with any kind of vascular abnormality. I am surprised that with these patients it does not occur more often.

DR. ROBIN: The clinical pearl that I am aware of is that patients with tetralogy of Fallot and with pseudotruncus arteriosus not uncommonly present with brain abscess. This manifestation may be the first clue that congenital cyanotic heart disease is present. I am unaware that the same frequency has been noted in patients with pulmonary A-V fistulae. If this is true, then I think one of the mechanisms might involve the entry of bacteria into the left side of the circulation.

DR. CUMMISKEY: The patient maintains that in 1972, after the third episode of CVA, she diagnosed hereditary hemorrhagic telangiectasia in herself and her family. Karen Hamilton, a medical student, provided a family tree. The mother of our patient had severe epistaxis; her maternal grandmother had hemorrhagic telangiectasia, and now her two children—a daughter aged 7 and a son aged 10—have telangiectasia on their skin and mucous membranes, but are asymptomatic. The patient was next seen, in Ohio, in 1972 because of increasing dyspnea and cyanosis. The hemoglobin value was 16.4 grams per dl. An electrocardiogram was normal. Liver and brain scans were normal. Lung scan was normal. Cardiac catheterization and pulmonary angiograms showed numerous A-V fistulae in the left lower lobe, posterior segment, and the right, middle and right upper lobe, anterior and posterior segments. It was decided not to operate because of the multiple fistulae and because there was uncertainty about which to deal with. Bronchoscopy was done in 1975. The indications are not clear, but the findings were negative.

DR. ROBIN: One reason might be the possibility (with recurrent hemoptysis) of telangiectasia in the bronchial mucosa which are surgically treatable. Surgical therapy may control hemoptysis.

DR. CUMMISKEY: That brings us to the present, when the patient went to the Palo Alto Clinic. One week after the patient was first seen, low right anterior and posterior chest pain developed. Blood pressure was 90/60 mm of mercury; pulse, 65 and regular; respirations, 60; temperature, 36°C (96.8°F). Telangiectasia of the mouth, lips, face and anterior chest; moderate clubbing, and slight cyanosis were noted. Examination of the chest found decreased excursion on the right, dullness in the right base with no friction rub. The S-2 was widely split and the P-2 was greater than A-2. An x-ray film of the chest showed right pleural effusion. Laboratory studies gave the following values: leukocyte count, 12,000 with 12 percent bands; hematocrit, 49 percent; hemoglobin, 16.7 grams per dl. Pao_2 was 60 torr on 35 percent oxygen, pH was 7.47, $Paco_2$ was 32 and bicarbonate was 23.

The patient was acutely ill. She was admitted with a diagnosis of possible hemothorax, versus pulmonary embolism. Thoracentesis showed bloody pleural fluid. A pneumothorax developed and a chest tube was placed. When the pneumothorax had resolved, pulmonary function tests were done. The results were interpreted as showing mild restrictive disease; possibly surgical resection could give rise to these changes.

DR. LYNNE-DAVIES: We could say it is mild restrictive disease consistent with a history of surgical resection, but I think it is an excellent example of what you find if you resect what in mechanical terms is normal lung tissue, because all lung volumes are reduced in the same proportion with the result that the residual volume and the expiratory reserve volume are maintained within normal limits.

DR. THEODORE: It might be better to use the terms restrictive defect under the circumstances.

ANTONIUS VAN KESSEL, BS:† What about the effect of pleural disease on the lung volumes? They are so different from normal values—the vital capacity and the total volume are about half normal.

DR. LYNNE-DAVIES: I do not know whether the

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hemoglobin was still elevated or not. I suspect it was at least on the high side of normal.

DR. CUMMISKEY: At that time the hematocrit was elevated. At present the hematocrit is normal (41 percent).

DR. LYNNE-DAVIES: The diffusion capacity is now measured at 100 percent in spite of a degree of restriction which is about 30 percent. I assume that, other things being equal, this means otherwise it would have come out higher than 125 percent—which is acceptable, particularly in the light of the minor degree of polycythemia.

DR. ROBIN: The discussion concerns the fact that among other things the measured diffusing capacity (DLCO) is proportionate to the amount of hemoglobin available to take up carbon monoxide. Many laboratories correct diffusing capacity to a normalized hemoglobin so that the DLCO provides an estimate of diffusing capacity related purely to lung function.

DR. CUMMISKEY: When we first saw the patient (February 1978), blood gas determinations and other studies were carried out with the patient breathing room air under four conditions—supine, standing, exercise and sitting (Table 1). The Pa_{O_2} supine decreased from 61 to 50 torr after the patient had stood for ten minutes. This was a definite drop in the Pa_{O_2} which we felt was due to shunting of more blood through the bases than through the upper lobes of the lung.

DR. ROBIN: That would be true only if the A-V fistulae were largely localized to the bases. Dr. James Phillips saw a classic case at the University of Arkansas. The patient had a single, large pulmonary A-V fistula located in the apex of the left lung. The major drop in Pa_{O_2} occurred when the patient was placed in the Trendelenburg position and improved greatly when the patient sat up (personal communication).

DR. CUMMISKEY: In the Trendelenburg position, there was the greatest shunt? How about the supine compared with the upright?

DR. ROBIN: I do not believe Phillips carried out studies in this case with the patient in the upright position.

DR. CUMMISKEY: Would there be a gradation going down toward the worst value when the patient was in the Trendelenburg position?

TABLE 1.—*Changes in Blood Gas Values and Shunt With Changes in Position and Exercise. Note Progressively Severe Orthodeoxia With Changes From the Supine to Standing Position*

	pH	P_{CO_2}	H_{CO_3}	P_{O_2}	FiO_2
Supine	7.46	31	21.9	61	room air
Standing for 10 minutes	7.45	30	20.8	50	room air
Exercise (6.5 minutes at 3.5 mph, slope 5 percent)	7.38	27	15.9	48	room air
Sitting for 20 minutes after exercise	7.44	29	19.6	55	room air
Shunt Study with Positional Changes					
Supine	7.46	27	18.8	273	100%
Sitting	7.44	29	19.3	120	100%
Standing	7.44	29	19.5	78	100%

DR. ROBIN: The standing position is really different than the sitting position, and I prefer to discuss that later. In some of the cases that Dr. Goris and I studied, for example, there was an additional further fall in oxygen pressure when patients stood, compared with when they were sitting. This suggests that it is not only gravitational effects on shunt flow that determines the Pa_{O_2}.

DR. CUMMISKEY: We also studied the effects of exercise on the patient. The Pa_{O_2} fell a little further on exercise, though not significantly. After sitting for 20 minutes after exercise, the Pa_{O_2} was 55 torr. We then carried out a 100 percent oxygen study: in the supine position the Pa_{O_2} was 273, in the sitting position it was 120 and when she stood up it was 78 torr indicating a large shunt that increased progressively from supine to sitting to standing (Table 1). Dr. Robin, would you comment on these data?

DR. ROBIN: The changes in P_{O_2} and shunt are so large that they must reflect true alterations in oxygen exchange. Decreased oxygen saturation in the upright versus supine position has been called orthodeoxia.[3] It should be emphasized that calculations of shunt without determining the value of mixed venous oxygen under these conditions are not accurate. Changes in position may well cause changes in cardiac output and influence mixed venous oxygen saturation. Technically, therefore, the shunt calculations are not satisfactory. Moreover changes in position may affect both the volume of flow through the shunt as well as the oxygen content of the blood flowing through the shunt. The findings in this case show the development of true orthodeoxia. This can be explained by preferential increase in shunt flow.

However, the further decrease in oxygen pressure in the standing position cannot be so explained. One possibility is that standing is associated with loss of fluid into the tissues leading to a fall in cardiac output, reducing mixed venous oxygen content which then reduces Pao_2 because of the reduced oxygen content of mixed venous blood going through the shunt vessels.[4]

DR. CUMMISKEY: At that stage, then we went on to do a lung perfusion scan with whole body counting in the standing position. This showed a shunt of 35 percent of the cardiac output.

DR. ROBIN: Dr. Goris, what we would really like to come out of this conference, among other things, is an appreciation for the errors in estimating shunts by whole body scanning compared with say, the 100 percent oxygen method or the West-Wagner multiple inert gas method.

DR. GORIS: We use microspheres made of albumin labeled with technetium 99m. The tracer, whose size is in the range of 35μ, is trapped in the pulmonary capillaries. We do know that in patients without vascular shunts, 95 ± 3 percent of the tracer remains in the lung. If a larger fraction goes to the systemic side, one assumes that the tracer found a larger arteriovenous connection. By quantitating extrapulmonary radioactivity, a shunt can be calculated.[6]

DR. ROBIN: Do you have any independent way of determining the size of the particles? How much small *tail* do you have?

DR. GORIS: If you look at the tracer we have used, you would have 5 percent, which would be less than 15μ, and not many particles larger than 60μ.

DR. ROBIN: And of that 5 percent material of small tail would it be close to capillary size or is a substantial fraction below 8μ?

DR. GORIS: There is a certain amount of slough that we cannot eliminate. We know that in most patients in whom there is no suspicion of any kind of shunt, not many spheres go to the systemic circulation.

DR. ROBIN: Clinically, therefore, we cannot distinguish between two processes: labelled particles which are small enough getting through the capillaries and that fraction of the cardiac output that normally goes through anatomical shunts.

DR. GORIS: It is just a coincidence that the calculations happen to correspond so well with calculations based on physiologic methods. Given a patient with a certain body volume but a variable body geometry, the lungs and the body generally contain radioactive particles that are emitting gamma rays. Some of the gamma rays never escape because they become trapped within the body as a result of absorption of the tracer. Quantitating gamma ray emission is not the same process as liquid scintillation counting of a very small sample whose geometry and absorption are tightly controlled. In fact, we do not even know for certain that we count the top portions of the patient with the same efficiency as we count the lower portions.

DR. ROBIN: I would like to ask an additional question. If you are just looking at the lung, how deep within the lung do you suppose you see with a ventilation scan? And how deep do you see in a perfusion scan? My impression is that with xenon (either 127 or 133) you are looking at an outer shell of lung tissue because of internal absorption. Perfusion scans in which you use higher energy provide deeper representation of the lung compared with ventilation scans. Are these fair questions?

DR. GORIS: Those are very fair questions. The absorption is important. The average patient does have a certain amount of fatty tissue and muscle and bone surrounding the lung. Because of internal absorption, which is more important for xenon 133 than for technetium 99m, activity in superficial tissues is relatively better detected with technetium 99m.

DR. CUMMISKEY: Does that mean that in a fat person the results are different than in a thin person?

DR. GORIS: Yet, it does. Absolutely.

DR. ROBIN: So, you make another assumption that is open to question: you assume the absorption is homogeneous. That is fine from the standpoint of homogeneity of one lung versus the other, but it is not so good in looking at regional changes. Is that a fair statement to make?

DR. GORIS: That is correct. Now one of the advantages of krypton 81m used for ventilation scanning is that the energy is exactly the same or very close to the same as the tracer that is used

for the perfusion scan (technetium). Comparison between the two would be more exact.

To go back to the detection of right-to-left shunting, in a patient without a shunt, activity is detected in the lung only, and not in the body, because 95 percent of the tracer sticks in the lung. In the patients whom we are discussing, you see a large amount of body, and the kidneys on the image representing the activity distribution. (If you do not recognize the kidneys as individual structures, there is something peculiar going on; either the patient does not have normal kidneys or your tracer is not behaving properly.) In the case of a shunt, the kidneys should be seen very well, since they get 15 percent of the cardiac output. When I look at the perfusion scan with the computer, I have to select the region that I will call the lungs. Even if some extrathoracic regions are included, the error is not large because even when only 50 percent radioactivity remains in the lung (and 50 percent in the rest of the body), a large fraction of the other 50 percent would still not be included by making the lung region too large. I think that I have now reviewed three types of error: (1) transposing 1:1 an anatomic observation into a physiological one (for example, that larger vessels are shunting vessels), (2) assuming that the tracer is homogeneous and distributes itself according to blood flow and (3) assuming that the measurements are based on an accurate recognition of anatomical regions that are uniformly detected.

DR. ROBIN: Can I ask you about one of the errors? Could filtering be used to eliminate at least the tail of small particles in order to have more homogeneous microspheres?

DR. GORIS: Yes, we could do that.

DR. CUMMISKEY: Does not the manufacturer say that 95 percent of the microspheres fall between 15 and 35μ?

DR. GORIS: Yes, something like that. From each individual batch they take only one sample which they check and then decide whether it passes muster. You would have to check each dose yourself.

DR. ROBIN: It would be inconceivable to me that you fill all of the pulmonary precapillaries with particles that were 35μ in diameter and that the patient would survive. So the truth of the matter is that you only count a fraction of the capillaries.

DR. GORIS: It is estimated as one in 10,000. The total number of spheres varies between 100,000 and 600,000.

DR. ROBIN: That estimate seems overly precise. How was it obtained? Has anyone carried out studies in animals to determine how many of the gas exchange units in the lung are being occluded by tracer particles?

DR. GORIS: Yes, studies in dogs have been done using continuous infusions and determinations of oxygen saturation at the same time. Before you can measure alterations of gas exchange in the lung, you have to inject much more tracer than we do.

DR. ROBIN: So there is no quantitative estimate of what fraction of the gas exchange units within the lung are being seen with a perfusion scan?

DR. HANCE: It must vary remarkably depending on how sick the patient is.

DR. GORIS: Yes, that is correct. Some patients are seen who are known to have very low oxygen saturation values. In these patients injection is done while we watch the distribution of the tracer because of two reported cases of death in patients with massive lung disease who had only a very small part of their lung perfused. In children and also in adults who appear cyanotic we do not inject the usual amount but dilute the tracer by another factor of ten because we do not want to embolize the brain.

DR. THEODORE: Basically, therefore, if you got further and further into the chest, then you would have a difference in terms of the ratio of counts.

DR. GORIS: That is absolutely correct if two tracers with different emission energies are used.

DR. ROBIN: When I read the original paper proposing ventilation scanning for the diagnosis of pulmonary embolism (incidentally, the first one came from Stanford[6]), my reaction was that aside from physiological problems, the approach was unrealistic because of the counting problems that you point out. Intuitively it seemed that it would be most difficult to look at a thin rim of tissue and try to make specific correlations between the anatomy and the counting. Specifically I thought that major decreases in ventilation might not be detected. Is that unfair?

DR. GORIS: No, it is not unfair. We were so much

aware of the problems that at one time we used xenon for both the ventilation and the perfusion in order to have at least the same type of physical restrictions, because comparison is the key.

DR. ROBIN: How do you go from the raw data to the results provided as Polaroid pictures?

DR. GORIS: The instrument we use has an oscilloscope. The detector detects a little flash on the oscilloscope screen in view of a Polaroid camera whose shutters remain open. The problem is calibration. You cannot really use this Polaroid image to decide whether the shunt is large or not, only to illustrate a shunt.

DR. PINSKY: So, can you subtract from the Polaroid picture?

DR. GORIS: No. Simultaneously the data are stored in a computer which is used for quantitation.

DR. CUMMISKEY: The second patient this morning is a 56-year-old man who presented with a brain abscess in 1969. In 1973 he was admitted with dyspnea at rest and increased sputum production. An x-ray study of the chest showed numerous nodules throughout the lung fields. A pulmonary angiogram at that time showed large A-V fistulae in the right and left lower lobes. Both these fistulae were resected with a minimum loss of lung tissue. A pulmonary angiogram done in the Palo Alto Veterans Administration Medical Center four years later showed these lesions to be absent and no other fistulae were noted. Pulmonary function tests and blood gas studies were done after surgical operation and showed hypoxemia and obstructive lung disease.

DR. ROBIN: So now after operation there is no evidence of an anatomical pulmonary vascular shunt by angiography or by scan. However, the patient is hypoxemic. This case suggests a new use for the Goris scan. As people get older, and especially if they are smokers, intrinsic lung disease develops. That must also be true of those persons who have pulmonary A-V fistulae. By using the Goris scan you could distinguish between patients with persistent vascular shunts and those with intrinsic lung disease and alveolar shunts.

DR. THEODORE: Would you discuss that further?

DR. ROBIN: One of the important things about the concept that there are three kinds of shunt—alveolar shunts caused by lung disease, pulmonary vascular shunts and cardiac shunts—is that they require quite different forms of therapy.[7] I have previously thought statically about these patients. You find one category of shunt or another in a patient and the patient remains in a given category indefinitely. The data from the second patient illustrate that one must consider the possibility of change with the passage of time. Let us say that a 35-year-old patient has a pulmonary vascular shunt documented by a Goris scan plus other data, and that you treat the patient successfully. The patient is a smoker and is subject to the same kinds of things that happen to lungs with aging and smoking. Later an alveolar shunt may develop. When the patient returns hypoxemic, you say "Oh my God, we didn't remove all of the pulmonary A-V fistulae and, therefore, we're going to angiogram the patient and look for resectable areas." Whereas an independent disease has developed.

DR. CUMMISKEY: And that was the interpretation in this patient in October 1977.

DR. LYNNE-DAVIES: His referral originated with a phone call: "We have a man here who is known to have the Rendu-Osler-Weber syndrome. He has had previous surgical therapy for it. He did well for a while, and now is much worse. We suspect he has other fistulae which must be resected." He was referred to us and the end results of the workup, in terms of the original disease, were negative. The management, therefore, was substantially different. Treatment for chronic bronchitis was required.

DR. CUMMISKEY: Now, if we can just go back to the first patient. The issue really is whether to reoperate to remove additional A-V fistulae. We ask "Should she be considered now for a pulmonary angiogram with a view to possible operation?" Or should we take the opinion of 1972, and say "Well, that is probably the way it still is five years later."

DR. ROBIN: I think the answer to that is easy. We should obtain the angiograms of 1972 and see. If these were technically satisfactory, then I think you have to assume that the hypoxemia relates to the known pulmonary vascular shunts. In addition, our studies suggest that the A-V malformations account for most of the hypoxemia now. Now, the question of whether it is surgically

approachable or not depends on what the previous angiograms showed. If we do not have those data or the material is not obtainable, then we ought to determine that we have little to offer except an operation. The focus of the clinical management is on that critical information: What did the old angiograms show? If they showed inoperability, then we have no right to have new angiograms made. However, if the angiograms are not available then we have to know whether there is potentially resectable disease. Simply getting new angiograms without trying to obtain the old ones is not acceptable. Pulmonary angiograms are dangerous and have their own inherent problems.

DR. CUMMISKEY: Perhaps some of those A-V fistulae of 1972 have opened up and now may be possible regions for excision?

DR. LYNNE-DAVIES: If by any standards they were inoperable in 1972 and since then have gotten worse, that really does not affect the issue of management. On the other hand, if the studies from 1972 are either unobtainable or unsatisfactory for any reason, we do not sufficient information. Clearly, we would have to go ahead and obtain the essential information.

DR. CUMMISKEY: Except it seems now that you are taking an opinion for a fact; that is, the operability of the lesions.

DR. ROBIN: We either have to get the 1972 angiograms and look at them ourselves, or we have to get new ones. But the first thing to do is to try and obtain the earlier data.

DR. CUMMISKEY: And now a second question: Is there any place in a case like this or in other cases of pulmonary A-V fistulae, for doing selective injections into the areas of the fistulae? What is the state of the art on that?

DR. ROBIN: You mean to try to obliterate them?

DR. CUMMISKEY: Yes, obliterate them.

DR. ROBIN: I think it would be very dangerous. But my answer is that I do not know.

DR. CUMMISKEY: Then the third thing, of course, is that this patient should probably be given oxygen.

DR. ROBIN: Yes, I would like to discuss that in a moment.

DR. THEODORE: That raises some questions too.

DR. GORIS: I would like to mention a small point: If your surgeon now looks at the old data, he then has an answer whether he would have operated based on that information. If one of those lesions has now become three times as large, then it is not only a question of technical feasibility but how "attractive" it looks to him.

DR. ROBIN: But we would have a voice in making that decision. In this type of case there is little accumulated experience. Our surgeon may look at the angiograms and indicate one large fistula and say "I feel confident that I should operate." And I may look at it and say "Yes, but look at the other 98 lesions. As you remove more lung tissue, you are going to increase pulmonary vascular resistance and the other ones are going to get larger. I do not think you should operate." Then we would reach some consensus based on best guess on how to manage the patient.

What I would like to do now is to indicate some of the questions that are unanswered in patients who have pulmonary vascular shunts. It is more or less settled that determining the difference between alveolar shunts and pulmonary vascular shunts can provide important information. One simple thing that we do not know is the prevalence of pulmonary vascular shunts. No one has any idea of the frequency of the occurrence of pulmonary vascular shunts in various patient populations. The general view until now has been that pulmonary vascular shunts are uncommon. Clinically important pulmonary vascular shunts were essentially limited to two circumstances: (1) the Rendu-Osler-Weber syndrome and (2) sporadic pulmonary A-V fistula, unassociated with either a hereditary component or with A-V fistulae occurring elsewhere in the body. At present we do not even know the prevalence of A-V communications in liver disease. It is to be hoped that, over the course of the next two years, Drs. Salfen and Rushing will give us a better estimate of how common this is in liver disease. There are a number of other disorders in which it is reasonable to speculate that significant pulmonary vascular A-V shunting is present. One of these is pulmonary hypertension. Patients with severe primary pulmonary hypertension not uncommonly have substantial degrees of hypoxemia—not easily accounted for by abnormal parenchymal lung function. In some of these

patients, hypoxemia develops as a result of right-to-left shunting in the heart, say through a patent foramen ovale. In other patients, who seem to have substantial degrees of hypoxemia, that explanation is not tenable, at least judging by angiographic or catheterization studies. If the Goris scan can provide insight into prevalence, then it would provide an important addition to our understanding of pulmonary hypertension.

DR. HANCE: However, these patients would be at increased risk from perfusion scanning.

DR. ROBIN: You would have to try to estimate the possible value of the procedure against the possible risk in individual patients. All I am saying is that cardiac catheterization and angiograms have a greater risk in all probability than perfusion scanning. The second group of patients who often have hypoxemia, the mechanisms of which are not completely defined, are patients with pulmonary embolism.* There are two possibilities to explain the development of direct A-V communications in these patients. One, which was first raised at least 35 years ago, is that in the normal lung there may be direct A-V communications. The reason that these are not the sites of shunting is that the pressure relationships are such that blood flow through them is small in normal persons. Now, with pulmonary embolism, shunts might open up not de novo, but because of a new set of pressure-volume flow relationships within the lung vasculature. The second possibility is that somehow with acute pulmonary hypertension, new vascular shunts develop. The third disease (or group of diseases) in which there is occasionally hypoxemia not explained easily by the kind of measurements commonly available is pulmonary carcinoma or, more accurately, pulmonary malignant lesions. Work conducted by Folkman suggests that there are humoral agents elaborated by tumor cells (capillary angiogenic factors) which cause the development of new vessels.[8]

I have seen two patients who were shown to have substantial A-V communications within the lung. One had Hodgkin disease of the mediastinum and the other had bronchogenic carcinoma. Each had hypoxemia of unknown cause. The basis of the abnormal A-V communications was not clear.

*The major mechanism is known. It is the development of regional hypoventilation in areas that are perfused.

DR. HANCE: Demonstrated by?

DR. ROBIN: Demonstrated during surgical procedure. I would speculate that with some tumors, important A-V communications may develop in the lung, and the possibility of vascular shunts should be considered in patients with hypoxemia of unknown cause.

A second important problem involves the regulation of lung shunt vessels; that is, determining the physiological mechanisms that modulate pressure, volume and flow in these vessels. The amount of flow through the shunt vessel, as compared with the normal pathway, will vary as a function of the resistance through the two pathways. If, in patients who have pulmonary A-V shunts related to liver disease, one measures pulmonary vascular resistance after administering low oxygen mixtures, no increase in pulmonary vascular resistance is noted. In a normal person there is an increase in pulmonary vascular resistance.[9] The workers who showed this considered the phenomenon to be a "failure of pulmonary vasoconstriction." In other words, as alveolar oxygen pressure decreased in patients with pulmonary vascular shunts, you did not evoke whatever it is that produces pulmonary vasoconstriction and, therefore, pulmonary vascular resistance did not increase. Having analyzed their data I think they show that as you lower Pa_{O_2}, by administering low oxygen mixtures to breathe, you vasoconstrict normal pulmonary arterioles. This increases flow through the low resistance shunt vessels and pulmonary vascular resistance is not increased. Therefore, I believe it is probable that there is a mechanical rather than a chemical explanation for failure of pulmonary artery pressure and pulmonary vascular resistance to rise.

One important physiological question is what happens then to the resistances in the normal and the shunt pathways as a result of low alveolar oxygen tensions. Another is whether it is possible that these communications actually respond to physiologic and pharmacologic stimuli like systemic vessels rather than pulmonary blood vessels? As you know, in systemic vascular beds, if you drop the oxygen pressure vasodilatation occurs. Is it possible then that as you drop alveolar oxygen pressure, you are not only vasoconstricting normal vessels, but you are vasodilating the shunt vessels? Should it turn out that the shunt vessels do act like systemic vessels, then is it possible that they respond like systemic ves-

sels to other kinds of pharmacological agents like beta-adrenergic-agonists and alpha-adrenergic-agonists. By administering these agents could you selectively produce vasoconstriction of the shunt vessels and, therefore, force more blood through the normal pathway? Even if the beta agonists increased resistance in both pathways, but selectively increased resistance more in shunt vessels than in normal vessels, you could decrease the volume of shunting in the patient, and improve gas exchange. The whole question of the response of shunt vessels to pharmacologic agents, as well as to oxygen, is an important one.

In the first patient, it might be useful to maintain alveolar oxygen pressure at the highest levels possible. Maintaining a high oxygen pressure might prevent, in many regions, alveolar hypoxia and, therefore, would tend to keep the resistance in the normal pathway as low as possible. A trial of oxygen administration during the time she sleeps might be warranted for this purpose.

DR. HANCE: We have no reason to think that her alveolar P_{O_2} is low, though. It is not in a range in which oxygen therapy normally would be needed.

DR. ROBIN: That is only mean alveolar P_{O_2}. We do not know what is happening regionally.

DR. HANCE: But we have no reason to suspect that it is bad.

DR. LYNNE-DAVIES: There are two aspects to it. I think that, as far as the shunt you have discussed, one can speculate on two or three things. First, it must be behaving differently than the others because it is a shunt vessel, and presumably exposed to much lower oxygen pressures going into it and coming out of it than vessels in the main transit. On the other hand, you might be right that it is behaving like a systemic vessel. An alternative possibility is that it is maximally vasoconstricted and is behaving like a pulmonary vessel. It could still have the same controlling mechanisms but, because throughout its course there is a continuously low oxygen tension, it might behave much differently.

DR. ROBIN: I am making the assumption that vasoconstriction does not take place in the capillary but in precapillary vessels, and that the normal vessels, precapillary vessels and shunt vessels are exposed to a low oxygen pressure.

DR. HANCE: But in the patient who has a normal alveolar oxygen level, the blood coming into the pulmonary capillary is low in oxygen.

MR. VAN KESSEL: Are you postulating that the shunt is proximal to the constriction? In other words, there would be a difference whether or not the shunt vessel with vasoconstrictors is a matter of hypoxemia or whether or not the shunt would take off proximal or distal. That could still be right, depending on where you place the shunt.

DR. LYNNE-DAVIES: I agree with Dr. Hance, in a sense, about high alveolar oxygen pressure in areas adjacent to the normal vessels. However, I am not quite sure, taking your model, how increasing it would alter vascular resistance.

DR. ROBIN: Suppose, for example, that by using high oxygen you increase her mixed venous oxygen pressure from 40 to 50 or 55 torr. Now, the control of these vessels, if they are systemic vessels, will not depend on what is happening to alveolar oxygen pressure. It will depend on what is happening to precapillary oxygen pressure. High oxygen tensions do vasoconstrict systemic arterioles. High oxygen tensions probably vasodilate pulmonary precapillaries. I would be delighted to improve arterial oxygen pressure by any combination of shunt vasoconstriction and pulmonary vascular vasodilatation.

DR. LYNNE-DAVIES: Even if we accept the first two possibilities, it then seems to me that you said "Well, let's see how she does with oxygen at night and so forth." Looking at the blood gas values, the most crucial time for her to get oxygen would appear to be when she is standing up.

DR. ROBIN: Do you consider that your objections, which are more or less theoretical, are sufficiently strong in your mind so that you would not try oxygen?

DR. LYNNE-DAVIES: No, they are not sufficiently strong that I would not try oxygen.

DR. ROBIN: Perhaps a summary of the conference might be worthwhile. We have discussed two cases of patients with pulmonary A-V communications. The first teaches us that these communications may be so large and diffuse that curative surgical procedures may not be possible. The second teaches us that even after curative surgical therapy, the patient is not immune to the

development of more common forms of lung disease. This may be mistaken for a recurrence of A-V communications.

We have also discussed a number of other points: (1) the application of Ockham's razor to clinical medicine, (2) the causes of cerebral disease in patients with right to left shunts, (3) the effects of position and exercise on gas exchange in the lung, (4) the use of the Goris scan in detecting and quantifying the lung vascular shunts, (5) the technical limitations of ventilation and perfusion lung scanning, (6) therapeutic approaches to pulmonary A-V communications and (7) the physiological regulation of shunt vessels in the lung.

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Nutritional and Metabolic Significance of End Portion of Small Bowel

A SIGNIFICANT DEVELOPMENT in recent years is the recognition that just as the proximal portion of the small bowel is essential in the matter of absorption, digestion and nutrition, so the last part of the small bowel is vital to our nutritional and metabolic status. And the last part of the small bowel is not an inert muscular tube; it is a vital structure. When it is resected for disease, there may be alterations in the recycling of bile salts and this will lead to a reduced bile salt pool. This, in turn, will interfere with absorption of fat; it will also lead to alterations in the bile salt biochemistry and lead to an increased incidence of gallstones. And so, as part of your workup, in my opinion, you should include a cholecystogram every so often, because there are at least two studies in addition to ours that suggest that there is an increased incidence of gallstones in these patients.

—JOSEPH B. KIRSNER, MD, *Chicago*

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