DETECTION OF INTRAPULMONARY HEMORRHAGE WITH CARBON MONOXIDE UPTAKE
Application in Goodpasture's Syndrome

PAMELA W. EWAN, M.B., M.R.C.P., HAZEL A. JONES, B.Sc., CHRISTOPHER G. RHODES, M.Sc., AND J. M. B. HUGHES, D.M., M.R.C.P.

Abstract We devised a noninvasive measure of pulmonary hemorrhage of value in the management of Goodpasture's syndrome. We reasoned that alveolar uptake of inhaled carbon monoxide during breath holding would increase in the presence of extravascular blood, but clearance of its radioisotope ($C^{15}O$) from a lung field would be delayed. Thus, the ratio of uptake to clearance would indicate lung hemorrhage.

In 15 controls and six patients with renal failure without hemorrhage, this ratio ranged from 0.73 to 1.5. In eight patients with Goodpasture's syndrome the ratio ranged from 1.5 to 16.5, returning to normal between episodes of bleeding. Measurements of carbon monoxide uptake alone in 10 patients with Goodpasture's syndrome were at times well above that predicted for their hemoglobin level, whereas in renal failure with acute pulmonary edema increased carbon monoxide uptake was rarely found.

Thus, monitoring of the single-breath carbon monoxide uptake alone can detect episodes of lung hemorrhage. (N Engl J Med 295:1391-1396, 1976)

THE recent successful treatment of Goodpasture's syndrome by immunosuppression and removal of antibody to glomerular basement membrane by plasma exchange[1,2] has highlighted the need for a simple, sensitive and repeatable method of measuring pulmonary hemorrhage. Until now, hemoptysis and chest x-ray changes have been the only indexes available, but it is recognized that lung hemorrhage can occur in the absence of either of these signs, and chest x-ray shadowing persists after active bleeding has ceased. Patients with Goodpasture's syndrome often have an unexpected degree of anemia, and we have observed sudden falls in hemoglobin without obvious signs of bleeding elsewhere, suggesting occult pulmonary blood loss. Furthermore, it may be difficult to distinguish the x-ray appearances of intra-alveolar and interstitial bleeding from those of pulmonary edema. The new approach to treatment of this syndrome stimulated us to devise a better method of detecting lung hemorrhage.

THEORY

After a single breath of an appropriate gas mixture, carbon monoxide will diffuse from alveolar gas into the pulmonary capillaries. The rate of uptake will then depend on the number of hemoglobin combining sites available to carbon monoxide — i.e., the pulmonary-capillary blood volume and its hematocrit (see the equation of Roughton and Forster[3]). The rate constant for carbon monoxide transfer (kCO), representing carbon monoxide uptake, is calculated from the single-breath measurement according to the equation of Marie Krogh[4]:

$$kCO = \frac{1}{t} \log_e (CO_0/CO_t)\ 100,$$ where kCO = CO clearance in % per second, t = seconds, and CO_0 and CO_t = alveolar concentrations of carbon monoxide during breath holding at zero time and after t seconds respectively.

In clinical practice with the routine single-breath technic, CO_0 is calculated from the inspired concentration of CO and the dilution of an insoluble tracer gas (usually helium) in inspired and expired air samples. CO_t is the concentration in expired alveolar gas after t seconds of breath holding. A low hemoglobin will reduce the kCO, and a correction is generally made for the degree of anemia.[5]

In the presence of lung hemorrhage, extravascular blood, in either the alveoli or the interstitium (Fig. 1), will take up an additional quantity of carbon monoxide so that the uptake, when corrected for anemia, will

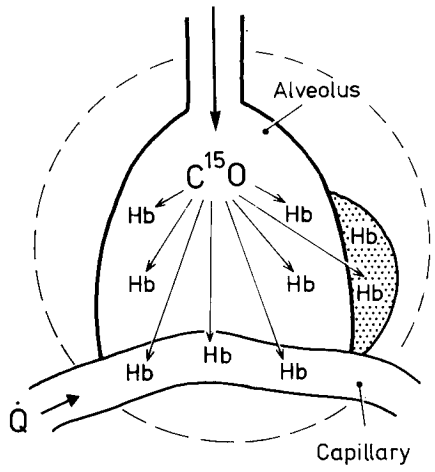

Figure 1. Diagram of Uptake of Radioactive Carbon Monoxide ($C^{15}O$) by Hemoglobin in Pulmonary-Capillary Blood and in Alveolar Spaces and Lung Interstitium.

The interrupted line indicates the area of tissue seen by a detector over the lung. Uptake of $C^{15}O$ will be high, but clearance from the counting field will be delayed because of the stagnant pool of hemoglobin (Hb). $\dot{Q}$ represents capillary blood flow.

From the Department of Medicine and the Medical Research Council Cyclotron Unit, Royal Postgraduate Medical School, Hammersmith Hospital (address reprint requests to Dr. Ewan at the Department of Medicine, Royal Postgraduate Medical School, Ducane Rd., London W12 OHS, England).

be abnormally high. But an elevated uptake is not sufficient to diagnose lung hemorrhage because it does not distinguish excess intravascular from excess extravascular blood.

To make this distinction, carbon monoxide uptake was measured in addition with the γ-emitting isotope of carbon monoxide ($C^{15}O$) and clearance of activity over the lung field after a single breath monitored by external counting. Although clearance of $C^{15}O$ from a lung counting field depends on two processes — transfer from alveolar gas to pulmonary-capillary blood by diffusion and removal of activity from the field by perfusion — diffusion is in practice the rate-limiting step. Therefore, the uptake of carbon monoxide from alveolar gas (kCO) should be the same as the clearance from the lung field of its radioisotope ($k'C^{15}O$), where k' is the rate constant for removal of the isotope from the counting field. In the presence of lung hemorrhage, the stagnant pool of labeled extravascular blood will delay the clearance of $C^{15}O$, and a low $k'C^{15}O$ will result. If it is assumed that the lung fields monitored for $k'C^{15}O$ are representative of the lungs as a whole, kCO and $k'C^{15}O$ should be equal in the absence of extravascular blood. On the other hand, lung hemorrhage will raise kCO and lower $k'C^{15}O$; thus, the ratio of lung uptake (kCO) to lung clearance ($k'C^{15}O$) provides a sensitive index of bleeding.

We have expressed the rate constants, kCO and $k'C^{15}O$, as per cent clearance per second. Most laboratories introduce a barometric pressure constant expressing kCO as min^{-1} $mmHg^{-1}$ or mmole $min^{-1}kPa^{-1}]^{-1}$, and clearance in % sec^{-1} should be divided by 1.2 and 4.3 respectively to convert to these units. kCO is the same as D_LCO/VA where D_LCO is the diffusing capacity for carbon monoxide and VA the alveolar volume.

Materials and Methods

Eleven patients (Table 1), six male and five female, 18 to 63 years of age, with Goodpasture's syndrome were studied, whose clinical details are given in separate communications (Cases 1-7[1,2], and Cases 8-11, unpublished data). All had nephritis at presentation. Ten patients had antibody to glomerular basement membrane; in the 11th patient, in whom there was no evidence of antibody, Goodpasture's syndrome developed after a course of penicillamine. Five patients were anuric on referrral, and the remaining six had deteriorating renal function. Lung hemorrhage occurred at some time in all patients. In the absence of hemoptysis suspicion of lung hemorrhage was raised by abnormal pulmonary radiographic shadowing or sudden falls in hemoglobin. Indeed, it was the search for explanation of such falls in hemoglobin that prompted the present study. Hemoptysis correlated poorly with pulmonary shadows. Although hemoptysis occurred at some time in all patients, two patients gave no history of hemoptysis at presentation. One patient had life-threatening lung hemorrhage. All were treated with a regimen of intensive plasma exchange, combined with steroid and cytotoxic drugs (cyclophosphamide with or without azathioprine).

In all patients serial measurements of kCO were made, and in eight patients $kCO/k'C^{15}O$ was also measured. We studied a control group of 13 normal males, two normal females and six patients (seven studies) with chronic renal failure, with levels of anemia and uremia similar to those with Goodpasture's syndrome but without lung disease or hemorrhage. Measurements of kCO and $k'C^{15}O$

Table 1. Summary of Peak and Base-line kCO Measurements and $kCO/k'C^{15}O$ Ratios in 11 Patients with Goodpasture's Syndrome.

Case No.*	Data at Time of Maximum kCO				Base-Line kCO Hemoglobin Corrected	Predicted Normal kCO	Maximum $kCO/k'C^{15}O$ Ratio
	X-ray Appearance	Hemoptysis	Hemoglobin	kCO Hemoglobin Corrected			
			g/dl	*% sec⁻¹*		*% sec⁻¹*	
1	Bilateral shadowing	None	6.7	15.0	6.4	8.5	3.4
2	Right-upper-zone opacities	None	7.5	5.3	4.2	7.1	–
3	Diffuse alveolar shadowing	None	7.9	13.7	6.2	8.8	1.7
4	Minimal haziness of left upper zone	None	5.7	14.8	6.1	8.2	–
5	Normal	Slight	5.3	8.6	5.3	7.1	–
6	Bilateral opacities	Trace	9.1	10.4	5.2	8.5	4.2
7	Gross diffuse shadowing	Frank	7.9	17.4	6.3	8.3	16.5
8	Fine mottling; consolidation, right lower lung.	Slight	7.2	17.2	4.5	7.3	14.6
9	Minimal shadowing	None	7.8	12.0	7.0	8.2	1.5
10	Bilateral lower-zone & right mid-zone opacities	Slight	7.0	13.0	6.0	7.7	6.1
11	Diffuse shadowing	Slight	12.1†	10.5	4.8	6.0	4.0

*Cases 1-7 in this series are cases of Lockwood et al[2].

†Transfusion given.

were made on the same day, at the same hemoglobin level in the same posture and at the same lung volume. In addition, measurements of kCO were made in five patients without Goodpasture's syndrome, whose renal failure was complicated by episodes of pulmonary edema, assessed on clinical and radiological grounds.

The single-breath diffusing capacity of the lung for carbon monoxide was measured in the standard way.[6] Subjects inspired a gas mixture containing 0.3 per cent carbon monoxide and 10 per cent helium and held their breath at total lung capacity for 10 seconds. The mean value for two or three measurements was calculated and converted to per cent clearance per second.

For k'$C^{15}O$, ^{15}O was prepared in the Medical Research Council cyclotron, and the gas converted to carbon monoxide in a chemistry laboratory; ^{15}O has a half-life of 2.07 minutes, and emits 511 keV gamma rays. Two pairs of scintillation detectors were placed anteriorly and posteriorly over the right lung; the output of each pair was summed. The upper counters were centered 3 cm below the manubriosternal junction, and the lower counters 10 cm lower, over the lower zone. The counters were shielded with several centimeters of lead and collimated to give a field of view 7.5 cm in diameter at a depth of 15 cm. Counts were recorded at 0.2-second intervals on a multichannel analyzer. Thirty to 50 ml of $C^{15}O$ (approximately 7 mCi) were injected into tubing close to the mouth while subjects paused at end expiration before making a rapid inspiration to total lung capacity. During the subsequent breath-holding period the clearance of activity was recorded on the analyzer and later transferred to a computer, where background and decay corrections were made. The curves were examined by eye, and a portion selected for single exponential analysis by the computer. The procedure was repeated once.

Clearance of $C^{15}O$ from a lung zone, when monitored by external counters, depends, as mentioned earlier, on diffusion and blood flow. West et al.[7] separated the rate constants for these two processes by comparing the clearance of highly diffusible $C^{15}O_2$ with the less diffusible $C^{15}O$. We likewise measured the clearance of $C^{15}O_2$ in our subjects immediately before or after that for $C^{15}O$, using the same single-breath technic. The $C^{15}O_2$ clearance, representing blood flow, was rapid and its effect on the $C^{15}O$ clearance was less than 5 per cent. This correction to the k'$C^{15}O$ has not been included.

The radiation dose to the lungs for two inhalations of 7 mCi was 200 to 250 mrads; two inhalations of $C^{15}O_2$ were taken at the same session, giving a total radiation dose of 450 mrads. Duplicate measurements were not made on the second or subsequent examinations.

Results

In the control group, kCO, measured from expired air analysis, and the k'$C^{15}O$, measured from the lower zone of the lung, were approximately equal (Fig. 2). In normal subjects the kCO/k'$C^{15}O$ ratio was 0.73 to 1.05, and in patients with chronic renal failure without evidence of lung disease the ratio was 0.85 to 1.5. There was a gradient of k'$C^{15}O$ up the lung because of the gradient of blood volume in the erect position, as previously described,[7,8] the upper/lower k'$C^{15}O$ ratio in our normal subjects being 0.46±.14 (±1 S.D.). The correlation of expired air kCO with lower zone k'$C^{15}O$ ($r = 0.92$) was stronger than that with the upper zone ($r = 0.67$) or with the average of the two zones ($r = 0.87$). Therefore, we took the lower zone k'$C^{15}O$ as more representative of the kCO for the lungs as a whole.

In eight patients with Goodpasture's syndrome, the kCO/k'$C^{15}O$ ratio was elevated at the time of lung hemorrhage, and ranged from 1.5 to 16.5. Normal values were obtained in these patients as lung hemorrhage ceased. An example of normal and abnormal kCO and k'$C^{15}O$ clearance is shown for Case 8 in Figure 3. The measurement made on January 9, 1976, showed that the clearance rate of carbon monoxide from alveolar gas was the same as the rate of removal of its isotope $C^{15}O$ from the lung field. Five days later there had been a marked increase in lung uptake and a corresponding reduction in the clearance of isotope

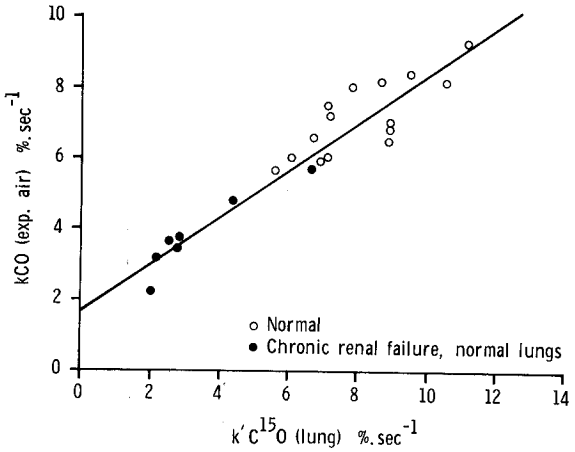

Figure 2. Carbon Monoxide Uptake as Percentage per Second (kCO) Measured by the Single-Breath Technic and Expired Air Sampling (on Ordinate) Plotted against Lower Zone $C^{15}O$ Clearance from the Lung (k'$C^{15}O$) Monitored by External Counting.

The regression line is that calculated for normal subjects and patients with renal disease without evidence of pulmonary hemorrhage.

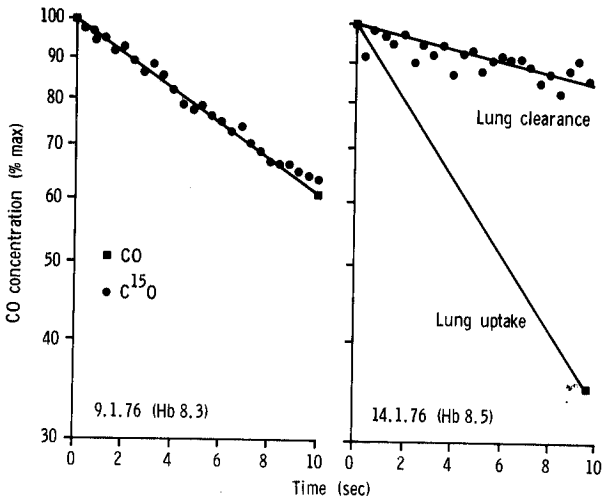

Figure 3. Carbon Monoxide (CO) Concentration as Percentage of Initial Value Plotted against Time for CO and Its Isotope $C^{15}O$.

Measurements were made in Case 8 at the same hemoglobin concentration (in grams per deciliter) in the presence (right) and absence (left) of lung hemorrhage.

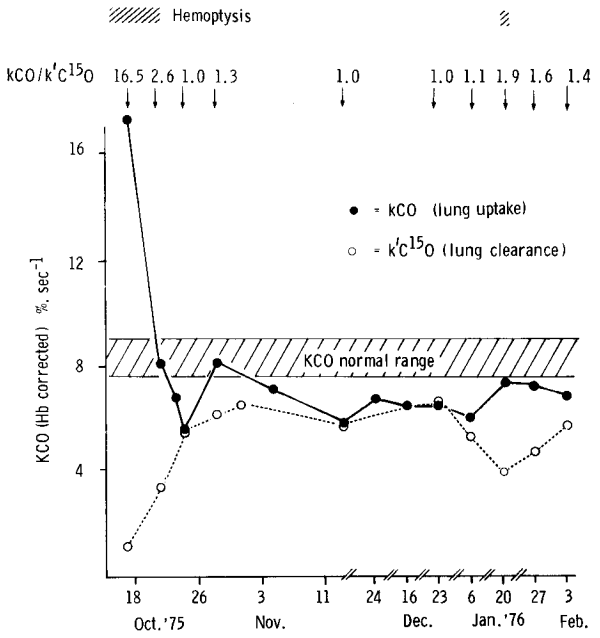

Figure 4. Serial Measurements of kCO (Lung Uptake) and k'C15O (Lung Clearance) Corrected for Hemoglobin Level in Case 7.

Shaded area is normal range of kCO for her age and height (mean ±1 S.D.). The ratio of kCO/k'C15O and episodes of hemoptysis are indicated.

from the lung field. This change was accompanied by a small amount of hemoptysis.

In Cases 1 and 3, single measurements of kCO/k'C15O were made, and both were elevated. In Cases 6 to 11, measurements were made serially during treatment with plasma exchange and immunosuppressive drugs, from the time of admission to Hammersmith Hospital. At some stage each patient had an abnormal ratio. Different patterns were seen, as illustrated by two patients (Cases 7 and 8).

Serial measurement of kCO and k'C15O in Case 7 are shown in Figure 4, each being corrected for hemoglobin according to the formula of Cotes et al.[5] to allow measurements on different occasions to be compared. The kCO/k'C15O ratio is also indicated. A wide gap between the kCO and the k'C15O indicates lung hemorrhage. This patient was admitted to the hospital because of life-threatening lung hemorrhage; at the time of our initial study seven days later, she still had frank hemoptysis, and gross shadowing throughout both lung fields (ratio of 16.5). Four days later the ratio was still abnormal (2.6), although hemoptysis was no longer present; x-ray study of the chest at that time showed fine nodular shadowing. At the time of the fourth measurement, the film became normal. After a remission lasting for nearly three months, a second episode of bleeding occurred, when the ratio rose to 1.9 (January 20). The single-breath kCO was initially very high in relation to the predicted value,[9] but after cessation of lung hemorrhage, as shown by the normal kCO/k'C15O index, it fell below the normal range, as is often found in uremic patients.[10]

Case 8 followed a more chronic and relapsing course. Figure 5 shows that the ratio rose and fell, suggesting intermittent lung hemorrhage. Five separate episodes of bleeding are suggested by five rises in kCO. On four of these occasions, the k'C15O was also measured, and the ratio kCO/k'C15O was elevated. As in Case 7, the base-line kCO in this patient, in the absence of lung hemorrhage, ran below the predicted normal range.

Serial measurements of kCO were made in all 11 patients, as shown in Table 1. An elevated kCO was found at some stage in each patient, and 23 episodes of lung hemorrhage (range of one to five per patient) were detected in this way. The base-line kCO (calculated from several measurements made when lung hemorrhage had ceased), when corrected for anemia, was found to be below the predicted normal value in all patients; the mean base-line value was 28 per cent below normal, with a range of 15 to 41 per cent. The maximum kCO/k'C15O ratio was usually greatly elevated (mean of 6.5).

Measurements of kCO in five patients with pulmonary edema are given in Table 2. Except in one (Case 15), kCO was below the predicted value. In Case 15, who was very ill, the edema was extensive both on clinical grounds and from the appearance of the chest x-ray film. The presence of pink, frothy sputum suggested that some hemorrhage was occurring. In this case, a measurement of kC15O was available; the lower-zone kCO/k'C15O ratio was 2.0, which is slightly raised.

Figure 5. Serial Measurements of kCO (Lung Uptake) and k'C15O (Lung Clearance) Corrected for Hemoglobin Level in Case 8.

Shaded area is normal range of kCO (mean ±1 S.D.) for patient's age and height.

Table 2. kCO Measurements in Five Patients with Chronic Renal Failure and Pulmonary Edema.

Case No.	X-Ray Appearance	Pink Sputum	Hemoglobin	kCO Hb Corrected	Predicted Normal kCO
			g/dl	*% sec⁻¹*	
12	Small pleural effusions	–	7.7	3.8	7.3
13	Confluent massive shadowing	–	7.4	6.5	8.2
14	Hazy shadowing, with Kerley B lines	–	5.3	6.9	8.2
15	Confluent massive shadowing	+	7.0	11.2	8.4
16	Perivascular & perihilar haze	–	9.2	5.6	7.3

Discussion

We noted that in a patient with Goodpasture's syndrome and hemoptysis, the kCO corrected for the low hemoglobin concentration was elevated. We supposed that this increase might be due to a stagnant pool of extravascular blood in the lungs. We established this fact by measuring the clearance of the isotope $C^{15}O$ by external counting over the lungs. We then went on to show that measurement of kCO, a simple test available in most hospitals with lung-function laboratories, might by itself be sufficient to detect and monitor pulmonary hemorrhage.

The ratio of lung uptake to lung clearance for carbon monoxide is particularly sensitive to the ratio between extravascular and intravascular hemoglobin contents, because pulmonary bleeding raises kCO at the same time as it lowers $k'C^{15}O$. The carbon monoxide uptake, calculated from the Roughton and Forster equation,[3] depends on the conductance of pulmonary-capillary membranes for carbon monoxide (D_M), in addition to the number of hemoglobin combining sites. This conductance may be higher for blood lying free in the alveolar space or interstitium of the lung than for that inside vessels. This elevation would lead to a further increase in the kCO and a further diminution of $k'C^{15}O$.

The rapid rise and fall of kCO in Figure 5 suggests to us that, with this technic, only fresh blood is measured, since the combination of oxygen (and presumably carbon monoxide) with hemoglobin depends on the linkage between the globin and heme fractions. Other methods of detecting latent pulmonary hemorrhage include the detection of hemosiderin in pulmonary secretions with use of bronchial lavage[11] and the rate of disappearance of ^{59}Fe from the circulation and its accumulation in the lungs.[12] These technics are not suitable for day-to-day monitoring and are not easily quantitated, nor are they specific for fresh blood.

An approximate estimate of the quantity of extravascular blood can be calculated in the following way. The ratio of extravascular to intravascular blood equals $(k'C^{15}O(a)/k'C^{15}O(b)) - 1$, where (a) and (b) refer to lung clearances measured in the absence and presence of bleeding respectively after correction for anemia. In Case 7, for example, the lower zone $k'C^{15}O$ after bleeding had stopped was 6.1 (a) as compared with 1.13 (b) for the initial measurement in the presence of bleeding (Fig. 4), giving a ratio of extravascular-to-intravascular blood of 4.3; the upper-zone ratio was similar (3.2). If we assume that her pulmonary-capillary blood volume was 70 ml, the volume of extravascular blood was about 300 ml. This amount represents 24 g of extravascular hemoglobin since the hemoglobin concentration was 8 g per deciliter.

The interpretation of a single measurement of kCO in patients with Goodpasture's syndrome and renal failure must take into account the reduced kCO found normally in patients with uremia. In this group of patients, the mean base-line value was 28 per cent below normal. This reduction is similar to that reported in patients with uremia not associated with lung hemorrhage and cannot therefore be attributed directly to the latter. For example, Lee, Stretton and Barnes[10] found a 38 per cent reduction in kCO in patients with renal failure of widely different causes, and were therefore unable to attribute this decrease to immunologic damage to the pulmonary capillaries. They suggested that a correlation may have existed between the gas-transfer defect and the severity of the renal impairment, but the mechanism remains uncertain. Within our group of patients, a similar reduction in base-line kCO was found, although during the time this figure was established, some patients had irreversible renal failure requiring dialysis whereas others had recovered good renal function. It seems that factors in addition to uremia contribute to this reduction in kCO, but the mechanism is unclear. The practical implication of a reduced base-line kCO is that an initial kCO in the normal range could reflect lung bleeding, since in our patients, a rise of more than 30 per cent above the base-line value was correlated with other evidence of lung hemorrhage. Before the base-line value is established, the $kCO/k'C^{15}O$ ratio can be particularly helpful, since it is more sensitive to bleeding than the kCO alone.

Twenty-three episodes of lung hemorrhage were suggested by a rise of kCO. Table 1 shows the maximum kCO in each patient; although some of these rises were accompanied by hemoptysis or changes on chest x-ray examination, others occurred either with a normal chest x-ray film or without hemoptysis. The rise in kCO in some of these cases was accompanied by otherwise unexplained sudden falls in hemoglobin (1.5 to 3 g per 24 hours), supporting the diagnosis of lung hemorrhage. Overall, five of the 23 episodes of bleeding suggested by kCO changes were not suspected on clinical grounds.

In Case 7 (Fig. 4) the clinical signs (a single minimal hemoptysis and a normal chest x-ray film) on January 20 seemed trivial; yet the rise in kCO and in kCO/k'$C^{15}O$ suggested definite pulmonary hemorrhage. This possibility led to the reintroduction of plasma exchange. When results of assays of antibody to glomerular basement membrane became available, the rise in kCO was found to have been associated with a rise in antibody titer. In Case 8 (Fig. 5) only three of the five episodes of lung hemorrhage suggested by kCO were clinically detectable. Interpretation of the chest x-ray film was particularly difficult since there was a background of discrete, fine pulmonary mottling.

In differential diagnosis, the most difficult problem is that of distinguishing pulmonary hemorrhage from pulmonary edema. In general, the kCO is elevated in the former (see Table 1) and reduced in the latter (see Table 2). Crosbie and Parsons[13] found a low pulmonary diffusing capacity for carbon monoxide after hemoglobin correction in four out of six patients with chronic renal failure requiring hemodialysis. Extravascular lung water, measured by the multiple indicator-dilution technics, was raised in all cases. From data supplied by the authors we calculated kCO, which ranged from 53 to 120 (mean of 76) per cent of predicted. In one patient in our series (Case 15) the kCO was raised. Extravasation of blood presumably played a part in this increase since his sputum was bloodstained and the kCO/k'$C^{15}O$ ratio slightly raised (2.0), but recruitment and distention of the pulmonary-capillary bed may also have contributed. In practical terms, an elevated kCO is rare in renal failure with pulmonary edema alone. If it occurs, it suggests pulmonary congestion and hemorrhage.

Thus, the measurement of carbon monoxide uptake provides a simple, repeatable and sensitive index of lung hemorrhage that in Goodpasture's syndrome gives an estimate of allergic damage in the lung.

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