The main difference, therefore, between the bacterial flora of the bladder urine before and after prostatectomy was the marked development of *Proteus* strains after that procedure. Presence or absence of organisms in the bladder urine before retention of an indwelling catheter did not appear materially to affect the nature of the bacterial flora which subsequently developed after retention of the catheter.

Comparing the organisms which occur coincidentally in the urethra and the bladder urine in the presence of an indwelling urethral catheter before prostatectomy, it is seen that there is little relationship between the bacterial flora of the two sites. *Staph. albus*, *Staph. aureus*, diphtheroids, and *Proteus* strains predominate in the urethra, whereas *Bact. coli* and *Str. faecalis* predominate in the bladder urine in these circumstances.

After prostatectomy, however, it is seen that there is a closer relationship. For there is a high incidence of *Bact. coli* in both the urethra and the bladder urine in these circumstances. Nevertheless, the relationship is not by any means complete, because there is also a high incidence of *Staph. albus*, *Str. faecalis*, and *Staph. aureus* in the urethra, whereas there is a high incidence of *Proteus*, *Str. faecalis*, paracolon bacilli, and *Ps. pyocyanea* in the bladder urine.

Summary

The nature of the bacterial flora which occurs coincidentally in the urethra and bladder in the presence of an indwelling urethral catheter has been investigated in patients before and after prostatectomy.

The bacterial flora of (a) the previously non-instrumented and non-catheterized male urethra, (b) the recently instrumented male urethra, and (c) the urine passed either shortly before (midstream) or withdrawn at the time of insertion of an indwelling urethral catheter, has also been studied.

It has virtually been confirmed that the saprophytic organisms of the virgin male urethra are staphylococci, *Str. faecalis*, diphtheroids, *Bact. coli*, *Str. viridans*, and bacilli of the *Proteus* group.

Recent instrumentation did not appear materially to affect the nature of the urethral bacterial flora.

Presence or absence of organisms in the bladder urine before retention of an indwelling catheter did not appear materially to affect the nature of the bacterial flora which developed subsequent to retention of a catheter.

Before prostatectomy the commonest urethral organism when an indwelling urethral catheter was retained was *Staph. albus*.

After prostatectomy the commonest urethral organism when an indwelling urethral catheter was retained was still *Staph. albus*. *Bact. coli*, however, was almost as common.

The main difference between the bacterial flora of the urethra before and after prostatectomy was the marked development of *Bact. coli* after prostatectomy.

The main difference between the bacterial flora of the bladder urine before and after prostatectomy was the marked development of *Proteus* strains after prostatectomy.

Little relationship was found between the coincidental bacterial flora of the urethra and bladder when an indwelling urethral catheter was retained before prostatectomy. The relationship was closer after prostatectomy, but was by no means complete.

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RESPIRATORY FAILURE IN ACUTE CHEST INFECTIONS

BY

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Since the introduction of chemotherapy in 1937-8, the mortality in England and Wales from lobar pneumonia among men aged 40-65 has fallen from 500-600 per million to 100 per million. There has, however, been no comparable fall in the death rate from "bronchitis," which has remained at the level of 800-1,000 per million for the last 10 years (Fig. 1). There are at least three possible explanations for this discrepancy: (1) That the majority of patients with "bronchitis" do not receive antibiotic therapy; (2) that the chemical, viral, and bacterial causes of exacerbations of "bronchitis" are not susceptible to the available therapeutic

Fig. 1.—Mortality from lobar pneumonia and bronchitis among males aged 40-65 in England and Wales (based on Registrar-General's figures).

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agents: (3) that there are factors additional to infection which influence the prognosis of acute respiratory infections in bronchitic subjects. This paper presents evidence for the third possibility. Bronchitic and emphysematous subjects often manifest an abnormal respiratory response to chest infection, and this may account for the sustained mortality despite the ready availability of penicillin, streptomycin, and chloramphenicol.

Material and Methods

The 30 patients studied included the majority of those with severe respiratory infections admitted to Hammett Hospital between December, 1953, and April, 1954. Six patients suffering from lobar pneumonia had no previous history of chronic respiratory disease. Twenty-four patients had a long history of chronic bronchitis and were admitted with exacerbations of acute bronchitis, bronchopneumonia, or lobar pneumonia—in 10 of these the respiratory infection had precipitated congestive cardiac failure. On admission a history was taken and a clinical examination made. A sample of arterial blood was obtained by brachial-artery puncture under local analgesia, using a few drops of heparin (5,000 units per ml.) as an anticoagulant. Some patients were too disorientated to give an accurate history, which was then obtained from relatives or from the patient himself on recovery. A sample of sputum was taken for bacteriological examination before starting antibiotic therapy.

Arterial blood was analysed for oxygen content, oxygen capacity, and total plasma carbon dioxide content by the Van Slyke manometric technique (Van Slyke and Neill, 1924). Plasma was obtained under anaerobic conditions by centrifuging blood in capped bijou bottles filled to the brim and transferred immediately to all-glass syringes. The arterial blood pH was measured at room temperature within 30 minutes of sampling, using a Cambridge pH meter and Stadie closed glass electrode. The meter was standardized with a phosphate-citrate buffer of pH 7.40 until a buffer solution of pH 7.00 checked within ± 0.01 unit. With careful restandardization between each measurement, duplicates agreeing within 0.02 unit could be obtained routinely. Correction of the observed blood pH to the patient's body temperature was made by Rosenthal's (1948) factor. Arterial $p\text{CO}_2$ was calculated indirectly from the blood pH and total plasma CO_2 content, using a formula derived from the Henderson-Hasselbalch equation.*

On full recovery a further sample of arterial blood was analysed for oxygen saturation, pH, and $p\text{CO}_2$ as previously described. The maximum breathing capacity (M.B.C.) was determined using a Siebe-Gorman box valve, collecting expired air through elephant tubing in a Douglas bag, and measuring the volume of gas with a gas meter. This was done both before and after inhalation of a bronchodilator (10 mg. of isoprenaline from a Collison inhaler). This measurement was made in triplicate on at least three occasions before discharge, and subsequently at intervals in out-patients until no further improvement was obtained: this might require a period of observation of three to four months. Repeated measurements of maximum breathing capacity provide as good an assessment of the degree of respiratory impairment in emphysema as any of the more complicated tests of respiratory function.

A diagnosis of chronic bronchitis was made in those patients who gave a history of chronic cough and repeated episodes of winter bronchitis; chronic bronchitis with emphysema if, in addition, a history of dyspnoea on exertion (unrelated to bronchospasm) could be elicited and the M.B.C. was less than 80 litres per minute in males and 60 litres in females. This distinction is purely arbitrary, but post-mortem experience (based on a small personal series) has shown that there is no significant structural emphysema in subjects whose M.B.C.s have previously been recorded as 80 litres or greater. A further diagnosis of cor pulmonale was made if on screening or at necropsy the heart showed right ventricular hypertrophy.

Results

The full results are given in Tables I and II. Fig. 2 depicts the change in oxygen saturation and arterial CO_2 tension between admission and recovery as an oblique arrow. The mean values for arterial oxygen saturation, plasma CO_2 content, $p\text{CO}_2$, and pH are given in Table III.

FIG. 2.—Arterial oxygen saturation and carbon dioxide tension on admission with and recovery from an acute respiratory infection. Single points represent patients who died.

The patients studied can be divided into three groups:

(1) *Normal Subjects* (6 cases). The acute respiratory infection was a lobar pneumonia in all subjects. In five the arterial $p\text{CO}_2$ on admission was below normal (less than 35 mm.) with a mild alkalaemia (pH 7.43-7.48). Arterial anoxaemia was slight, and in only one case was the oxygen saturation below 90%. In one subject (Case 4) there was no significant change in pH or $p\text{CO}_2$. No normal subject had a $p\text{CO}_2$ above normal (higher than 45 mm.) on admission to hospital.

(2) *Bronchitic and Emphysematous Subjects Without Congestive Cardiac Failure* (14 cases).—The acute respiratory infection was a lobar pneumonia in 3, bronchopneumonia in 4, and bronchitis in 7 (this distinction being made on radiological findings). On admission the arterial $p\text{CO}_2$ was below normal in only one patient (Case 18), and above normal (46.2-76.2 mm.) in 9. There was moderate anoxaemia (O_2 saturation 50.8-90.6%), mild to moderate CO_2 retention, and the pH was either within normal limits or slightly

* $p\text{CO}_2 = \frac{\text{Total plasma carbon dioxide content} \times 14.9}{(\text{antilog pH} - 6.1) + 1}$

TABLE I

No.	Age and Sex	Diagnosis*	Acute Respiratory Infection	Congestive Cardiac Failure	Sputum Bacteriology
1	25 M	Normal chest	Lobar pneumonia	—	<i>H. influenzae</i>
2	38 F	" "	" "	—	<i>Str. pneumoniae</i>
3	44 M	" "	" "	—	<i>H. influenzae</i>
4	54 M	" "	" "	—	<i>Str. pneumoniae</i>
5	58 F	" "	" "	—	<i>H. influenzae</i>
6	53 M	" "	" "	—	<i>Str. pneumoniae</i>
7	41 M	CB	" "	—	<i>H. influenzae</i>
8	72 M	CB, E	Broncho-pneumonia	—	No pathogens
9	67 M	CB, E, HTHD, CP	Bronchitis	—	<i>Staph. pyogenes</i>
10	63 M	CB, E	"	—	<i>H. influenzae</i>
11	59 F	CB, HTHD	"	—	No pathogens
12	58 F	CB, A, E, CP	"	—	No sputum obtained
13	62 M	CB, E, CP	"	—	<i>Str. pneumoniae</i>
14	54 M	CB, E, CP, HTHD	Broncho-pneumonia	—	<i>H. influenzae</i>
15	58 M	CB, B	"	—	<i>Str. pneumoniae</i>
16	64 M	CB, E	Bronchitis	—	No pathogens
17	50 M	CB, HT	Broncho-pneumonia	—	" "
18	59 F	CB	Lobar pneumonia	—	<i>H. influenzae</i>
19	62 M	CB, E	" "	—	<i>Str. pneumoniae</i>
20	55 M	CB	Bronchitis	—	<i>H. influenzae</i>
21	76 M	CB, E, CP	Bronchitis, Broncho-pneumonia	+	<i>Str. pneumoniae</i>
22	60 M	CB, E, CP	" "	+	<i>H. influenzae</i>
23	54 M	CB, E, CP, HT	" "	+	No sputum obtained
24	44 F	CB, E, CP	" "	+	<i>Str. pneumoniae</i>
25	67 M	CB, E, CP	" "	+	No pathogens
26	67 F	CB, CP	Bronchitis	+	<i>Str. pneumoniae</i>
27	70 M	E, CP	"	+	<i>H. influenzae</i>
28	67 M	CB, E, CP	"	+	" "
29	52 M	CB, E, CP	Lobar pneumonia	+	" "
30	64 M	CB, E, CP, HT	Broncho-pneumonia	+	<i>Str. pneumoniae</i>

* CB=chronic bronchitis; E=emphysema; A=asthma; CP=cor pulmonale; HT=hypertension; HTHD=hypertensive heart disease; B=bronchiectasis.

TABLE II

No.	On Admission						On Recovery					
	Respiratory Rate	Temperature (°F.)	Oxygen Saturation (%)	pH	Plasma CO ₂ in Vols. (%)	pCO ₂ in mm.	Oxygen Saturation (%)	pH	Plasma CO ₂ in Vols. (%)	pCO ₂ in mm.	M.B.C. in per min. after a Bronchodilator	
1	30	102	94.4	7.48	51.4	30.7	97.4	7.40	57.2	40.7	115	
2	34	102.6	96.4	7.44	43.3	28.4	97.0	7.42	59.5	40.6	91	
3	60	101	92.5	7.46	48.7	30.6	95.2	7.40	59.9	42.5	118	
4	32	103	88.9	7.41	59.8	41.7	95.9	7.39	57.1	41.2	96	
5	24	103	90.5	7.48	44.8	26.7	97.9	7.44	60.0	38.9	96	
6	48	104.6	94.1	7.43	48.4	32.1	98.5	7.44	56.4	36.9	108	
7	34	104	89.9	7.44	56.6	37.2	97.0	7.40	58.5	41.6	100	
8	40	101.6	65.5	7.32	83.1	70.2	86.9	7.43	61.8	41.2	55	
9	26	99.2	82.2	7.31	78.6	67.6	95.9	7.40	52.6	36.9	51	
10	28	99.1	63.9	7.39	75.6	54.5	91.0	7.40	61.7	44.4	—	
11	40	101.1	78.4	7.28	67.8	48.3	—	—	—	—	—	
12	32	100.2	53.1	7.28	72.8	76.2	—	—	—	—	—	
13	24	100.8	64.0	7.26	73.8	71.6	—	—	—	—	—	
14	36	101.6	50.8	7.36	76.9	60.1	—	—	—	—	—	
15	34	103.2	71.5	7.43	60.1	39.8	89.0	7.37	56.4	40.1	42	
16	40	98.4	90.6	7.41	65.9	46.2	94.1	7.39	59.5	43.4	47	
17	24	100.6	74.4	7.40	67.7	48.1	94.3	7.38	62.2	46.2	93	
18	44	100.4	88.9	7.50	56.3	32.1	94.6	7.40	58.0	40.9	66	
19	38	101.2	82.6	7.38	60.2	44.4	93.0	7.41	58.8	40.9	58	
20	22	100.4	89.6	7.42	60.0	41.2	93.0	7.40	55.7	39.6	81	
21	40	99.8	81.4	7.34	64.4	51.7	—	—	—	—	—	
22	30	98.2	61.5	7.29	96.5	86.5	89.5	7.41	78.1	53.9	55	
23	40	101	73.0	7.34	83.1	67.9	92.6	7.38	67.2	50.2	50	
24	30	98.2	44.0	7.22	73.0	76.4	—	—	—	—	—	
25	26	100	65.4	7.38	69.5	51.7	—	—	—	—	—	
26	25	98.8	38.4	7.25	75.4	73.7	—	—	—	—	—	
27	45	98.4	72.3	7.29	87.1	79.2	88.8	7.31	67.2	51.5	53	
28	55	97.4	57.5	7.32	79.2	66.5	—	—	—	—	—	
29	32	100	53.4	7.33	79.6	65.7	88.8	7.40	61.1	43.4	43	
30	30	101	42.1	7.31	90.0	77.5	—	—	—	—	—	
Normal Values ..	>94	7.36-7.44	54-66	35-45							>100 (males) >80 (females)	

low. On recovery, mild anoxaemia persisted in 5 of the 10 survivors, but pH and pCO₂ returned to normal limits in all.

(3) *Cor Pulmonale with Congestive Cardiac Failure* (10 cases).—The acute respiratory infection was lobar pneumonia in 1, bronchopneumonia in 7, and bronchitis in 2. Moderate or severe anoxaemia (O₂ saturation 38.4-81.4%), acidaemia (pH 7.22-7.38), and hypercapnia (pCO₂ 51.7-86.5 mm.) were present in all. Of the 4 survivors mild anoxaemia was present on recovery in all and slight carbon dioxide retention in 3.

A severe degree of anoxaemia and hypercapnia on admission to hospital was associated with a grave prognosis, since of the 10 patients in whom the arterial oxygen saturation was less than 70% and the CO₂ tension higher than 60 mm., only 3 recovered. Fig. 2 graphically illustrates the magnitude of the change in pCO₂ that occurred in some subjects and the fundamentally different respiratory response to pulmonary infection in normal and emphysematous subjects.

Illustrative Case Reports

Case 3. Lobar Pneumonia; Normal Chest.—Man aged 44. Admitted on December 21, 1953, with a week's history of malaise, shivering, and right-sided pleuritic pain. No previous history of cough, dyspnoea, or respiratory illness. Respirations 60 per minute; temperature 101° F. (38.3° C.). Chest radiograph: consolidation of right lower lobe with small pleural effusion. Sputum: *Str. pneumoniae* and *H. influenzae*. Arterial blood: mild anoxaemia with respiratory alkalaemia and hypocapnia. O₂ saturation 92.5%; plasma CO₂ 48.7 vols.%; pH 7.46; pCO₂ 30.6 mm. Treated with penicillin and streptomycin, but developed a massive sterile empyema requiring frequent aspiration. Finally, decortication and resection of the empyema was performed on February 10, 1954. On recovery blood gases had returned to normal (Table II) and the M.B.C. was 118 litres per minute.

Case 8: Chronic Bronchitis, Emphysema, and Broncho-pneumonia.—Man aged 72. A 35-years history of chronic cough with mucoid sputum; increasing dyspnoea on exertion for five years; severe attacks of winter bronchitis in 1952 and 1953 following exposure to fog. Admitted on November 10, 1953, with bronchopneumonia: stuporous and unable to give any history; deeply cyanosed. Respirations 40; temperature 101.6° F. (38.7° C.). Too weak to expectorate any sputum. Considerable expiratory bronchospasm. Arterial blood: moderate respiratory acidaemia and hypercapnia; O₂ saturation 65.5%; plasma CO₂ content 83.1 vols.%; pH 7.32; pCO₂ 70 mm. A chest radiograph showed diffuse coarse mottling; no cardiac enlargement. Treated with penicillin, inhalations of isoprenaline, and continuous oxygen tent. Remained confused, rowdy, aggressive, and uncooperative for a week, but then improved rapidly. On recovery remained chronically anoxaemic (O₂ saturation 86.9%), but pH and plasma CO₂ had returned to normal—pH 7.43, plasma CO₂ 61.8 vols.%, pCO₂ 41.2 mm. M.B.C. was reduced to 27 litres, rising to 38 after inhalation of isoprenaline, but gradually increased over succeeding months till in April, 1954, it had become stabilized at 55 litres per minute (after inhalation of isoprenaline).

Case 12: Chronic Bronchitis, Asthma, Emphysema, Cor Pulmonale. Morphine Narcosis.—Woman aged 58. A 30-years history of chronic productive cough, recurrent winter bronchitis, and intermittent attacks of asthma. Previously admitted to Hammersmith Hospital in 1949 moribund, following administration of morphine—comatose, deep cyanosis, jugular venous pressure raised to angle of jaw, respiratory rate 12 per minute—but made an unexpected recovery with oxygen, nikethamide, aminophylline, and penicillin. Investigations in February, 1951, showed right ventricular hypertrophy with mild pulmonary hypertension (pulmonary artery pressure 43/7 mm. Hg); O₂ saturation 84%; mixing curve and subdivisions of lung volumes typical of emphysema. Readmitted on January 6, 1954, with a severe attack of asthmatic bronchitis. Complained of severe throbbing

TABLE III.—Arterial Blood Gases and pH in Acute Respiratory Infections

Group	On Admission				On Recovery					Differences between Values on Admission and on Recovery*			
	O ₂ Satn. %	Plasma CO ₂ Vols. %	pH	pCO ₂ in mm.	O ₂ Satn. %	Plasma CO ₂ Vols. %	pH	pCO ₂ in mm.	M.B.C. l./min.	O ₂ Satn.	pH	Plasma CO ₂ Vols. %	pCO ₂ in mm.
1. Normal (Cases 1-6) ..	92.7	49.4	7.45	31.7	96.8	58.3	7.41	40.1	104	+4.1	+0.04	+8.9	+8.4
2. Chronic bronchitis and emphysema without cardiac failure (Cases 7-20) ..	74.6	69.1	7.38	51.6	92.9	58.5	7.40	41.5	66	+13.4	+0.01	-7.2	-4.7
3. Cor pulmonale and congestive cardiac failure (Cases 21-30) ..	54.9	79.8	7.31	69.7	89.9	68.4	7.38	51.0	42	+24.9	-0.07	-18.1	-23.8

* In groups 2 and 3, the differences between admission and recovery are based on surviving patients and not the total number originally studied.

headache and wheeziness. Rational and co-operative despite deep cyanosis. No signs of congestive cardiac failure; blood pressure 145/80; respirations 32; temperature 100.2° F. (37.9° C.). Arterial blood: severe respiratory failure—O₂ saturation 53.1%; plasma CO₂ 82.5 vols.%; pH 7.28; pCO₂ 76.2 mm. Treated with penicillin, oxygen tent, and a mixture of aspirin, phenacetin, and "nepenthe" (containing 8 mg. of morphine). Even this small dose had a disastrous effect, as by the following day the patient was deeply comatose with shallow gasping respirations, rate 15-20; blood pressure 80/60. Arterial O₂ saturation (taken in an oxygen tent) was only 47.8%, and there was a gross respiratory acidemia—pH 6.83 and pCO₂ 187 mm. 10 mg. of "nalorphine" was given intravenously, together with nikethamide, aminophylline, and intramuscular cortisone, but respiratory failure had become irreversible, and death occurred eight hours later. There was no necropsy.

Case 13: Chronic Bronchitis, Advanced Emphysema, Cor Pulmonale. Acute Bronchitis; Carbon Dioxide Narcosis.—Man aged 62. A 34-years history of chronic cough with mucoid sputum; increasing dyspnoea on exertion for 7-8 years; recurrent winter bronchitis. Spontaneous tension pneumothorax in December, 1949. Admitted in February, 1954, with a two-weeks history of dyspnoea, wheeziness, increased purulent sputum; visual and auditory hallucinations. On admission: orientated and able to give a reasonable history; moderate pallid cyanosis; diminished air entry over entire chest with expiratory wheeze; respirations 24; temperature 100.8° F. (38.2° C.); no signs of cardiac failure. Chest radiograph: clear lung fields; heart normal size but pulmonary conus prominent. Sputum: profuse growth of *Str. pneumoniae*. Arterial blood: O₂ saturation 64%; pH 7.26; plasma CO₂ 73.8 vols.%; pCO₂ 71.6 mm. Treated with penicillin, streptomycin, and continuous oxygen therapy in a tent. After four hours' oxygen therapy he became semicomatose, with profuse sweating and myoclonic movements of arms—carbon dioxide narcosis had developed: arterial pH 7.13 and pCO₂ 105 mm. After 24 hours' oxygen therapy, spontaneous improvement occurred and he was conscious though rather confused: the arterial pH had returned to 7.26 and the pCO₂ had fallen to 93 mm. Bronchospasm disappeared and the sputum became mucopurulent with a scanty growth of *Bact. coli* only. However, there was no further improvement, and on the seventh day he became semicomatose with a rise in arterial pCO₂ to 121 mm. and a fall in pH to 7.12. Donald's (1954) positive-pressure patient-cycled respirator was used in an attempt to increase ventilation, but after 30 minutes the arterial pCO₂ was unchanged and the machine was therefore abandoned. Necropsy: gross structural emphysema of the lungs with bulla formation; mild acute bronchitis with a little mucoid secretion in the trachea and main bronchi; no bronchopneumonia. Heart weight was within normal limits (310 g.), but showed right ventricular hypertrophy (right ventricle 123 g.; left ventricle 113 g.).

Case 14: Chronic Bronchitis, Mild Emphysema, Hypertensive Heart Disease. Bronchopneumonia. Progressive Respiratory Failure.—Man aged 54. Chronic cough with mucoid or mucopurulent sputum for years; intermittent wheeziness; mild dyspnoea on exertion for one to two years; never in bed with chest illness previously. Admitted in March, 1954, with acute bronchitis and bronchopneumonia:

mildly disorientated, deep cyanosis; blood pressure 150/95 (230/120 in 1951); presystolic gallop rhythm over ziphisternum but no other signs of cardiac failure; respirations 36; temperature 101.6° F. (38.7° C.). Arterial blood: O₂ saturation 50.8%; pH 7.36; plasma CO₂ 76.9 vols.%; pCO₂ 60.1 mm. Sputum: tenacious and purulent, profuse growth of *H. influenzae* and *Str. pneumoniae*. Treated with penicillin, but no oxygen. Six hours later became restless, stuporous, and finally comatose with deepening cyanosis. Attempts at resuscitation with oxygen, nikethamide, aminophylline, and digoxin proved ineffective. Necropsy: acute tracheobronchitis with gross excess of purulent sputum; chronic bronchitis with generalized dilatation of the smaller bronchi; slight emphysema in the anterior fringes of the lung only; pinhead areas of bronchopneumonic consolidation scattered throughout both lower lobes. Heart enlarged (weight 485 g.), with both left and right ventricular hypertrophy. No coronary atheroma.

Case 22: Chronic Bronchitis, Moderate Emphysema, Cor Pulmonale and Congestive Cardiac Failure. Chloramphenicol Proctocolitis with Terminal Acidemic Coma.—Man aged 60. "Chesty" all his life; nocturnal wheeziness and increasing dyspnoea on exertion for five years; following exposure to fog in December, 1952, developed a prolonged exacerbation of bronchitis and was admitted to West Middlesex Hospital in May, 1953, in mild congestive cardiac failure. The oedema responded to mersalyl and did not recur until November, 1953. Admitted on November 19, 1953, with a three-weeks history of delusions and nocturnal hallucinations, in moderate congestive cardiac failure and severe respiratory failure; mildly disorientated, euphoric, deeply cyanosed, apyrexial; respirations 40. Arterial blood: O₂ saturation 61.5%; pH 7.29; plasma CO₂ 96.5 vols.%; pCO₂ 86.5 mm. Pulmonary artery systolic pressure moderately raised to 56 mm. Hg. Sputum: scanty growth of *H. influenzae*. Treated with penicillin, streptomycin, digoxin, mersalyl, and oxygen tent for five days. Remained disorientated and hallucinated for a further three weeks, but on discharge on December 20 his mental state had returned to normal, the chest was clear of added sounds, and there was only minimal central cyanosis. The M.B.C. varied between 40 and 55 litres per minute. Sputum was mucoid and grew no pathogens. Arterial blood analysis still showed moderate carbon dioxide retention: O₂ saturation 89.5%; plasma CO₂ 78.1 vols.%; pH 7.41; pCO₂ 53.9 mm. Eight days later he was readmitted with a recurrence of *H. influenzae* bronchitis with profuse purulent sputum and severe bronchospasm. A transient episode of acute respiratory failure with stupor, profuse sweating, coarse myoclonic twitching of the limbs, and rapidly deepening cyanosis was observed on the second day, but this responded to the administration of oxygen and aminophylline. The *H. influenzae* infection was treated with a course of chloramphenicol, but after 24 g. intractable diarrhoea developed and death with severe metabolic acidemia occurred on the twelfth day (pH 7.03; plasma CO₂ 38.9 vols.%; pCO₂ 61 mm.). Necropsy: chronic bronchitis; mild structural emphysema with small bullae in the upper lobes; a few small areas of bronchopneumonia in the lower lobes; heart enlarged (weight 496 g.) with marked right ventricular hypertrophy (right ventricle 188 g.; left ventricle 172 g.); ulceration of sigmoid colon and rectum.

Case 29: Chronic Bronchitis, Emphysema, Cor Pulmonale, and Early Congestive Cardiac Failure. Lobar Pneumonia and Carbon Dioxide Narcosis.—Man aged 52. A 16-years history of chronic cough with large quantities of mucopurulent sputum and increasing dyspnoea on exertion. Since pneumonia in 1950 had been unable to work because of dyspnoea. Intermittent oedema of ankles for 18 months. Admitted on January 5, 1954, in early congestive cardiac failure with a confluent left basal bronchopneumonia. Rational and able to give a coherent history despite deep cyanosis. Blood pressure 120/70; respirations 32; temperature 100° F. (37.8° C.). No gallop rhythm. Arterial blood: O₂ saturation 53.4%; pH 7.33; plasma CO₂ 79.6 vols.%; pCO₂ 65.7 mm. Treated initially with penicillin and oxygen by "polymask" at 6 litres per minute. After three hours oxygen therapy, lapsed into coma with imperceptible respirations; hypotension: blood pressure 90/20. A loud presystolic gallop rhythm was audible over the xiphisternum. Arterial blood analysis showed that carbon dioxide narcosis had developed: O₂ saturation 97.5%; pH 7.07; pCO₂ 102.3 mm. Resuscitated by manual artificial respiration, intravenous nikethamide (15 ml.), aminophylline (0.5 g.) and digoxin (0.5 mg.). Oxygen was temporarily discontinued and three hours later he was again conscious and rational; the gallop rhythm had disappeared and the blood pressure had risen to 120/55. Oxygen therapy was continued at low rates of flow (2–3 litres per minute): this was insufficient to relieve his cyanosis completely. Thereafter recovery was slow but uneventful. Mild central cyanosis persisted (O₂ saturation 88.8%), but pH and pCO₂ returned to normal (7.40; 43.4 mm.). The transverse diameter of the heart shrank by 4 cm. (from 15 to 11 cm.), but screening showed hypertrophy of the right ventricle. He remained incapacitated by dyspnoea, with an M.B.C. fluctuating between 25 and 43 litres per minute.

Discussion

In healthy subjects the sensitivity of the respiratory centre to small change in CO₂ tension provides a delicate homeostatic mechanism for adjusting pulmonary ventilation to the metabolic needs of the body. The day-to-day variation of pCO₂ during rest, sleep, and moderate activity is probably not more than ± 4 mm. (Mills, 1953). The increased tissue production of carbon dioxide associated with a respiratory infection requires a small increase in pulmonary ventilation to maintain the arterial CO₂ tension at its previous level. However, the combined stimuli of pyrexia, anoxaemia, and the presence of pulmonary consolidation often increase ventilation beyond the level necessary to maintain a normal pCO₂, and the arterial blood CO₂ content may actually be lower than normal (Barach and Woodwell, 1921; Hastings *et al.*, 1924; Meakins and Davies, 1925; Binger *et al.*, 1927). In the six subjects without previous respiratory disease the arterial pCO₂ on admission was either unchanged or lower than the level on recovery (Fig. 2). This may be taken as the normal response to an acute respiratory infection.

By contrast, the physiological response of the chronic bronchitic and emphysematous subject is often grossly abnormal, and the arterial pCO₂ on admission may be up to 32 mm. higher than the patient's habitual level (Fig. 2). Despite the additional stimuli of anoxaemia and pyrexia, the increase in ventilation is insufficient to prevent a rise in the arterial pCO₂ and H-ion concentration. This paradox of hypoventilation in the face of anoxaemia and hypercapnia may be called *respiratory failure*, since it implies a breakdown of the homeostatic function of the respiratory centre in maintaining the arterial CO₂ tension and H-ion concentration within normal limits. On this definition many emphysematous subjects are in chronic respiratory failure even when free from intercurrent respiratory infection (Scott, 1920; Baldwin *et al.*, 1949), since their arterial CO₂ tensions are permanently raised above 45 mm. However, a chest infection will frequently precipitate acute respiratory failure in subjects whose CO₂ tensions are within normal

limits when well. This occurred in 10 of the 24 bronchitic subjects studied. It should be noted that it is unnecessary to measure pCO₂ to detect the presence of respiratory failure. Unless there are grounds for suspecting concomitant metabolic alkalaemia, a total plasma carbon dioxide content of arterial blood raised above 66 volumes indicates respiratory failure (Table II).

In general, a respiratory infection in the emphysematous subject is associated with a more severe degree of anoxaemia than in a normal subject. In a study of 130 cases of lobar pneumonia, Binger (1928–9) found that the oxygen saturation was above 70% in 104 (80%); by contrast, 12 of the 24 bronchitic subjects in this study had saturations less than 70%. There are two reasons for this.

Firstly, many emphysematous subjects are chronically anoxic. Imbalance between alveolar perfusion and ventilation may reduce the arterial oxygen tension (pO₂) to 50–80 mm. (normally 90–100). With the development of a respiratory infection, alveolar perfusion-ventilation ratios may become even more abnormal, and the arterial oxygen saturation rapidly falls to seriously low levels with the appearance of deep cyanosis and mental confusion.

Secondly, respiratory failure with rising carbon dioxide tensions is inevitably associated with arterial anoxaemia. The interrelationship between alveolar oxygen and carbon dioxide tensions can best be appreciated by consideration of the equation derived by Fenn, Rahn, and Otis (1946).^{*} When the barometric pressure is 760 mm. and the respiratory quotient (RQ) is 0.79, this simplifies to alveolar pO₂ = $150 - 1.21 \times \text{alveolar pCO}_2$. If the alveolar pCO₂ rises to 70 mm. the alveolar pO₂ must fall to 65 mm.—and the arterial pO₂ cannot, of course, be higher than this. The severe degrees of anoxaemia found in emphysematous subjects during acute respiratory infections are therefore due to a combination of respiratory failure—causing hypoventilation and a low alveolar oxygen tension—and the direct effect of pulmonary infection increasing an already large alveolar-arterial pO₂ gradient: in many instances the former is quantitatively more important than the latter.

The Mechanism of Respiratory Failure

It may be physically impossible to maintain adequate pulmonary ventilation when the maximum ventilatory capacity is grossly diminished. In severe status asthmaticus intense bronchospasm may reduce the ventilatory capacity *below* the normal level of resting ventilation: under these circumstances anoxaemia and carbon dioxide retention must rapidly occur. However, most patients in respiratory failure have a small breathing reserve. I have often been able to demonstrate at the bedside that a considerable increase in ventilation occurs when these patients are commanded to breathe more slowly and deeply. When the extra cortical stimulus to respiration is withdrawn they rapidly revert to ineffective shallow gasps. In these patients the respiratory centre must have become insensitive to the stimuli of anoxaemia, hypercapnia, H-ion concentration, and pyrexia. It is well known that the respiratory response to carbon dioxide is considerably diminished in emphysema (Scott, 1920), and Prime and Westlake (1954) have shown that the response diminishes with rising levels of resting arterial pCO₂. At a resting carbon dioxide tension of 65–70 mm. the respiratory response is only 10–20% of normal. Anoxia may be an important factor precipitating respiratory failure, since Newburgh *et al.* (1916) and Ivy *et al.* (1947) have shown that severe anoxia depresses the sensitivity of the respiratory centre to carbon dioxide. Thus respiratory failure may become a rapidly progressive process (cf. Case 14); for, as Drinker (1945) has shown, low oxygen tensions cause pulmonary oedema with consequent further increase of anoxaemia.

^{*}Mean alveolar pO₂ = (Barometric pressure – 47) × 0.21 – alveolar pCO₂ $\left(0.21 + \frac{0.79}{RQ}\right)$

The Clinical Picture of Respiratory Failure

Acute respiratory failure is responsible for the distinctive clinical features observed during exacerbations of respiratory infection in bronchitic subjects. Anoxaemia, acidaemia, and hypercapnia give rise to cerebral vasodilatation and increased cerebral blood flow, which in turn raises C.S.F. pressure and causes papilloedema and headache (Patterson *et al.*, 1952; Westlake and Kaye, 1954). They also result in increased cardiac output with warm extremities and increased pulse pressure (McMichael and Sharpey-Schafer, 1944), impaired cerebral function with disorientation, restlessness, hallucinations, delusions, myoclonic twitching, and profuse sweating. It is well known that cardiac failure in pulmonary heart disease is always associated with anoxaemia and high levels of blood carbon dioxide (Peters, Bulger, and Eisenman, 1925; Taquini *et al.*, 1948). In the 14 patients studied by Platts (1953) the oxygen saturation was below 72% and the CO₂ content of whole arterial blood higher than 56 volumes in all but one. In this study moderate or severe anoxaemia, acidaemia, and hypercapnia were present in all ten patients with congestive failure. These observations suggest that congestive cardiac failure in pulmonary heart disease is secondary to respiratory failure. The exact mechanism involved is not fully elucidated, but there is no doubt that anoxaemia raises the pulmonary artery pressure by direct vasoconstrictor action on the pulmonary arterioles (Motley *et al.*, 1947); high carbon dioxide tensions have a similar effect (von Euler and Liljestrand, 1946; Yu *et al.*, 1953). Lange *et al.* (1951) have shown that acidaemia causes a considerable increase in cardiac output and fall in peripheral resistance. In the final stages, respiratory failure causes cardiovascular collapse with coma, falling cardiac output, peripheral vasoconstriction, hypotension, pulmonary oedema, diminished renal blood flow, and elevated blood urea levels.

The Treatment of Respiratory Failure

Treatment is based on: (1) antibacterial treatment to counter the pulmonary infection; (2) oxygen therapy to relieve anoxaemia; (3) relief of respiratory obstruction by the use of antispasmodics, postural drainage and coughing. *H. influenzae* is an important pathogen in exacerbations of respiratory infection in the chronic bronchitic (Mulder *et al.*, 1952; May, 1953; Elmes, Knox, and Fletcher, 1953), and was isolated from the sputum in 12 of my 24 bronchitic subjects. The predominance of this organism suggests that the initial treatment (prior to obtaining a full bacteriological report) should be one capable of eradicating *H. influenzae*. Streptomycin and chloramphenicol in doses of 1 g. six-hourly are effective, whereas crystalline penicillin in usual doses is not. However, massive doses of one of the penicillin esters—for example, “estopen,” 1 mega unit b.d.—may raise the concentration of penicillin in the sputum to inhibitory levels. Apart from the minor risk of subsequent aplastic anaemia, chloramphenicol has one disadvantage: the intractable diarrhoea that occasionally follows its use may tip the scales against recovery in a gravely ill patient (cf. Case 12 and two others not included in this series).

In the severely anoxic patient oxygen therapy is essential to prevent sudden cardiovascular collapse or death from progressive respiratory failure. It is not, however, without dangers of its own. In respiratory failure, ventilation is principally maintained by the reflex drive of anoxia stimulating the carotid and aortic chemoreceptors. Relief of anoxia abolishes this drive and ventilation falls, with consequent further rise in the arterial CO₂ content. Eventually a new respiratory equilibrium is reached when the higher level of arterial pCO₂ and H-ion compensates for the absent anoxic stimulus (Westlake, 1953). The rise in carbon dioxide content may be sufficient to cause carbon dioxide narcosis with mental confusion, twitching, headache, sweating, stupor, and coma (cf. Cases 13 and 29). Severe carbon dioxide narcosis can often be prevented by giving oxygen at low rates of flow so that anoxaemia is only partially relieved and the consequent rise in blood carbon dioxide is

too small to cause adverse symptoms. Oxygen via a B.L.B. mask or the lightweight “polymask” (B.O.C.) at 1–3 litres per minute is a satisfactory technique (Barach, 1948; Simpson, 1954). An oxygen tent cannot be used, since with low rates of flow of oxygen the internal temperature rises too high.

Patients with respiratory failure are often given morphine on the erroneous assumption that they are suffering from pulmonary oedema. This mistake may prove rapidly fatal by abolishing the residual sensitivity to carbon dioxide, but, fortunately, the depressant effect of morphine can be immediately reversed by an injection of *n*-allyl normorphine (“nalorphine,” “lethidrone”), but this must be administered before respiratory failure has progressed to an irreversible stage (cf. Case 12). Nalorphine is of no value in reversing spontaneous respiratory failure or that due to barbiturate overdosage. Bronchospasm will usually respond to standard therapeutic measures, but in resistant cases A.C.T.H. or cortisone may avert a fatal outcome. Cortisone appeared to be life-saving in Case 10, but A.C.T.H. was given too late in Case 21. The importance of clearing the bronchial tree of secretions cannot be overemphasized. Patients in respiratory failure are often too weak or apathetic to cough up their sputum spontaneously. They should be encouraged to cough at regular intervals (every one to two hours) by the nursing staff, but if this fails to raise the sputum the rapid intravenous injection of 3–4 ml. of nikethamide accompanied by vigorous thumping on the chest may be effective (Elmes, personal communication, 1954).

A direct method of treating respiratory failure (by increasing ventilation mechanically)—of proved effectiveness and general applicability—is not yet available. Callaway and McKusick (1951) have reported favourably on the use of a pneumoperitoneum, and Boutourline-Young and Whittenberger (1951), Stone *et al.* (1953), and Lovejoy *et al.* (1954) have claimed successes with mechanical ventilation in a Drinker tank respirator. In my own experience, the Paul-Bragg pulsator, the Drinker tank respirator (Westlake, 1953), and Donald's positive-pressure patient-cycled respirator (cf. Case 13) have all proved ineffective in increasing the ventilation of patients in severe respiratory failure.

Conclusion

The importance of respiratory failure lies in the frequency with which it proves fatal before therapeutic measures have had time to cure the causal pulmonary disease. It is well known that many deaths occurred within a few hours of exposure to the dense fog of December, 1952 (Logan, 1953). Further advances will depend on the discovery of effective methods of maintaining or increasing ventilation in bronchitic subjects. In many cases, however, we are dealing with an irrevocably damaged lung and can do little more than postpone death for a few years. It is unlikely that there will be any substantial fall in the overall mortality from “bronchitis” until the incidence of chronic bronchitis and emphysema is itself reduced. This will depend on the discovery of all the aetiological factors involved. Overcrowding, excessive smoking, and atmospheric smoke pollution are probably important, but their correction will involve forms of social therapy which are, unfortunately, not within the direct grasp of the medical profession.

Summary

Arterial blood gases and pH have been studied in 30 patients admitted to hospital with an acute respiratory infection: in 6 subjects without previous history of chest disease the arterial CO₂ tension was unchanged or was lower than the level on recovery. This is the normal physiological response to respiratory infection.

In 18 of the 24 subjects with bronchitis or emphysema the response was abnormal and the initial arterial CO₂ tension was 5–32 mm. higher than on recovery. These patients may be said to have been in respiratory failure on admission to hospital.

Acute respiratory failure with increasing anoxaemia, hypercapnia, and acidaemia is responsible for the distinctive clinical picture observed during exacerbation of infection in the chronic bronchitic and emphysematous subject: headache, raised intracranial pressure, papilloedema, mental confusion, hallucinations, sweating, myoclonic jerking, increased cardiac output, pulmonary hypertension, and congestive cardiac failure.

Mortality from "bronchitis" has not declined in the last 10 years despite antibiotic therapy: respiratory failure may be a partial explanation of this phenomenon.

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In 1950 Dr. ERIK WALLER, of Stockholm, presented his library to the University of Upsala (see *Journal*, December 23, 1950, p. 1452). This library comprises about 21,000 items, principally concerned with the history of medicine and science. More than twice the size of Osler's library at McGill, it is one of the most valuable collections of its kind in the world, and represents the result of scholarly collection over a period of forty years. It includes 150 books printed before 1500, a hundred editions of Vesalius (including a unique copy of an edition of the *Epitome*), fifty editions of Harvey, forty-three of Paré, and a large collection of Linneana. Almost all the great names in medicine are represented; there are also many works on the history of medicine. The catalogue of the Bibliotheca Walleriana has now been compiled (in English) by the university librarian of Upsala and is to be published early next year by Messrs. Almqvist and Wiksell, Stockholm, at a subscription price of 175 Swedish kronor (200 kr. after December 31).

THE FACTOR OF INFECTION IN HEART FAILURE

BY

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"A neglected cold is frequently the original cause
of the most severe diseases of the heart."—

LAENNEC, 1834.

This review of 300 patients suffering from congestive heart failure (159 males and 141 females) who were admitted consecutively to the City General Hospital, Sheffield, between March 17, 1952, and March 16, 1953, is designed to call attention to the high incidence of respiratory infections in heart failure and to demonstrate their importance as the commonest precipitating cause of heart failure, even in patients with intrinsic heart disease.

In this survey a diagnosis of congestive heart failure demanded an unequivocal rise of cervical venous pressure above the sternal angle during all phases of respiration, and either peripheral oedema or hepatic engorgement. In most cases all three signs were present.

Each patient was examined by me for the purpose of this investigation and a full clinical history was recorded on a standard "pro-forma" which paid particular attention to respiratory symptoms. Routine investigation comprised an electrocardiogram, an x-ray film and screening of the chest, leucocyte count, examination of the urine and sputum, and estimation of the haemoglobin and Wassermann and Kahn reactions.

Clinical Material

Cases having more than one cause are classified under the heading of the major lesion, except for 12 cases of cor pulmonale in which the pulmonary lesion was thought to be predominant, but which are classified under the heading of the associated cardiac lesion and designated "associated cor pulmonale."

1. *Cor Pulmonale*.—Total, 76 (64 males, 12 females); 26 deaths; 24 necropsies. All these patients had severe lung disease, manifested central cyanosis, and had sinus rhythm. None showed evidence of hypertensive, ischaemic, rheumatic, or other intrinsic heart disease.

Chronic bronchitis	..	..	..	..	42 cases
Bronchiectasis	..	..	..	..	21 "
Asthma	..	..	..	..	5 "
Pneumoconiosis	..	..	..	..	5 "
Severe kyphoscoliosis	..	..	..	..	2 "
Organizing pneumonia	..	..	..	..	1 case

2. *Rheumatic and Non-specific Valvular Lesions*.—Total 68 (26 males, 42 females); 18 deaths; 14 necropsies.

Isolated mitral valve disease	..	..	..	..	38 cases
Isolated aortic valve disease	..	..	..	..	9 "
Combined aortic and mitral valve disease	..	..	..	..	21 "
Associated cor pulmonale	..	..	..	..	3 "

3. *Ischaemic Heart Disease*.—Total, 65 (33 males, 32 females); 34 deaths, 23 necropsies.

Recent myocardial infarction	..	..	..	..	26 cases
Old myocardial infarction	..	..	..	..	28 "
Infarction not proved (angina in all)	..	..	..	..	11 "
Associated hypertensive heart disease	..	..	..	..	7 "
Associated aortic stenosis	..	..	..	..	1 case
Associated cor pulmonale	..	..	..	..	4 cases

4. *Hypertensive Heart Disease*.—Total, 63 (26 males, 37 females); 24 deaths; 20 necropsies.

"Primary hypertension"	..	..	..	..	49 cases
Chronic nephritis with uraemia	..	..	..	..	11 "
Acute nephritis	..	..	..	..	3 "
Associated cor pulmonale	..	..	..	..	4 "