HYPOTENSION AND OLIGURIA IN STAPHYLOCOCCAL PNEUMONIA*

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Since the introduction of antibiotic therapy over eighteen years ago the *Staphylococcus aureus* has gradually acquired considerable notoriety, not only for an ability to develop resistance to each new antibiotic discovered but also for a tendency to produce severe toxicity where there is systemic involvement.

Recent intensive studies of staphylococcal infections provide much information concerning epidemiology (Williams *et al.*, 1959; Bernstein and McDermott, 1960), drug-resistant strains (Barber *et al.*, 1958; Waisbren and Strelitzer, 1959; Lowbury, 1960), efficacy of treatment with various antibiotics (Walker *et al.*, 1958; *Lancet*, 1960; Kirby *et al.*, 1960; Douthwaite and Trafford, 1960), and radiological features (Gibson and Belcher, 1951; Oswald *et al.*, 1958; Meyers and Jacobson, 1959) where there is lung involvement. Detailed evaluation of the course of treated staphylococcal pneumonia and of the complications encountered has received less generous attention.

The purpose of this paper is to report the occurrence of hypotension and oliguria or anuria as a complication of staphylococcal pneumonia. The mechanism of production and the management of patients are discussed. The relationship between salient features in patients thus affected and in those with staphylococcal pneumonia not showing these sequelae is examined.

Material

All patients with radiologically proved pneumonia in Green Lane Hospital during a 12-month period in 1959-60 were investigated to establish aetiology and to permit accurate assessment of progress on treatment. In addition to repeated sputum examination and culture, investigations included fluid-balance observations; four-hourly blood-pressure, temperature, pulse, and respiration recordings; electrocardiograms; and estimations of non-protein nitrogen. Where hypotension was recorded blood-pressure and pulse were noted half-hourly. Only patients with bacteriologically proved evidence of coagulase-positive organisms have been accepted as suffering from staphylococcal pneumonia.

The criteria adopted for oliguria, anuria, and hypotension were as follows: oliguria, urinary output less than 450 ml. per 24 hours; anuria, no urine per 24 hours; hypotension, systolic blood-pressure below 95 mm. Hg.

There were 165 patients with pneumonia. In 132 this was the principal condition treated. In the remainder pneumonia occurred as a secondary or terminal event where another irremediable condition was responsible for death. These latter cases have been excluded from further deliberation.

Of the 132 patients considered, 48 (36%) produced sputum which repeatedly gave cultures of coagulase-positive *Staph. aureus*. The mortality among this group was 25% (Table I). *Staph. aureus* coagulase-negative organisms were cultured from a further 14 patients, the death rate being 21%. Pneumococci were responsible for pneumonia in 10 patients, while in 60 subjects no

TABLE I.—*Aetiology and Mortality in 132 Consecutive Patients with Radiologically Proved Pneumonia*

Organism	Patients		Results		
	No.	%	Alive	Died	% Died
<i>Staph. aureus</i> , coag. positive	48	36	36	12	25
<i>Staph. aureus</i> , coag. negative	14	11	11	3	21
Pneumococcus	10	8	9	1	10
No pathogenic organism ..	60	45	54	6	10
	132	100	110	22	17

pathogenic organisms were recovered from serial sputum cultures. In the latter group *Escherichia coli* alone, although not regarded as a primary pathogen, was cultured consistently from the sputum of 10 patients. The mortality in non-staphylococcal pneumonia was 10%.

Incidence

Of the 48 cases with staphylococcal pneumonia, 15 either presented with or later developed hypotension and/or significant impairment of renal function (Table II). Twelve patients had both hypotension and oliguria or anuria, two had oliguria without hypotension, and one was hypotensive alone. For simplicity patients with hypotension and oliguria or anuria are hereafter

TABLE II.—*Detailed Observations on 15 Patients with Staphylococcal Pneumonia Complicated by Hypotension and Significant Depression of Renal Function*

Case No.	Sex and Age	State on Admission	Influenza or Chronic Lung Disease	Time from Hospital Admission to Death	Oliguria, Anuria, Hypotension
1	F 59	Fair	C.L.D.	29 days (1 day*)	O.H.
2	M 72	Coma	'Flu. 5 days	58 hours	A.H.
3	F 30	Very ill	" 10 "	—	O.H.
4	M 60	Post-op.	" 10 "	48 hours	O.H.
5	F 30	Coma	'Flu. 5 days	29 "	A.H.
6	M 17	Post-op.	—	5 days	A.H.
7	M 13	Fair	C.L.D.	—	O.
8	F 55	Very ill	'Flu. 10 days	—	O.H.
9	M 63	Semi-coma	C.L.D.	22 days (3 days*)	O.H.
10	F 64	" "	" "	2 hours	O.H.
11	F 50	Post-op.	—	12 "	O.H.
12	M 60	Very ill	'Flu 4 days	10 "	O.H.
13	F 45	" "	C.L.D.	—	O.H.
14	F 33	" "	Pulm. infarct.	—	H.
15	M 64	Semi-coma	—	50 hours	A.H.

A. = Anuria. O. = Oliguria. H. = Hypotension. * Interval between relapse and death.

termed the "complicated" group while others with staphylococcal pneumonia not showing these complications are referred to as the "uncomplicated" group.

Detailed Observations

The relevant data concerning patients in the "complicated" group has been analysed and the prominent features are recorded.

Antecedent History and State on Admission

Of the 15 patients studied, five gave an antecedent history of influenza-like illness beginning 4 to 10 days before admission to hospital (Table II). The interval between onset of pneumonia and arrival in hospital was approximately 12 to 72 hours. Five further patients had suffered from chronic respiratory disease (four with

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chronic bronchitis and one with bronchiectasis) for many years, and in these an exacerbation of respiratory infection had been present between 3 and 12 days. Three patients developed pneumonia in the immediate post-operative period after major surgery for remediable conditions. One of these had suffered from boils of the lower limbs three weeks earlier and another had been treated for a staphylococcal infection of a former operation wound 17 days before surgery. Of the remaining two patients one suffered a pulmonary infarct three weeks before developing the staphylococcal lung infection and the other had no preceding history of influenzal illness or of chronic respiratory complaint.

All three post-operative patients rapidly became confused and two of them were semi-comatose when medical treatment was begun. The remaining 12 subjects presented varying clinical states when seen initially in hospital (Table II). Two were in coma, three were semi-comatose, five were very ill but mentally alert without confusion, and the condition of two was thought to be "fair."

Outcome

The five comatose and semi-comatose patients died, four of them within three days. The condition of two steadily deteriorated until death, but in two others initial improvement was striking, so that for 24 hours recovery appeared likely and mental acuity became normal; both, however, relapsed into a comatose state within 48 hours and died. The fifth patient in this group died after an exacerbation of respiratory infection three weeks later.

The three patients with post-operative pneumonia all died, but of the five who were "very ill" on admission, four survived. One of the two subjects who were "fair" when admitted died from a recrudescence of infection after 29 days.

The time interval between admission to hospital and death was less than 24 hours in three cases, between 24 and 48 hours in two cases, between 48 and 72 hours in two cases, more than 72 hours in one case, and within three days of a relapse in two cases.

Hypotension and Impairment of Renal Function

In most instances hypotension and impairment of renal function were present on admission. Oliguria preceded anuria in three patients, and in the fourth who was thus affected anuria was present at the time of admission. In the few instances where oliguria appeared after admission to hospital it occurred either before or at the same time as hypotension, but not subsequent to a fall in blood-pressure. There were two cases in which oliguria was present on admission and hypotension developed later. In one subject hypotension was present without oliguria or anuria.

The three patients who failed to survive 24 hours in hospital were all hypotensive and while under observation passed no urine. Since at necropsy a few millilitres of urine was found in the bladder of each they were classified amongst the group of oliguria patients (Table II). In general, severe hypotension was associated with a grave prognosis (Table III); however, three patients survived after a period of moderately severe hypotension, in the range of 70 to 95 mm. Hg. Anuria was associated with death in each instance where it occurred, although in one patient anuria had been replaced by a diuretic phase at the time of demise. Four of the nine patients with oliguria survived. These were

the patients in whom oliguria was least severe. Where hypotension or impairment of renal function occurred, one without the other, the three patients concerned survived.

TABLE III.—*Degree of Hypotension and Mortality in Patients with "Complicated" Staphylococcal Pneumonia*

Systolic Blood-pressure	No. of Patients	Outcome		
		Survived	Died	% Died
95+ mm. Hg ..	2	2	0	0
75-95 " ..	8	2	6	75
50-75 " ..	3	1	2	67
<50 " ..	2	0	2	100

Necropsy Findings

Nine of the 10 patients who died were seen at necropsy. All had extensive pneumonia with variable areas of consolidation. Although when alive only two had been adjudged radiologically to have lung abscesses,

TABLE IV.—*Necropsy Findings in Patients with Staphylococcal Pneumonia Complicated by Hypotension and Oliguria or Anuria*

Case No.	Anuria	Pallor	Swelling	Toxic Changes	Tubular Necrosis
1					
2	+	+			+
4					
5	+	+			+
6	+	+	+		
9		+	+	+	
10		+			+
11		+		+	
12					
15	+		No necropsy		
	4	6	2	2	3

FIG. 1.—Case 2. High- and low-power histological appearance of kidney sections, showing renal tubular necrosis. The convoluted tubules are severely affected while the collecting tubules are satisfactory and glomeruli normal.

at necropsy seven had multiple small abscesses and one had two moderate-sized abscess cavities.

Macroscopic renal examination revealed considerable pallor in six cases, with swelling of the kidneys in two instances (Table IV). Histologically renal tubular necrosis was present in two patients (see Fig. 1, Case 2), both of whom had been hypotensive and anuric. In another subject a similar but less definite appearance of tubular damage was observed. Generalized toxic changes were apparent in two further cases. In all subjects adrenal tissue was normal. There were no demonstrable lesions of the myocardium, macroscopically or microscopically.

Comparative Observations

Comparison of salient features in the "complicated" and "uncomplicated" groups of staphylococcal pneumonia were undertaken to elucidate further relationships between the two.

General

The mortality among patients in the "uncomplicated" group was 6% compared with 67% in the "complicated" group (Table V). The average age of patients in the former group was 54.4 years, and among those who died 69 years; in the latter group the corresponding figures were 47.7 years and 53.9 years.

TABLE V.—Outcome of Treatment of the "Complicated" and "Uncomplicated" Groups of Patients with Staphylococcal Pneumonia

Group	Male	Female	Total	Died	% Mortality
"Complicated"	7	8	15	10	67
"Uncomplicated"	19	14	33	2	6

The occurrence of hypotension and oliguria or anuria complicating pneumonia was observed in two patients from the general group of non-staphylococcal pneumonias. In one instance a pneumococcus was responsible and the patient survived. In the other a coagulase-negative *Staph. aureus* was repeatedly cultured from the sputum and the patient died.

Radiological Features

In addition to counting the number of zones involved, further radiological comparison between the "complicated" and "uncomplicated" groups was attempted by awarding points for the density of shadowing in each zone: four points for a complete "white-out," three points for moderately severe opacification, two points for light to moderate shadowing, and one point for minimal opacity. Interpretation of x-ray films was made without knowledge of the group to which each subject belonged and of the outcome.

The results of this assessment are seen in Tables VI and VII. In general more extensive lung involvement

TABLE VI.—Zones of Lung Involved Radiologically in Patients with "Complicated" and "Uncomplicated" Staphylococcal Pneumonia

Zones	"Complicated" Group			"Uncomplicated" Group		
	Alive	Dead	Total	Alive	Dead	Total
4 or more	4	7	11	1	0	1
3	0	3	3	6	0	6
2	1	0	1	9	2	11
1	0	0	0	15	0	15
	5	10	15	31	2	33

and heavier shadowing of zones concerned were associated with a more serious outlook: 93% of the "complicated" group had three or more zones involved, while 18% of the "uncomplicated" group had radio-

TABLE VII.—Comparison of Density of Shadowing Radiologically in the Same Groups as in Table VI

Zones	Average Scores			
	"Complicated" Group		"Uncomplicated" Group	
	Alive	Dead	Alive	Dead
4 or more	8.25	10.4	11.0	—
3	—	9.0	7.1	—
2	6.0	—	4.5	4.5
1	—	—	2.3	—

logical evidence of equally extensive involvement. Among patients in the "complicated" group the points scored for density of shadowing were significantly higher in those who died than in those who survived (Table VII).

Six of the 48 patients with staphylococcal pneumonia were observed to have lung abscesses. Four were large, and occurred in the "uncomplicated" group; two were small and multiple, being observed in patients from the "complicated" group.

Sensitivity to Antibiotics

Routine antibiotic sensitivity tests to organisms cultured from sputum collected on admission are shown in Table VIII. Since no sputum was produced initially from three patients these have been omitted from this assessment. Five antibiotics were routinely tested in each of three groups: coagulase-positive *Staph. aureus*,

TABLE VIII.—Drug-resistance to Penicillin, Streptomycin, Tetracycline, Chloramphenicol, and Erythromycin by Coagulase-positive and Coagulase-negative Staphylococci

Organisms	No. of Cases	% Drug Resistance				
		Pen.	Strep.	Tetr.	Chlor.	Erythr.
Coagulase-positive:						
"Complicated" group	12	83	8	17	0	0
"Uncomplicated" group	33	76	12	43	12	3
Coagulase-negative	14	50	11	36	9	2
Total	59	71	17	34	10	2

"complicated" patients; coagulase-positive *Staph. aureus*, "uncomplicated" patients; coagulase-negative *Staph. aureus*. In each group an increasing sensitivity and decreasing resistance was apparent in the series penicillin, tetracycline, streptomycin, chloramphenicol, and erythromycin. In general, organisms from the "complicated" group showed less resistance to antibiotics than those from other groups. Penicillin alone was an exception. Only one of the 59 patients produced organisms that were resistant to erythromycin, and in this instance there was sensitivity to novobiocin. Tests for the latter drug were undertaken only where resistance was present to four or more of the antibiotics normally considered. No examples of resistance to novobiocin were encountered.

Sputum and Blood Investigations

Twelve of the "complicated" group were able to produce sputum, and a tentative diagnosis of staphylococcal pneumonia was made on examination of a direct smear. The remaining three cases were too ill to produce sputum, but the diagnosis was strongly suspected from x-ray appearances and clinical toxicity. The bacteriological diagnosis was proved at necropsy. In the

"uncomplicated" group diagnoses were possible from sputum culture in all cases. The volume and appearance of sputum gave no indication of whether subjects belonged to the "complicated" or "uncomplicated" groups.

The leucocyte count likewise was of little assistance. In some instances where pneumonia had been present for a few days counts of 30,000 per c.mm. or higher were obtained from either group, but in some of the most seriously affected patients the counts were within normal limits, especially if pneumonia had been of short duration.

Estimations of non-protein nitrogen gave corroboratory evidence of impairment in renal function; however, this was a less sensitive index of progress than simple observation of fluid balance.

Treatment

Patients were treated with antibiotics, bed rest, and oxygen. Additional problems included management of renal failure, preservation of a satisfactory airway, and maintenance of systolic blood-pressure above 90 mm. Hg. Antibiotics were initially administered in various combinations, but as the pattern of sensitivities from sputum culture became clearer (Table VIII), erythromycin plus novobiocin was used for the immediate treatment in later patients of the series. In some instances massive doses of penicillin were added. The number of occasions each antibiotic was used, together with the dosage, is shown in Table IX.

TABLE IX.—Antibiotics Used in Treatment of Staphylococcal Pneumonia Complicated by Hypotension and Oliguria or Anuria, with Dosage Used and the Outcome

Antibiotic	Total Treated	No. Died	Dose Used
Erythromycin	9	5	2 g. day
Novobiocin	9	5	2 " "
Chloramphenicol ..	6	4	2 " "
Streptomycin	5	4	1 " "
Penicillin	10	8	2-60 mega u. day

In earlier patients antibiotic therapy was continued for 10 to 14 days. Later, however, after two patients (Cases 1 and 9) had both suffered an exacerbation of pneumonia with fatal outcome, the routine duration of treatment was lengthened. Antibiotic therapy was maintained for at least four and up to eight weeks.

Hydrocortisone, 100 mg. six-hourly, was the initial choice in combating hypotension. In two patients who were not severely hypotensive it proved sufficient to maintain the desired systolic blood-pressure. In cases where it was ineffective, either phenylephrine hydrochloride ("neophryn," "neosynephine") or mephentermine sulphate was administered. In one patient the former was effective where mephentermine sulphate had failed, and in another it was adequate where hydrocortisone had previously been ineffective. In two subjects, however, phenylephrine proved valueless. Mephentermine sulphate was used without satisfactory result in three subjects. Noradrenaline was given to six patients, all of whom had previously received some other agent in an unsuccessful attempt to raise blood-pressure. In five it was effective, but in the sixth even massive doses were ineffectual.

Oxygen was most satisfactorily administered by oxygen tent except on two occasions when positive-pressure artificial respiration was necessary. Respiratory obstruction by secretions was helped by tracheostomy and suction on two occasions. One patient required

digitalis and one was given quinidine for multiple ventricular extrasystoles. Severe oliguria or anuria was managed by a modified Bull regime (Bull *et al.*, 1955).

The pattern of management is illustrated by two case histories.

Case 2.—A man aged 72 developed influenza five days before admission. He had been treated with penicillin, streptomycin, and tetracycline for three days. On admission he was comatose, the blood-pressure was unrecordable, and the carotid pulse 106 a minute. Chest x-ray examination showed patchy shadowing in all areas of the lungs. The score for density of opacification was 11. Treatment began with erythromycin and novobiocin. Hydrocortisone, phenylephrine, and mephentermine sulphate did not produce a recordable blood-pressure. Ten minutes after introducing noradrenaline intravenously the blood-pressure was 110/70 (Fig. 2). The rate of infusion was subsequently reduced

FIG. 2.—Case 2. Temperature, pulse, respiration, and blood-pressure on admission and at intervals. Hydrocortisone, mephentermine sulphate, and phenylephrine produced no effect upon blood-pressure. The response to noradrenaline is illustrated. Restoration of blood-pressure led to marked clinical improvement. After 58 hours there was sudden deterioration and death ensued.

gradually until a satisfactory blood-pressure was maintained without assistance in 12 hours. The patient was then mentally bright and alert. Twenty-four hours later generalized muscular twitching developed. After passing 240 ml. of urine initially there was no further production of urine. The T.N.P.N. rose to 84 mg. per 100 ml. Fifty-eight hours after admission there was a precipitate fall in blood-pressure, coma reappeared, and death rapidly ensued. At necropsy there was widespread pneumonia with numerous small abscesses. Histologically the kidneys showed renal tubular necrosis (Fig. 1).

Case 3.—A woman aged 30 had influenza for 10 days. Her three children were treated for recurrent staphylococcal skin infections during the preceding four weeks. Two days before admission her chest was considered to be clear on clinical examination, but 12 hours later pneumonia was apparent and treatment was begun with penicillin and streptomycin. In hospital, chest x-ray examination showed patchy shadowing of the right mid and lower zones and the left lower zone. The opacity score was 8. She was given erythromycin and novobiocin. The leucocyte count

was 46,000 per c.mm., and the blood-pressure, initially 100/70, soon fell to 70/45 (Fig. 3). This was corrected and maintained by intravenous hydrocortisone. Thirty hours later the systolic blood-pressure again fell to 70 mm. Hg despite continuous hydrocortisone therapy. After mephentermine sulphate had proved ineffective an adequate blood-pressure was maintained by use of phenylephrine. The condition steadily improved and recovery ensued. Chest x-ray examination after three weeks showed complete clearing, while the leucocyte count had fallen to 7,300 per c.mm.

FIG. 3.—Case 3. Temperature, pulse, respiration, and blood-pressure on admission and at intervals for three days. It is apparent that hydrocortisone was initially effective in restoring satisfactory blood-pressure. Later mephentermine sulphate (M) then phenylephrine (N) was necessary to maintain improvement. After three days blood-pressure remained satisfactory without assistance.

Discussion

The incidence of staphylococcal pneumonia and the degree of toxicity encountered vary from country to country and even from time to time in any one country. Stuart-Harris (1959) thought that with staphylococcal pneumonia increased incidence and heightened toxicity occur in association with epidemic influenza. Williams (1959) concluded that there were substantial differences in the pathogenic abilities of different phage types of staphylococci, and this may help explain the considerable variation in incidence and mortality published in recent years. Whereas Ede *et al.* (1959), in the U.S.A., found the incidence of staphylococcal pneumonia to be 1.5% and mortality in these subjects less than 3%, Oswald *et al.* (1958), in London, reported the incidence as 12% and the death rate as 28% compared with 12% in non-staphylococcal pneumonia. In Australia, among children, Harley (1957) found the mortality in 32 cases to be 28%; while, in New Zealand, Hay (1960) reported the death rate among patients having staphylococcal pneumonia and septicaemia to be 45%. The mortalities in the present series of staphylococcal (25%) and non-staphylococcal (10%) pneumonia appear average and are similar to the findings of Oswald *et al.*

The incidence, however, at a time when there were no notable epidemics of influenza in New Zealand was surprisingly high. Less than one-third of patients presented in conjunction with an influenzal illness. Approximately a further one-third of the cases followed an exacerbation of chronic lung disease, while the remaining one-third occurred as primary pneumonia or as a post-operative complication. The relatively low incidence of pneumococcal pneumonia and the absence of pneumonia due to *Haemophilus influenzae* during the interval under surveillance suggests that staphylococci are the commonest respiratory pathogens in this area. Experience with acute and chronic bronchitis shows a similar trend. It is possible that the incidence of staphylococcal pneumonia is influenced not only by influenzal epidemics, varying pathogenicity, and changing virulence but also by local or national tendencies for predominance of certain pathogenic organisms.

Despite the prevalence of staphylococcal pneumonia resistance to antibiotics appears no more pronounced here than in other countries. Ede *et al.* attributed their favourable therapeutic results to the organisms in their patients being acquired outside hospital, since more resistant types of staphylococci are to be expected within such institutions. They thought that more-resistant organisms caused more severe rapidly advancing infections that were difficult to control. This, however, has not been the experience in this series, where resistance to antibiotics was in fact less in patients who developed hypotension and impairment of renal function than in those who developed uncomplicated staphylococcal pneumonia.

Although severe circulatory collapse has been encountered previously (Lefroy and Keall, 1954; Oswald *et al.*, 1958) we have been unable to find any reference to hypotension and oliguria or anuria in papers relating to staphylococcal pneumonia. Lefroy and Keall noted unrecordable blood-pressures in two patients with staphylococcal pneumonia, while Oswald *et al.* mentioned peripheral circulatory collapse, but, apart from the use of cortisone and hydrocortisone, further measures to tide patients over the critical period of toxicity were not mentioned and in neither instance was reference made to renal function.

Depression of renal function in patients with pneumonia has been noted less directly in papers dealing with acute renal tubular necrosis. Bluemle *et al.* (1959) found pneumococcal pneumonia to be the principal cause in 2 out of 100 cases of acute renal tubular necrosis, while Loughridge *et al.* (1960), in describing 28 cases of uncomplicated acute tubular necrosis which survived and in which the primary cause was medical or obstetrical, listed two as being due to staphylococcal pneumonia. In the same paper, among 11 patients with uncomplicated acute tubular necrosis who failed to survive were two cases caused by staphylococcal pneumonia and both were also hypotensive. Neither was treated with haemodialysis and there was no indication regarding the management of hypotension.

Circulatory collapse in staphylococcal pneumonia has been attributed to severe toxæmia (Oswald *et al.*, 1958), and the necropsy findings in our patients do not disagree with this concept. The causation of anuria and oliguria, however, is possibly more complex. Renal tubular necrosis occurred in at least two and possibly three of this series, and it is probable that toxicity played a major part in its production. Where impairment of renal

function was less severe and tubular damage could not be demonstrated histologically at necropsy, however, hypotension, anoxia, and even the use of hypertensive agents in treatment may be contributory factors and require consideration. Some indication of the part played by hypotension may be derived from present evidence. There were occasions in this series when oliguria occurred without low blood-pressure. When hypotension developed after admission its appearance was preceded by oliguria in each instance. In these cases at least, and in the subject who was hypotensive but not oliguric, hypotension was unlikely to have been a major factor in producing impairment of renal function.

The influence of anoxia is more difficult to assess. In pulmonary heart disease with anoxia and acute cardiac failure, renal tubular necrosis has been reported in the absence of a staphylococcal infection causing toxicity (Kellaway, 1959). The arterial oxygen saturation in this series was estimated in one-half of the patients with hypotension and depression of renal function. It varied from 62% to 88%. This is only a little higher than the levels (50% to 75%) commonly seen in pulmonary heart disease with cardiac failure (Kellaway, 1961), and many cases were actually in this range. In the latter patients not having renal tubular necrosis there is considerable impairment of renal function for several days even after restoration of satisfactory arterial oxygen levels. It does not seem possible, therefore, to exclude anoxia as at least a contributory factor in the causation of oliguria, and even anuria, in patients with staphylococcal pneumonia.

The diagnosis and the original choice of antibiotics are of extreme importance in the management of patients with severe staphylococcal pneumonia. We found that direct examination of a Gram-stained sputum smear was the single most valuable examination available where the patient appears ill and this condition is suspected. It can be undertaken in a matter of minutes. Chest x-ray examination is also useful, not only because staphylococcal pneumonia is often suggested by the widespread dissemination of lesions but also because the number of zones involved and the intensity of opacity are a guide to the severity of infection and prognosis.

It has been rightly stated that each case requiring antibiotic treatment should be judged on its own merits when deciding which drug is to be administered (Garrod and Scowen, 1960). Immediate treatment is necessary in severe staphylococcal pneumonia before drug sensitivities are known. The initial choice of antibiotics therefore logically depends upon the known local pattern of organism resistances. At present in this locality only 2% of staphylococci are insensitive to erythromycin and novobiocin, hence this combination has been accepted as first choice. Although Hirsch and Finland (1960), in extensive studies of antibiotic combinations, have been unable to show synergism in any combination assessed, the use of a mixture appears reasonable in avoiding the development of resistance (Barber *et al.*, 1958). Where erythromycin and novobiocin are concerned staphylococcal resistance develops particularly rapidly when they are used singly, but in combination there is delay in the appearance of drug-resistant strains both *in vitro* and *in vivo* (Lowbury, 1957).

The combination of erythromycin and chloramphenicol is probably less satisfactory, and Barber

et al. (1960) have reported that it did not prevent the development of resistant organisms, possibly because a degree of cross-resistance exists between these two antibiotics. Once sputum culture and drug-sensitivity results are known resistance to antibiotics in common use may necessitate the use of more recently introduced agents such as vancomycin (Kirby *et al.*, 1960) or the newer penicillin derivatives (*Brit. med. J.*, 1960).

Hypotension complicating staphylococcal pneumonia was found to be associated with a poor prognosis. Three patients were successfully tided over the period of severe toxicity by use of hypertensive agents. It has been suggested by Walker *et al.* (1958) that the use of steroids in staphylococcal pneumonia is dangerous. Where circulatory collapse is present, however, Oswald *et al.* (1958) recommended that they be used, and in two patients encountered here hydrocortisone proved sufficient to maintain the required blood-pressure where discontinuation of its administration led to reappearance of hypotension. More profound lowering of blood-pressure, however, demands the use of specific hypertensive agents, of which noradrenaline proved most effective.

The group of patients with pneumonia and *Staph. aureus* coagulase-negative organisms repeatedly cultured from the sputum have been detailed separately from other groups in this series. The mortality for this group, not generally regarded as genuine staphylococcal pneumonia, was 21%—twice the mortality of non-staphylococcal pneumonia. It can be argued that insufficient sputum specimens were examined for coagulase-positive organisms to be isolated. The average number of sputa per patient studied in this group, however, was 5.3, which compares closely with the coagulase-positive group, where the average was 5.5. Resnekov (1959) found that coagulase-negative staphylococci occurred on more occasions than coagulase-positive organisms in his series of patients with staphylococcal endocarditis after mitral valvotomy. This suggests that coagulase-negative staphylococci in some instances may be more pathogenic than is generally accepted. Whether this is in fact correct or not the clinical implication is that where staphylococcal pneumonia is suspected and coagulase-negative organisms are persistently cultured it is probably wise to treat patients as for staphylococcal pneumonia, accepting the sensitivities reported for the organisms cultured.

Summary

At Green Lane Hospital, Auckland, New Zealand, *Staphylococcus aureus* is the commonest pathogen causing pneumonia. Hypotension, oliguria, and anuria are reported as complicating severe staphylococcal pneumonia. These sequelae were related to prominent features in 48 consecutive cases of staphylococcal pneumonia. Whereas the mortality in 83 patients with non-staphylococcal pneumonia was 10%, in subjects with staphylococcal pneumonia it was 25%, and in 15 cases with hypotension and significant depression of renal function it was 67%.

The immediate management of patients with staphylococcal pneumonia is important, especially where impairment of renal function and hypotension are present. Clinical evidence of toxicity, direct sputum examination, and radiological features provide the most useful evidence for the early diagnosis, and, where suspected, blood-pressure and urinary output require close observation.

The initial choice of antibiotic combinations for treatment depends largely on the local pattern of drug resistances and knowledge of pairs of drugs which delay development of resistance. Noradrenaline was the most effective hypertensive agent used for maintenance of systolic blood-pressure at a satisfactory level, but in less severely affected subjects hydrocortisone and phenylephrine hydrochloride proved useful substitutes.

In some instances depression of renal function was due to acute renal tubular necrosis. Toxaemia appeared to be mainly responsible and appropriate treatment was necessary. In other instances anoxia and to a less extent hypotension and hypertensive agents used in treatment were at least contributory in causing oliguria.

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Mental Health in International Perspective is the report of an international study group held in June, 1961, at the Roffey Park Institute, Horsham. Its primary function was to make a broad survey of the progress being made in the many aspects of the mental health field throughout the world. An attempt was made to cover the spectrum of interests from research and care of the mentally sick at the one end to international relationships at the other. A more detailed report is to be published in the summer of 1962. The study was financed by the U.S. Public Health Service (National Institute for Mental Health). The report is not for sale, but single copies are available free from the World Federation for Mental Health, 19 Manchester Street, London W.1.

TREATMENT OF STAPHYLOCOCCAL INFECTIONS WITH METHICILLIN

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Since the introduction of methicillin several authors have published papers reporting results of treatment with this drug. Douthwaite and Trafford (1960) quoted 13 cases, in all of which infection was eliminated. Stewart *et al.* (1960) quoted 17 cases, in all of which the staphylococcus was eliminated from the infected sites, although not necessarily from carrier sites. Douthwaite *et al.* (1961) reported 46 cases that responded to methicillin, but in six of these the staphylococcus recurred. Lowbury *et al.* (1961) treated 54 patients with burns colonized by *Staph. pyogenes*, but the organism persisted in 20.

In this hospital methicillin has been in use since January, 1960, and 34 cases had been treated with the drug up to the end of May, 1961. Although in many of these cases the response to methicillin was excellent, in some, mostly those with serious underlying disease, the response has not been so good.

In most cases methicillin was given alone so that its clinical effectiveness could be judged. This is an exception to the practice of this hospital of always giving two antibiotics in combination (Barber *et al.*, 1960). In a few instances, usually in patients with severe illness, other antibiotics were given concurrently; however, the interval between starting these and methicillin was sufficient in almost all cases to give some indication of the response to the latter. The dose, except in children, was 6 g. daily for the first 48 hours and 4 g. a day thereafter by intramuscular injection. Courses varied from a total of 24 to 136 g.

Clinical Material.—The conditions for which methicillin was used are set out in Tables I and II. The following brief comments and histories illustrate some of the different cases treated.

Respiratory Infections

Of the 12 patients who had respiratory infections, seven had staphylococcal pneumonia, two a presumed staphylococcal pneumonia, two had exacerbations of bronchitis with *Staph. pyogenes* in the sputum, and one patient had a lung abscess. Most of these patients had severe underlying disease, as can be seen from Table I, which also shows the phage type and the clinical response to methicillin. All strains of staphylococci isolated were resistant to at least penicillin and one other antibiotic, and in most cases to three or four antibiotics.

Successes

Six patients with pneumonia and one with bronchitis did well, all having failed to respond to previous antibiotics.

Case 1. Staphylococcal Pneumonia.—A woman aged 65 had a local excision and deep x-ray therapy for carcinoma