division is detailed. Complete gastric nerve section is demonstrated by stimulation.

Two series of cases are compared. Since the coeliac innervation has been preserved there has been no case of diarrhoea.

REFERENCES

- Burge, H., and Pick, E. J. (1958). *Brit. med. J.*, 1, 613.
— and Vane, J. R. (1958). *Ibid.*, 1, 615.
McCrea, E. D. (1924). *J. Anat. (Lond.)*, 59, 18.
— (1926). *Brit. J. Surg.*, 13, 621.
von Mering and Aldehoff (1899). *Zbl. inn. Med.*, 20, 462.

VANCOMYCIN: REPORT ON TREATMENT OF PATIENTS WITH SEVERE STAPHYLOCOCCAL INFECTIONS

BY

A. A. C. DUTTON, M.A., B.M., B.Ch.

Assistant Lecturer, Department of Bacteriology,
Postgraduate Medical School of London, Hammersmith

AND

P. C. ELMES, M.A., M.D., M.R.C.P.

Senior Registrar, Department of Medicine, Postgraduate
Medical School of London, Hammersmith

This paper describes the use of vancomycin in the treatment of nine patients in Hammersmith Hospital who suffered from severe staphylococcal infection of the blood stream, lungs, or operation wounds.

The prevalence in hospital of strains of *Staphylococcus pyogenes* resistant to several antibiotics has led to "the present-day pharmaceutical equivalent of the Gold Rush . . . for new antibiotics" (*Lancet*, 1957). Hospital in-patients are now not uncommonly infected by strains of staphylococci resistant to four or five of the antibiotics to which this species is normally sensitive. Furthermore, all the antibiotics which can be used in the treatment of staphylococcal infections of the lungs, blood stream, or other deep-seated lesions, and which have been introduced since penicillin and streptomycin, are predominantly bacteriostatic.

The isolation of vancomycin from *Streptomyces orientalis* by McCormick *et al.* (1956) was important, for the drug is bactericidal for Gram-positive cocci

(Ziegler *et al.*, 1956; Geraci *et al.*, 1956). Moreover, the numerous strains of *Staph. pyogenes* tested against it have been almost invariably sensitive (Fairbrother and Williams, 1956). As shown by Garrod and Waterworth (1956), neither cross-resistance with other antibiotics nor the development of material degrees of resistance *in vitro* has been found.

The drug is poorly absorbed from the intestine. The current preparation is too irritant for intramuscular injection, and, in any case, the drug is not well absorbed by this route. It must therefore be given intravenously.

Geraci *et al.* (1956) found that vancomycin was almost entirely excreted in the urine with a small amount in the bile and faeces. It begins to accumulate in the blood after the first two or three days' treatment.

Although direct intravenous injections can be given, there is a material risk of thrombophlebitis unless veins are used in rotation. The method of intravenous administration least likely to cause thrombophlebitis is by infusion in about 250 ml. of diluent over about 30 minutes or, where applicable, by admixture with a saline or 5% dextrose "drip." Because of the need to give the drug intravenously, and because of its toxicity (see below), vancomycin is at present mainly used for severe staphylococcal infections in hospital, and it is such a group of nine patients that is described here.

Treatment of Patients

The nine patients were not selected; they comprise all those treated with vancomycin at Hammersmith Hospital up to August, 1958, except for three patients who received the drug only when *in extremis*. Information given in the following case reports is summarized in Tables I, II, and III. Eight of the nine patients (Cases 1-8) had failed to respond to other antibiotics before vancomycin was used.

Table I shows the patients' presenting illness, the nature of the staphylococcal infection, and the response to vancomycin. Those who received an adequate course of the drug responded well clinically.

Table II indicates the antibiotic sensitivity pattern and phage type of the strains of *Staph. pyogenes* isolated and the preceding courses of antibiotics given to the patients.

Severe loss of auditory acuity followed treatment in several patients, and Table III shows the incidence and its relation to high blood urea levels.

TABLE I.—Infections and Response to Treatment

Case No.	Age and Sex	Admitted to Hospital for Treatment of	Site(s) of Staphylococcal Infection(s)	Response to Vancomycin Treatment	
				Clinical Response	Elimination of Infecting Staphylococcus
1	78 M	Gangrene of foot (arterio-sclerotic) with mild diabetes	Transfusion and amputation wounds (leg), lungs	Rapid complete recovery	No
2	37 F	Asthma with chronic suppurative bronchitis	Lungs	Slow but good recovery from acute-on-chronic infection	"
3	19 wks. M	Paroxysmal cough	Lungs (throat swabs)	Slow but good recovery	Yes
4	28 F	Bilateral lobar pneumonia with anuria	Blood	" " " "	"
5	42 M	Bronchopneumonia with renal failure	Lungs, blood	Rapid recovery	"
6	49 M	Post-operative anuria (following partial nephrectomy)	Wound, blood	Recovery from staphylococcal infection but died of <i>Ps. pyocyanea</i> septicaemia	"
7	55 F	Oliguria and biliary peritonitis (following cholecystectomy)	Cholecystectomy wound, lungs, peritoneal cavity		No
8	73 M	Bilateral basal pneumonia	Lungs	Rapid initial improvement on vancomycin but relapsed and died when other chemotherapy substituted	No follow-up specimens seen, but presumed not eliminated
9	63 F	Persistent vomiting (due to carcinoma of stomach)	Blood		No

Table IV gives the results of serum vancomycin assays by a rapid method in a tenth patient who was anuric. The dosage of vancomycin was controlled by the assay results.

Method of Administration.—Vancomycin was given intravenously by direct injection in 20 ml. of saline over a five-minute period; by infusion in 250 ml. over a 30-minute period; or, diluted with larger volumes of saline or 5% glucose, through a vena cava catheter over several hours. The total daily dose (Table III) was 1–2 g., except for Case 3, and was given as two equal 12-hourly doses. No patient received vancomycin for longer than 15 days, and the maximum course was 22 g.

Bacteriological Methods

Bacterial strains referred to in the case notes were isolated from the patient's specimens by routine laboratory methods. The amount of growth is shown as +, ++, or +++. The sensitivity of strains of *Staph. pyogenes* to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, and vancomycin was tested on nutrient agar or horse blood agar by a ditch-plate technique, using the Oxford strain of staphylococcus as a control and incubating at 37° C. for 18 hours. Sensitivity (S) or resistance (R) to each antibiotic is indicated in the case notes in the order of drug just given—for example, RRRSSS denotes that the strain was resistant to penicillin, streptomycin, and tetracycline, but sensitive to chloramphenicol, erythromycin, and novobiocin. All strains were sensitive to vancomycin; those not eliminated from the body by treatment remained sensitive. Bacteriophage typing of the strains was carried out in this laboratory by the method of Williams and Rippon (1952), using 21 phages. The types are indicated in Table II and follow the sensitivity pattern in the case notes. Serum vancomycin assays were not undertaken routinely during the treatment of these nine patients but have been introduced subsequently (see below and Table IV).

Case 1

A man of 78 with mild diabetes—admitted with arteriosclerotic gangrene of one foot. Treated for the sepsis of one toe with penicillin and streptomycin.

Day 30: Toe excised—pus yielded *Staph. pyogenes* (+++, SSSSSS, 52/52A). Days 32–39: Erythromycin alone. Progressive local and general deterioration. Day 49: Above-knee amputation. Day 53: Chest pain—myocardial infarction. Day 57: *Staph. pyogenes* (RRRSRS, 80) isolated from sputum (+) and transfusion wound (+++). The latter also yielded *Clostridium welchii*, treated with penicillin. Day 59: Chloramphenicol started.

Day 62: Left basal pneumonia. Sputum yielded *Staph. pyogenes* (+++, RRRSRS, 80).

Days 62–68: Vancomycin (total 10 g.) with rapid improvement in general and local condition after first two days. Day 64: Type 80 staphylococcus (+++) isolated from amputation and transfusion wounds. Days 78–80: Improvement maintained, but type 80 organisms were still recovered from his amputation wound (+++) and sputum (+) on these two days in spite of a further course of 4 g. of vancomycin. For this reason he was transferred to a fever hospital, where he recovered after further vancomycin.

TABLE II.—Antibiotic Sensitivity and Bacteriophage Types of Infecting Strains of *Staph. Pyogenes*

Case No.	Courses of Chemotherapy before Vancomycin	<i>Staph. pyogenes</i> Strains							Phage Type
		Antibiotic Sensitivity Pattern							
		P	S	T	C	E	N		
1	{ (1) P+S (2) E, (3) C	S R	S R	S R	S S	S R	S S	52/52A 80	
2	{ P, T, C, Sulphonamides .. E+C	R R R	R R R	R R R	S S R	S R R	S S S	79/47/53/77 + *	
3	{ (1) T+sulphonamides .. (2) E+C, (3) E+S+N ..	R R	S S	R R	S S	S R	S S	80+ 80	
4	{ (1) P, (2) E, (3) S .. (4) E+T, (5) C+T ..	R R	S S	S S	S S	R R	S S	N.T. N.T.	
5	{ (1) S+C (2) S+T+C, (3) E+C ..	R R	R R	R R	S S	S S	S S	80/53+ 80/53+	
6	(1) E+C, (2) T+C ..	R R	R R	R R	S S	R R	S S	53/54/77	
7	E+C	R R R	R R R	R R R	S S R	S S R	S S S	77+ 77+ 77	
8	{ (1) P+S (2) T, (3) C	R R	R R	R R	S S	S S	S S	47/53/77	
9	Nil	R	R	R	S	S	S	47/53/77	

P=Penicillin. S=Streptomycin. T=Tetracycline. C=Chloramphenicol. E=Erythromycin. N=Novobiocin. All strains were sensitive to vancomycin. * Strain failed to type at 1,000 × routine test dose of bacteriophages. N.T.=Not tested. In columns 3–8, under "Antibiotic Sensitivity Pattern," "S"=Sensitive.

TABLE III.—Incidence of Deafness in Relation to Renal Function

Case No.	Approximate Blood Urea (mg./100 ml.) during Vancomycin Treatment	Vancomycin Dosage (g.)			Effect on Hearing
		Daily Total*	No. of Days	Total	
1	60 falling to 24 ..	{ 1st course 1–2 2nd .. 2	6 2	14	Nil
2	Normal	{ 1st .. 1–2 2nd .. 2	4 5	22	..
3	Presumed normal ..	{ 400 mg. 1 1st course 2	5 2	2	..
4	400 falling to 100 ..	{ 1st course 2 2nd .. 1	5 4	13	Severe
5	440 310 ..	{ 2 1	2 3	7	..
6	385, reduced to 200 by dialysis, and then rising again	{ 2 1	2 2	6	..
7	380 falling to 280 ..	{ 2 1	5 2	12	Not known
8	380 68 ..	{ 2 1	1 5	7	Probably deaf†
9	16 rising to 66 ..	{ 2	6	12	Severe

* Given as two equal doses at 12-hourly intervals except Case 3 (=100 mg. six-hourly).

† Patient very disorientated.

TABLE IV.—Serum Vancomycin Levels During Treatment of a Uraemic Patient

Day:	1	2	3	4	5	6	7	8	9	10	11
Renal function: Blood urea (mg./100 ml.) ..	270	281	300	296	260	192	193	150	88	104	102
Vancomycin: Dosage* (mg.) ..	500	0	250	375	250 t.d.s.	250 b.d.	250	250 b.d.	500, 250	500, 250	250 b.d.
Route	I.V.								I.V.	infusion	
Vol. diluent/dose ..	20 ml.								500 ml. (8 hrs.)	200 ml. (30 mins.)	
Serum vancomycin levels (μg./ml.):											
Highest ..	33†	12	6	10	9	16.6	20	8	14	14.4	6
Lowest ..	—	9.3	5	3.3	8	8	10.8	6.2	4.4	7	3.8
No. of assays	1	2	4	4	3	3	3	2	4	4	3

* Total amount given, 5.125 g.

† High level probably due, in part, to chloramphenicol treatment, which ceased on this day.

Whilst at Hammersmith Hospital the blood urea did not exceed 60 mg./100 ml., subsequently falling to 24 mg./100 ml. The patient was slightly hard of hearing throughout. He suffered no further loss of auditory acuity as the result of vancomycin treatment.

Case 2

A woman of 37, asthmatic since childhood, with suppurative bronchitis for 10 to 15 years, leading to pulmonary fibrosis and cavitation. Admitted for control of the infection after out-patient chemotherapy had failed (penicillin, tetracycline, chloramphenicol, sulphonamides).

Days 2-19: Erythromycin + chloramphenicol. *Day 4:* Sputum: *Staph. pyogenes* (+ + +, RRRSSS, 79/47/53/77+). *Days 8, 9:* Sputum: still positive. *Days 4-19:* After brief improvement her condition deteriorated, with progressive breathlessness and sputum increasingly purulent. *Days 17-19:* *Staph. pyogenes* (+ + +, now additionally resistant to erythromycin, RRRSRS).

Days 19-23: Vancomycin given by direct injection (total 6 g. only), with chloramphenicol, produced dramatic improvement, with marked diminution of sputum. *Day 23:* So much improvement that patient was allowed home for Christmas.

Readmission.—Four days later was readmitted with a relapse. *Days 1-9:* Sputum yielded a varying flora, including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Steady improvement with streptomycin and tetracycline, in spite of the reappearance, on *Days 10-12*, of the original strain of *Staph. pyogenes* (+), apparently now with a less virulent role.

Days 14-24: Second course of vancomycin was given (total 16 g.) to eliminate the staphylococcus, but it was consistently isolated from six sputum specimens between *Days 15* and *28*. Her convalescence was not further hastened by the drug; she was discharged on *Day 28*. Over the next three months she remained well: the original strain of *Staph. pyogenes* was isolated occasionally from several specimens of sputum.

The patient showed no signs of renal incompetence and maintained excellent hearing both in hospital and after her discharge. There was severe thrombophlebitis of arm veins after vancomycin injections, and immediately after injections she experienced marked but very temporary hot flushes.

Case 3

A boy of 19 weeks with persistent nasal discharge and severe paroxysmal cough was admitted with pneumonia, with consolidation and, later, cavitation in the upper lobe of his right lung. Over three successive periods of about 18 days clinical improvement gave way each time to serious relapse.

Days 1-18: Remittent fever. Treated with tetracycline and sulphonamides for 12 days with some improvement. *Day 13:* Temperature rose to 103° F. (39.4° C.) and *Staph. pyogenes* (RSRSSS, 80) was isolated from a neck boil and consistently (*Days 16, 17, 18*) from both nose and throat swabs (+ + +).

Days 19-36: From *Days 18-30* chloramphenicol and erythromycin given and the temperature became and remained normal for about two weeks except on one occasion (105° F.—40.6° C.). Blood cultures (*Days 26, 29*) were sterile. From *Day 29* novobiocin replaced chloramphenicol. *Day 33:* Throat swab again positive (+) with the type 80 staphylococcus. *Day 36:* Patient again very ill—temperature rose to 102° F. (38.9° C.). *Pseudomonas pyocyanea* was isolated from an indwelling feeding-tube.

Days 37-57: Patient on streptomycin, erythromycin, novobiocin, and prednisolone. Temperature fell and remained down for three weeks. Throat swab cultures on *Days 42* and *54* did not yield staphylococci, but the child's condition began to deteriorate and he got much worse towards the end of this period.

Vancomycin given *Days 57-62*, total 2 g., and the child had a blood transfusion. From *Day 59* until *Day 99* there was slow but increasing improvement. The chest cleared clinically, although leaving an area of consolidation with some cavitation in the upper lobe of the right lung. On *Day 99* the boy was discharged home very well.

The child had always been somewhat mentally retarded, but it was not felt that he suffered any loss of auditory acuity. His renal function was apparently normal throughout.

Case 4

A woman of 28 with two weeks' history of fever, weakness, and vomiting after a cold was admitted to another hospital with a temperature of 102° F. (38.9° C.). Penicillin was given, but bilateral patchy pulmonary consolidation developed. Sputum culture yielded *Staph. pyogenes*. Erythromycin treatment was begun; a blood culture taken only three days later yielded an erythromycin-resistant strain of *Staph. pyogenes* (RSSRS). Change to streptomycin and prednisolone did not halt a marked deterioration, with oliguria; the blood urea was now 205 mg./100 ml. She became desperately ill and was transferred to Hammersmith Hospital.

On admission she had consolidation of both lower lobes and rapidly became anuric. After intravenous tetracycline, erythromycin, and prednisolone (given by transfusion through a vena cava catheter) there was a dramatic improvement in her general condition and renal function. It was then learnt that the original blood culture staphylococcus had been erythromycin-resistant, so chloramphenicol was substituted. The temperature rose, and both blood culture and sputum taken on *Day 7* yielded *Staph. pyogenes* (RSSRS).

Vancomycin given from *Days 7-14* and *18-21* (total 13 g.), and, *Day 8* only, staphylococcal antitoxin. A small quantity of streptomycin was given—because of the anuria, only intermittently. Over this period there was a gradual and sustained improvement and the blood urea fell from 400 to 100 mg./100 ml. *Day 21:* Vancomycin was replaced by tetracycline. No further infection by staphylococci occurred, but malignant hypertension had developed and she died four months later of renal failure.

The patient had become totally deaf; at first this was attributed to streptomycin, but only 2 g. had been given. The course of 13 g. of vancomycin is the more probable cause.

Case 5

A man of 42, previously fit, admitted to another hospital with pain in the right hypochondrium. His temperature was 101° F. (38.3° C.) and the blood urea 340 mg./100 ml.

He was transferred to Hammersmith Hospital; his blood urea was then 640 mg./100 ml. He was dialysed on the artificial kidney twice—on admission and on *Day 4*. His electrolytes were thereby controlled and the blood urea fell to 192 mg./100 ml. Bronchopneumonia developed and, *Days 12-17*, he was treated with chloramphenicol and a single 0.5-g. dose of streptomycin. *Day 17:* The temperature had fallen to normal, but subsequently it rose again and on *Day 23* sputum culture yielded *Staph. pyogenes* (+ + +, RRRSSS, 80/53) together with a lesser growth of *Ps. pyocyanea*. From *Days 24-26* the treatment given included streptomycin, intermittently and in low doses, with tetracycline and chloramphenicol, but, *Day 26*, temperature reached 103° F. (39.4° C.) and the same staphylococcus was isolated from sputum (+ + +) and blood culture. Meanwhile the blood urea had risen to 400 mg./100 ml. *Days 26-30:* Erythromycin and chloramphenicol given without improvement. *Day 28:* Gastrostomy performed because of vomiting. *Day 29:* Blood urea 436 mg./100 ml.

Days 30-35: Vancomycin given (total 7 g. only); temperature fell to normal and blood culture (*Day 31*) was sterile. *Day 35:* Patient disoriented and found to have severe nerve deafness, so vancomycin stopped. A single

serum vancomycin level was 20 $\mu\text{g./ml.}$ —10 days later it was still 5 $\mu\text{g./ml.}$ Day 37: Blood urea now down to 308 mg./100 ml. Urinary output improved to 3 litres daily, and on Day 45 the blood urea had fallen to 184 mg./100 ml. Subsequently the patient again ran a fever for a few days and developed a pericardial effusion; *Staph. pyogenes* (SSSSSS, 52) was isolated (Day 54), and the infection was treated by tapping. No further staphylococcal infection occurred. The blood urea rose steadily from Day 45 and reached 580 mg./100 ml. on Day 90, when he died of renal failure.

Case 6

A man of 49 in good health until he required a partial nephrectomy for a calculus at another hospital. He became anuric, and three days later was transferred to Hammersmith Hospital.

After admission urinary output improved on vena cava drip infusions, but by Day 4 the blood urea had risen from 278 to 378 mg./100 ml., falling again to 274 mg. by Day 8. Days 2–9: Erythromycin and chloramphenicol given to combat some pyrexia, but from Days 7–10 the temperature rose and reached 103° F. (39.4° C.). Day 10: Operation wound and urine yielded *Staph. pyogenes* (+++, RRRSRS, 53/54/77) and blood culture was also positive. Blood urea 385 mg./100 ml. Days 10–12: Tetracycline and chloramphenicol.

Days 10–14: Vancomycin (total only 6 g.), with chloramphenicol and hydrocortisone. Day 12: Temperature began to fall. Day 13: Blood urea 500 mg./100 ml., but this was reduced to 200 mg./100 ml. by dialysis the same day on the artificial kidney. By Day 17, however, it had again risen to 444 mg./100 ml., and remained at about this level till death. Day 14: Sputum and faeces cultures yielded *Ps. pyocyanea* (+++), but no *Staph. pyogenes* was isolated. Day 15: Gastrostomy operation as patient was not taking fluids by mouth. Days 14–20: Chloramphenicol. By Day 17 the temperature had fallen to and remained normal, but on Day 25 there was marked pyrexia; blood culture yielded *Ps. pyocyanea*. The infection did not respond to polymyxin and neomycin, and the patient died on Day 30.

Necropsy revealed that there was adequate normal renal tissue to sustain life and that death was due to the septicaemia, for which no original focus was found.

On Day 17 the patient had become very deaf; thought to be due to vancomycin.

Case 7

A woman of 55 with chronic gall-bladder infection was treated by choledochotomy and cholecystectomy at another hospital; oliguria and paralytic ileus followed. Five days post-operatively, laparotomy revealed biliary peritonitis. Two days after this the patient was transferred to Hammersmith Hospital with renal failure.

Day 1: Oliguria, with blood urea 426 mg./100 ml. Temperature normal. Day 2: Dialysed on artificial kidney and blood urea reduced to 270 mg./100 ml. Days 2–6: Chloramphenicol and erythromycin for the biliary peritonitis. Day 3: Marked oedema. Patient collapsed and given a blood transfusion. Day 6: Right basal pneumonia, with temperature 100° F. (37.8° C.); cultures of sputum and from biliary drainage tube yielded *Staph. pyogenes* (+++, RRRSSS, 77). Blood urea rose to 380 mg./100 ml.

Days 6–13: Vancomycin given (total 12 g.). Over this period blood urea fell from 380 to 280 mg./100 ml. At first the temperature fell, but on Day 8 again reached 100° F. (37.8° C.). On this day a perinephric abscess was drained—culture yielded *Ps. pyocyanea* (+++). From Day 8–16 the temperature was swinging (up to 102° F.—38.9° C.), then subsided, and then rose again to 101° F. (38.3° C.). Day 15: Sputum culture yielded *Ps. pyocyanea*. Blood cultures were not taken, but clinically the patient had septicaemia. From Day 13 the blood urea continued to fall and at Day 22 was 194 mg./100 ml. Days 15–21:

Polymyxin given, but patient failed to respond to treatment and she died on Day 25.

No information was available about any effect of the vancomycin treatment on hearing.

At necropsy *Staph. pyogenes* (now RRRRRS, still 77) was isolated from peritoneal fluid in paracolic gutter, from gastrostomy opening, and from septic infarcts in the lung. *Ps. pyocyanea* was isolated from sites deep to the right paramedian and flank incisions, from the bladder wall, and from the upper and lower parts of the peritoneal cavity.

Case 8

A man of 73 admitted with bilateral non-specific basal bronchopneumonia and a normal blood urea. The infection was treated first with penicillin and streptomycin, then with tetracycline, and then with chloramphenicol—each course lasting three to four days. During the first three days of the illness consolidation of the upper lobe of the left lung developed, with cavitation, but his temperature fell from 102° F. (38.9° C.) to subnormal. *Staph. pyogenes* (RRRSSS, 77) was isolated from sputum on Days 5 (+), 13 (+++), and 15 (+++). There was retention of urine and increasing uraemia—the blood urea rose from 29 mg. per 100 ml. (Day 3) to 380 mg./100 ml. on Day 13.

Vancomycin was given (Days 14–23, total 7 g.), with dramatic clinical improvement, although specimens of sputa on Days 19, 21, and 23 still yielded small numbers of the same staphylococcus. The patient had a good uresis, and the blood urea fell to 68 mg./100 ml. (Day 24). Day 23: Erythromycin and chloramphenicol substituted for vancomycin; the temperature slowly rose and the blood urea, Day 29, was 235 mg./100 ml. He became disorientated, and died on Day 32 in coma with renal failure.

The disorientation made assessment of his hearing difficult, but it was believed that he had become partly deaf. Necropsy was not performed, and the nature of the underlying disease was therefore not determined.

Case 9

A woman of 63 with carcinoma of the stomach was admitted as an emergency case, with a six-months history of persistent vomiting and loss of weight.

Days 2–14: Increasing pyrexia, rising to 103° F. (39.4° C.). Blood culture (Day 12) yielded *Staph. pyogenes* (RRRSSS, 53). Day 14: Subtotal gastrectomy. Day 15: Blood urea 16 mg./100 ml.

Days 14–21: Vancomycin given (total 12 g.). The infecting strain of *Staph. pyogenes* was again recovered from a blood culture and from a "polythene" intravenous transfusion catheter on Day 16. The blood urea rose to 66 mg./100 ml. (Day 19), but the temperature fell to and remained normal. Day 21: Vancomycin replaced by erythromycin and chloramphenicol. For six days the temperature remained normal, but the patient became jaundiced. Days 27–34: The temperature rose again, and blood culture, Day 30, was again positive. The blood urea rose continuously, and on Day 46 reached 134 mg./100 ml. Throughout this period she received treatment with chloramphenicol, erythromycin, and novobiocin, either singly or in combination. She died with septicaemia on Day 47.

Necropsy was not performed. Severe nerve deafness was noted at the end of the course of vancomycin.

Response to Treatment

The results of treatment with vancomycin in these nine cases supports the view of Kirby and Divelbiss (1957) that it is valuable for use in hospitals in severe staphylococcal infections. All the patients were very ill—in each case the drug was used only as "a life-saving measure," and, except for Case 9, after the failure of previous chemotherapy.

Vancomycin was effective in saving the lives of five patients (Cases 1–5) (Table I). Patients 6 and 7 appeared

to have recovered from their staphylococcal infections with the aid of vancomycin, but succumbed to infection by *Ps. pyocyanea*, against which the drug is ineffective. Vancomycin is bactericidal for staphylococci *in vitro*, but it nevertheless failed to eliminate the organisms from four of these seven patients, although clinical cure of the staphylococcal infection was achieved. The chronic suppurative nature of the lesions in Cases 1, 2, and 3 presumably prevented the drug reaching all the organisms in adequate concentrations, and a proportion of viable bacteria therefore remained. Three of four patients with positive blood cultures (Table II, Cases 4, 5, and 6) were given an adequate course of treatment—in all three cases subsequent blood cultures were sterile.

The initial response of the infection to vancomycin of Cases 8 and 9 was good, but other antibiotics were substituted prematurely and the patients suffered a relapse and died. Had the course of vancomycin treatment been continued it is possible that a cure might have been effected where the bacteriostatic drugs were unavailing.

Toxic Effects of Treatment

Thrombophlebitis and gross loss of auditory acuity occurred with a number of the patients. One patient experienced brief hot flushes immediately after each dose of 0.5 g. of the drug in 20 ml. of saline. Some degree of thrombophlebitis eventually occurred with simple intravenous injections unless care was taken to use veins in rotation. No thrombosis occurred when vancomycin was given in 250-ml. saline infusions (over a 30-minute period) or by slow transfusion through a vena cava catheter.

Deafness was a serious sequel to treatment in Cases 4, 5, 6, and 9: it occurred either during or soon after treatment ended (Table III). Case 8 was also probably affected similarly, but the patient died before it could be confirmed. Cases 4, 5, 6, and 8 had variable degrees of renal failure with high blood urea levels at the time of vancomycin treatment. No. 7 also had a high blood urea level during treatment; but he died, and any effect the drug may have had on his hearing is not known. The other three patients had normal renal function and sustained no auditory damage. No subsequent improvement in hearing was noted in patients who were affected.

This clear indication of the danger of producing deafness in patients with renal failure suggests that the toxicity may be due to exceptionally high blood levels. If vancomycin is to be used for such patients then serial serum assays are essential to ensure that a maximum "safe" level is not exceeded, and to obtain an indication of the doses likely to maintain serum levels in the region of 10 µg./ml., which is an effective therapeutic concentration in most cases. The treatment of one such patient is described below, and the results of serum assays undertaken are shown in Table IV.

Control of Vancomycin Treatment in Patient with Renal Damage

An anuric patient with severe staphylococcal pneumonia after an emergency laparotomy was treated with vancomycin on failure of other chemotherapy and when he was apparently dying of his infection. When treatment began his blood urea was 270 mg./100 ml. Dosage was therefore controlled by serial serum assays. For each assay some eight dilutions of his serum, usually from 1 in 2.5 to 1 in 25, were made in fluid medium in 1-ml. volumes, using 6 by ½-in. (15 by 2-cm.) tubes. Standard concentrations of

vancomycin in human serum were diluted in the same medium. All tubes were then inoculated with 0.02 ml. of an overnight broth culture of *Staph. pyogenes*. The cultures were aerated on a Kahn shaker in a room at 37° C. It was found possible to read the end-points of inhibition of growth after four to five hours and so be able to adjust the next dose. Assay results calculated from readings made at the end of 18 hours' incubation were not materially different.

The initial dose of vancomycin administered was only 500 mg., and subsequent doses (250 or 500 mg.) were given or omitted according to the results of the assays. Daily variations in dosage and the number of assays undertaken are shown in Table IV. The total drug given over 11 days was only 5.125 g. Serum vancomycin levels lay between 3.3 and 20 µg./ml., except after the initial dose: 24 of the 32 levels were between 5 and 12 µg./ml. On this regime the pneumonia subsided, his condition greatly improved, and the blood urea fell to 102 mg./100 ml. over the 11 days. The assay results indicated the need, therefore, to increase the dose as renal function improved. Several sputum cultures were made—all were free from *Staph. pyogenes*. The patient, however, also had a retroperitoneal infection with the same strain of staphylococcus, and continued to discharge the pus through his abdominal operation wound. This did not apparently delay his recovery from the pneumonia. During treatment, and in the month following, no impairment of hearing was detected. However, a month after the first course he was given a second, assay-controlled, course for the retroperitoneal infection. Some time after the second course ended he suffered some loss of auditory acuity in the upper wavelengths, although during treatment the blood urea was not raised.

Serum vancomycin assays are now undertaken routinely with patients having a raised blood urea, and audiometric tests are made before, during, and periodically after treatment for as long as they remain in hospital.

Discussion

The response of patients in this series to vancomycin therapy confirms that the drug is an effective weapon. It would seem that acquired resistance is unlikely to be a problem, and natural resistance to the antibiotic occurs with few strains. All strains of *Staph. pyogenes* isolated from routine bacteriological specimens and nasal swabs from patients and nurses in Hammersmith Hospital for 13 months from the beginning of 1958 have been tested by a ditch-plate technique for their sensitivity to vancomycin and no resistant strains have been found.

Because the drug must be given intravenously and because of its toxicity to the eighth nerve, it should be used mainly for severe staphylococcal infections when other chemotherapy is ineffective either because of the resistance of the infecting strain or for other causes. The drug is bactericidal and therefore especially valuable for patients particularly prone to infection or whose own defences are impaired.

Failure of treatment, and the death of four patients in this series were due neither to resistance of the organism to the drug nor to undue delay before change of treatment to vancomycin was made. Two of the patients (Cases 6 and 7, Table III) recovered from the staphylococcal infection but died of *Ps. pyocyanea* septicaemia. The other two (Cases 8 and 9) improved while on vancomycin, but after six days' treatment in each case the drug was prematurely withdrawn and bacteriostatic chemotherapy was substituted. Thereafter the patients' condition deteriorated and they died. Failure to eliminate the infecting strains of staphylococci in a number of cases, even where clinical

recovery was achieved, underlines the need to give an adequate course of the drug.

Our experience with patients with high blood urea levels shows that a check of blood vancomycin levels must be kept if deafness is to be avoided, although fewer assays might be required than were undertaken for the case described above.

The nine patients in this series were all treated with vancomycin in a nine-months period from the beginning of November, 1957. Dosage had seemed fairly conservative, for no patient received more than 1-2 g. a day and no patient with renal failure more than 13 g. in all. At that time the danger of deafness in patients with high blood levels—that is, with impaired renal function—was not appreciated by us and routine serum vancomycin assays were not undertaken. Subsequently Geraci *et al.* (1958) reported moderate degrees of perceptive deafness without labyrinthine disorder in one of a series of six patients and in one other patient. One had normal renal function and the other blood urea levels of 60-100 mg./100 ml.—in both patients serum vancomycin levels were very high (80-95 µg./ml.). In clinical studies two years earlier the same workers encountered no auditory impairment (Geraci *et al.*, 1956). Kirby and Divelbiss (1957) did not note any loss of hearing in two patients with impaired renal function. One was treated with 2 g. of vancomycin a day for eight days and had consistent 24-hour blood levels of 20-32 µg./ml.; the other, on 4 g. a day, had 12-hour levels of 100 µg./ml. on three occasions.

Geraci *et al.* (1958) noted a number of other toxic effects, including skin rashes of various types, fever, and chills. They detected no toxic effects on the kidneys, liver, or haemopoietic system. They found that the average serum vancomycin levels in normal subjects given 2 g. of the drug a day in divided doses was 13 µg./ml. and that damage to the eighth nerve did not result with such levels. Such levels should be adequate in treating staphylococcal infections, for nearly all strains tested by a number of workers have been sensitive to 2.5 µg. of vancomycin per ml. or less.

Kirby and Divelbiss (1957) found that when patients with normal renal function were given 1 g. of vancomycin 12-hourly or 0.5 g. six-hourly the serum levels 12 hours after each dose were mainly of the order of 3-10 µg./ml.; after two to three days' treatment a cumulative action was noted. We found similar levels in two patients treated with the drug since the series described in this paper. Further experiments are required to determine levels which can be maintained without adverse sequelae. Toxic effects are easier to avoid when the drug is administered by continuous drip transfusion. The concentration of the drug in the serum varies slowly when it is given by this method and therefore few serum assays are needed. Moreover, closer and more rapid control of the serum level can be achieved by altering the concentration of vancomycin in the transfusion fluid.

Summary

The treatment by intravenous vancomycin of nine patients with severe staphylococcal infections is described; of these, only three had normal renal function. The infecting strains of *Staph. pyogenes* were all resistant to several antibiotics, and treatment with other antibiotics had failed. Vancomycin therapy led to a good clinical response. Two of the patients died

when vancomycin was withdrawn before the infection was controlled. Two others recovered from the staphylococcal infection but died subsequently of *Ps. pyocyanea* septicaemia.

Although vancomycin is bactericidal *in vitro*, three of the five surviving patients continued to harbour the infecting staphylococcus in lesions.

The danger of drug deafness in uraemic patients is stressed. This may occur during or after treatment. Several uraemic patients developed toxic deafness on dosage of 1-2 g. daily, although none received more than 13 g. in the course. A regime of lower doses controlled by "rapid" serum assays is outlined, and was used successfully in the management of a uraemic patient with staphylococcal pneumonia. The total amount given was only 5.125 g. over 11 days.

Thrombophlebitis occurred in some patients when the vancomycin was given by simple intravenous injection in 10 ml. of saline, but not when it was administered in 250-ml. infusions over a 30-minute period or in larger volumes in saline or 5% glucose transfusions.

The drug must be given intravenously, and as it is also toxic to the eighth nerve it is likely to be used mainly in hospital for severe staphylococcal infections, especially where this organism is resistant to several other antibiotics or where other chemotherapy is otherwise unavailing. It is also valuable when a bactericidal drug is particularly desirable—that is, staphylococcal infections in patients whose normal defence mechanisms are defective.

We thank the physicians and surgeons in charge of the reported cases for their co-operation; Mr. V. J. Briffa, of the department of surgery, for undertaking the audiometric tests; and Messrs. Eli Lilly, who supplied the vancomycin for trial. We are particularly grateful to Dr. Mary Barber for a great deal of help and advice, and to Mr. A. Medway, who carried out the bacteriophage typing of the infecting strains of staphylococci.

REFERENCES

- Fairbrother, R. W., and Williams, B. L. (1956). *Lancet*, 2, 1177.
 Garrod, L. P., and Waterworth, P. M. (1956). *Brit. med. J.*, 2, 61.
 Geraci, J. E., Heilman, F. R., Nichols, D. R., and Wellman, W. E. (1958). *Proc. Mayo Clin.*, 33, 172.
 ——— and Ross, G. T. (1956). *Ibid.*, 31, 564.
 Kirby, W. M. M., and Divelbiss, C. L. (1957). *Antibiotics Annual, 1956-1957*, p. 107. Medical Encyclopedia, Inc., New York.
 ——— (1957). *Lancet*, 1957, 1, 85.
 McCormick, M. H., Stark, W. M., Pittenger, G. E., Pittenger, R. C., and McGuire, J. M. (1956). *Antibiotics Annual, 1955-1956*, p. 606. Medical Encyclopedia, Inc., New York.
 Williams, R. E. O., and Rippon, J. E. (1952). *J. Hyg. (Camb.)*, 50, 320.
 Ziegler, D. W., Wolfe, R. N., and McGuire, J. M. (1956). *Antibiotics Annual, 1955-1956*, p. 612. Medical Encyclopedia, Inc., New York.

The Education Advisory Committee of the Universities Federation for Animal Welfare has protested to the United States Ambassador about the action of the National Science Teachers Association, Washington, in awarding a prize in their "1958 Science Teacher Recognition Program" to a biology teacher in Buffalo, New York, who has encouraged his high school pupils to carry out experiments on live animals. According to U.F.A.W., the experiments done with and by the children include "forcing into the lungs pepper and other dusts and smoke of such density as to provoke violent shutting of the glottis; toxicity tests to find what dose of inhaled nicotine will kill 50% of treated animals; perfusion with amateur apparatus devised by a schoolgirl; weekly routine transfers of cancer cells peritoneally; and the production in live animals of metastases, especially in the lungs."