diagnosis, chloride should be regarded as "absent" if the end-point colour change occurs with the first drop. This may happen in normal persons if the urine is very dilute because a large amount of fluid has been taken, but if it occurs in the absence of diuresis it is indicative of salt depletion, though the depletion may not have reached a degree sufficient to cause symptoms. In concentrated urine (with a specific gravity of more than 1020) less than 3 g. per litre suggests depletion. If the urine contains 5 g. per litre or more the patient, except in Addison's disease or during the administration of intravenous saline, is unlikely to be suffering from salt depletion. The test was found useful in India and South-East Asia Commands during the war in the detection of salt-depletion heat exhaustion and of salt depletion complicating many medical and surgical illnesses. In M.I. room work it was valuable in the hot weather as a quick method of separating cases of salt-depletion heat exhaustion from those of neurotic collapse and ill-health from other causes. White (1943) so applied it at Air Headquarters, Delhi, during June and July, 1943, to a series of 140 patients, of whom 29 were proved to be suffering from heat exhaustion. Its potential scope is not as great in temperate as in hot climates but is still enormous, for it is applicable in the diagnostic assessment and therapeutic regulation of all cases of threatened or actual dehydration or of overt oedema. Whenever fluid tends to be lost from or retained in the body, the measurement of urinary excretion of sodium chloride is as important, in many instances more important, than the measurement of urine volume. It is my belief that the means for performing this simple test should be available in all ward test-rooms and in every doctor's bag. A similar simple quantitative test for sodium would be even more valuable if it could be evolved.

(To be concluded, with a full list of references, in our next issue.)

MEDICAL ASPECTS OF PENICILLIN TREATMENT

BY

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This paper is based on a survey of the cases treated in the medical wards of St. Alfege's Hospital with systemic penicillin alone, or with systemic and local penicillin combined, from January, 1945, to September, 1946. In all, 129 patients were so treated. The cases are unselected, except that they were considered worthy of penicillin therapy on clinical or bacteriological grounds, and are consecutive cases. They were not the subject of special investigation as part of an experimental trial of penicillin treatment, but we have been continually alive to the fact that each case undergoing penicillin treatment is, even at the present time, an experiment in a new form of therapy, the application of which is by no means finally settled.

Our first regular supplies of penicillin became available in April, 1945, when we were allocated 5,000,000 units a month. This quota was gradually increased until at the time of writing our monthly consumption is between 150,000,000 and 200,000,000 units. The majority of cases were therefore treated in 1946. The 129 cases include the most serious and potentially fatal illnesses treated. An analysis according to the final diagnosis is shown in Table I.

The pneumonias form the largest group with 53 cases. Carbuncles, meningitis, and empyema are the next largest with 13, 11, and 10 cases respectively. The appearance of

carbuncles, cervical adenitis, and diabetic gangrene among a series of cases treated in medical wards alone is part of the revolution in medical practice which penicillin has

TABLE I.—Medical Cases Treated with Systemic and Local Penicillin

Disease	No. of Cases	Disease	No. of Cases
Respiratory diseases:		Streptococcal tonsillitis	4
Pneumonia	53	Diabetic gangrene	3
Acute bronchitis	3	Perinephric abscess	2
Empyema	10	Cellulitis	1
Lung abscess	2	<i>Staphylococcus aureus</i>	1
Carbuncles	13	Septicaemia	1
Meningitis	11	Vincent's angina	1
Secondarily infected skin lesions	8	Acute pyelonephritis	1
Acute nephritis	6	<i>E. coli</i> septicaemia	1
Subacute bacterial endocarditis	5	Lobar pneumonia	1
Cervical adenitis	5	Pemphigus, chronic nephritis	1

brought about. Particularly, and most dramatically, in the case of carbuncles is this change of practice welcome, most of all to the patient.

Below is given an analysis of the results of treatment of the more important groups of diseases, with a brief description of the methods used, and such points of importance bearing on treatment that have been brought to light.

Pneumonia

From January to December, 1945, 12 cases of pneumonia were treated, with 5 deaths, and from January to September, 1946, 41 cases, with 3 deaths. This represents an overall mortality of 15%. Of the 53 patients 26 were over 40 years of age and 10 were under 6 months; and the majority were cases of great severity. During the first period penicillin was scarce and dosages were in consequence low. The figures for the second period, giving a mortality of 7.3%, must be regarded as very gratifying. Four of the eight fatal cases were moribund on admission and death occurred within 24 hours; three had signs of congestive cardiac failure on admission; and one was a premature infant. Seven patients who recovered, two who improved, and five who died were also treated concurrently with sulphonamides. Fifteen cases received penicillin after the infection had failed to respond to sulphonamide therapy.

TABLE II.—Cases of Pneumonia

Variety	Recovery	Improvement	No Change	Death	Total
Lobar, unclassified	11	3	—	3	17
Bronchopneumonia, unclassified	11	—	2	5	18
Pneumococcal	4	—	—	—	4
Staphylococcal	4	1	—	—	5
Streptococcal	4	—	—	—	4
Mixed flora	4	—	—	—	4
Atypical	—	—	1	—	1
Total	38	4	3	8	53

The bacteriological classification of the cases is not complete, partly because many of the patients treated were too ill or too young to produce sputum, and partly because we were loath to ask too much of our ever-willing but over-worked laboratory staff. We now regard a bacteriological diagnosis, with a penicillin-sensitivity test of the organism, as an essential in the penicillin treatment of pneumonia. Such information offers valuable guidance to the physician, particularly on the necessity for increasing the dose or for prolonging the course, in a case not initially responding to penicillin. Without this information he works in the dark. It may be significant that of the cases bacteriologically classified none were fatal.

Indications for Penicillin Treatment in Pneumonia.—Administration of sulphonamides is still our method of choice. Our indications for penicillin are: (1) Cases with a bad prognosis owing to clinical severity with signs of extreme toxæmia, old age, and infancy, particularly prematurity. In these cases penicillin and the sulphonamides

may be combined. (2) Cases failing to respond to sulphonamides within 36 hours, or cases known to be sulphonamide-sensitive. (3) Cases with congestive heart failure or renal disease where the excretion of sulphonamides is likely to be deficient. (4) Cases with complications such as diabetic ketosis or anaemia.

Treatment

Up to April, 1946, the usual adult dose of penicillin was 30,000 units initially by intramuscular injection, followed by 15,000 units three-hourly (120,000 units in 24 hours). For the past six months the initial dose has been 60,000 units, followed by 30,000 units four-hourly (180,000 units in 24 hours). In cases with a very bad prognosis the dose has been increased to 60,000 units four-hourly (360,000 units in 24 hours). The dose in infants has been of the order of 2,000 to 4,000 units per pound (454 g.) of body weight in the 24 hours, depending on the severity of the infection. Doses for children have been intermediate between this and the adult dose. All doses are made up to a volume of 1 ml. with distilled water. Larger volumes are likely to increase the discomfort of the injection.

Increased supplies of penicillin have therefore permitted the administration of larger doses at longer intervals, to the benefit both of patients and of nursing staff. The duration of treatment has been from 5 to 10 days, the majority of cases receiving a six-day course. Cases have responded to treatment in from one to four days—in most instances within 48 hours. Increased dosage at greater intervals is now a growing tendency in our practice. We are experimenting with doses of 250,000 units at intervals of 8 to 12 hours. The number of cases so treated is small, but the impression gained up to the present is that 250,000 units eight-hourly gives a more satisfactory response than a similar dose 12-hourly: 500,000 units 12-hourly is also under trial. This winter we should treat enough cases of pneumonia to form a definite opinion on this system of dosage.

I have included the above generalizations under the pneumonias as they form by far the largest group. These remarks apply equally to the treatment of my other groups.

Empyema

Ten cases of empyema have been treated, with eight recoveries and two deaths (Table III). Of the two deaths, one was that of a woman of 80 who died within 24 hours of admission; the other case was complicated by the presence of chronic pulmonary tuberculosis and grew *Haemophilus influenzae* in the pleural fluid.

TABLE III.—Cases of Empyema

Variety	Recovery	Death	Total
Pneumococcal	3*	1†	4
Staphylococcal	1*	—	1
Streptococcal	3	—	3
No organism	—	—	—
Influenzal (chronic pulmonary tuberculosis)	—	1	1
Total	8	2	10

* One pneumococcal and one staphylococcal case were treated by surgery.
† Female patient, aged 80, moribund; death within 24 hours.

Treatment has been by the administration of systemic penicillin in doses of 30,000 to 60,000 units four-hourly, with repeated aspiration of the fluid and intrapleural injection of 60,000 to 120,000 units of penicillin in 20 to 50 ml. of distilled water on alternate days. The pleural fluid, given a penicillin-sensitive organism, is usually sterile after the second intrapleural injection, five to seven injections being the usual number. Aspiration must be complete and be continued for a prolonged period if a satisfactory result is to be obtained. In the majority of our cases we were

fortunate in beginning penicillin treatment early in the disease. In two cases surgery has been necessary, rib-resection being carried out. The indications for surgery are a thick exudate which cannot be aspirated, empyemas coming under treatment late in the disease, loculation of the fluid, and failure to sterilize the empyema with penicillin.

The series is too small for a dogmatic opinion to be given, but my impression is that if aspiration and penicillin replacement are started early, with a penicillin-sensitive organism, good results can be obtained by aspiration and penicillin injection only, provided aspiration is frequent, continued, and complete. If surgery is indicated the patient is handed over to the surgeon in good condition, without toxæmia and with a sterile effusion.

Meningitis

Eleven cases have been treated, with seven recoveries and four deaths (Table IV). Of the four fatal cases, one was an influenzal meningitis; one proved at necropsy to be a case of meningococcal meningo-encephalitis (in this case, although the cerebrospinal fluid became sterile two days after treatment with intrathecal and systemic penicillin, no clinical improvement resulted); the third was low-grade meningitis, with otitic hydrocephalus, which did not respond to penicillin treatment, the patient dying after operation at a cranial surgery unit. The fourth, a meningitis of unknown aetiology, proved fatal within 24 hours of admission.

TABLE IV.—Cases of Meningitis

Variety	Recovery	Death	Total
Meningitis, meningococcal	2*†	—	2
Meningo-encephalitis (meningococcal)	—	1*	1
Meningitis, pneumococcal	2*	—	2
" influenzal	2*	1*	3
" acute purulent	1*	1*†	2
" low-grade with otitic hydrocephalus	—	1*	1
Total	7	4	11

* Also treated with sulphonamides.

† Systemic penicillin only.

‡ Death within 24 hours of admission.

In view of the excellent results obtained with sulphonamides, intrathecal penicillin is probably unnecessary in cases of meningococcal meningitis. The fever hospitals can advise us with more authority on this point. Our cases were treated with sulphadiazine and systemic penicillin only, and made rapid recovery.

Pneumococcal meningitis was treated by the intrathecal injection of 10,000 to 30,000 units of penicillin on alternate days for three injections. In each case the fluid was sterile after the first injection and recovery dramatic. Intrathecal therapy was supplemented by 60,000 units of penicillin four-hourly by intramuscular injections for 10 days and full doses of sulphadiazine.

The three cases of meningitis due to *H. influenzae* are most interesting and instructive. Dr. B. Gottlieb, in whose wards they were treated, is shortly submitting for publication a detailed account of their investigation and treatment. The *H. influenzae* was thought to be penicillin-resistant. We now realize that this organism is only relatively resistant to penicillin. Penicillin-sensitivity tests in one case showed that the organism (*H. influenzae*, Pittman type b), although insensitive to a penicillin solution of 10 units per ml., using the punch-plate technique, was inhibited by the same technique using a solution of 100 units per ml. The same organism was not sensitive to sulphadiazine or sulphathiazole in concentrations of 10 mg. per ml.

The first case, that of a child of 10 months, was treated with 27 intrathecal injections of 30,000 units of penicillin, with 15,000 units three-hourly systemically to a total of 4,440,000 units, and full doses of sulphadiazine. After the seventh

intrathecal injection the cerebrospinal fluid became sterile, but in spite of continued treatment the organism reappeared and the child died after nearly three months' treatment.

The second patient, a child of 21 months, received 10 intrathecal injections of 50,000 units in 15 days, 120,000 units three-hourly systemically for 48 days (46,000,000 units), and full doses of sulphadiazine. The cerebrospinal fluid became sterile after six intrathecal injections, and the child made a full recovery.

The third and most recent case, that of a child of 10 months, received three intrathecal injections of 50,000 units and three of 30,000 units in 10 days, with 60,000 units four-hourly systemically for 16 days (5,760,000 units). The fluid was sterile after the third day, and the child made a rapid and full recovery. The dosage has been progressively increased from the first to the third case, with an improvement in the result.

These three cases are of the greatest importance in demonstrating that resistance may be purely relative, and the administration of overwhelming doses of penicillin will save life where smaller doses will fail. Close co-operation with the bacteriologist is essential in the treatment of such cases.

To minimize the risk of meningeal reactions, only pure penicillin of a concentration of 1,660 units per mg. is used for intrathecal injection, and to lessen the even greater risk of introducing infection by a penicillin-resistant organism each dose is made up separately in a sealed ampoule. One reaction in the form of convulsions was noted in the 10-months-old infant, three convulsions occurring immediately after the sixth and last intrathecal injection. The child appeared very shocked during the reaction, but made a rapid recovery.

A problem which the physician often faces in treating meningitis is to decide on the line of action to be taken if a turbid cerebrospinal fluid is withdrawn and no immediate expert bacteriological opinion is available. The introduction of penicillin into the cerebrospinal fluid is not without risk, and it appears to be unnecessary in meningococcal meningitis. The risks are very slight, however, if the precautions I have previously mentioned are taken. My practice is to wait for a bacteriological diagnosis, if one can be obtained within a few hours, before giving intrathecal penicillin. If this is not available 10,000 units of penicillin are given intrathecally pending a bacteriological diagnosis on fluid previously removed. In very ill patients penicillin is given intrathecally immediately turbid fluid is withdrawn.

Carbuncles

Thirteen cases of carbuncle have been treated. Nine uncomplicated cases responded rapidly to 30,000 units given four-hourly. A disappearance of malaise and toxic symptoms occurred after 24 hours, and there were signs of local improvement on the second or third day. Treatment was continued for from five days in the smaller carbuncles to seven to nine days with large carbuncles. More recently, excellent results have been obtained by the administration of 100,000 units twice daily to a number of patients not admitted to hospital. Four cases had complications—two with staphylococcal septicaemia and bronchopneumonia and two with diabetes mellitus. The former were gravely ill, but made remarkable and rapid recovery with moderate doses of 15,000 units three-hourly for 14 days. These patients were treated early in 1945; the larger doses available later would have resulted in a more rapid response. One of the diabetics, treated with 40,000 units four-hourly for 7 days, relapsed with a slight flaring-up of the local infection. She quickly responded to a second course. The second case required 30,000 units four-hourly for 12 days. It would seem wise to continue the penicillin course in a diabetic for a longer period than in an uncomplicated case.

Before summarizing the more important general points I should mention that we were not able to convince ourselves that systemic penicillin influenced the course of the six cases of acute haemorrhagic nephritis so treated.

Summary and Conclusions

The following are the more important points that have arisen in our experience during the treatment of cases with systemic or systemic and local penicillin.

1. A bacteriological diagnosis should be obtained whenever possible, and penicillin-sensitivity tests on the organism carried out. This should not delay the institution of treatment in urgent cases, which may be started while bacteriological investigations are in progress.

2. Intermittent intramuscular therapy is our method of choice, injections being given four-hourly. The usual dose in adults is 30,000 units four-hourly, with 60,000 units four-hourly in severe infections. The present tendency is further to prolong the intervals, with increase in dosage. More work on these lines is necessary.

3. The volume of a single dose should not exceed 1 ml. Up to 250,000 units of the penicillin at present supplied (1,400 to 1,500 units per mg.) can be dissolved in this amount of distilled water.

4. Intrathecal therapy should be undertaken with the strictest aseptic technique; only pure penicillin of 1,660 units per mg. should be used. Each dose should be made up separately in a sealed glass ampoule.

5. The scope of penicillin treatment should include that group of organisms previously classified as penicillin-resistant. Tests for penicillin-sensitivity should be carried out in concentrations up to several hundreds of units of penicillin per ml. before resistance is considered a contraindication to treatment. This conclusion I consider to be of the greatest importance.

Penicillin therapy calls for the highest standard of diagnostic technique from the physician, and for an experimental and scientific approach to each case under treatment. A constant survey of the results obtained with given dosages for the various diseases is necessary until the position regarding optimum dosage and method of administration is stabilized. This may not be for some years.

The demands on the pathologist are increasing and will continue to increase with penicillin and allied therapy. His laboratory must be adequately staffed to meet these demands. The pharmacist is an indispensable member of the "penicillin team" and must be able to deal adequately with all forms of penicillin preparations, including those in non-hospital practice calling for a licence under the Therapeutic Substances Act. His pharmacy must be equipped at least up to the standard demanded by the Act.

More Recent Experience

Since November, 1946, when this paper was written, twenty adults suffering from pneumonia have been treated by the systemic administration of 250,000 units of penicillin at twelve-hourly or eight-hourly intervals. These cases were not selected, as were those of the paper, on grounds of clinical severity but were consecutive patients suffering from pneumonia admitted to two medical wards. Of the twenty cases, sixteen were classified as lobar pneumonia and four as bronchopneumonia. A radiological diagnosis was obtained in each case. Three cases were treated by 250,000 units twelve-hourly. One (*pneumococcus*) responded satisfactorily; two (*Streptococcus viridans*, penicillin-sensitive) gave responses delayed to four and seven days, as shown by the temperature, pulse, and clinical condition.

On the experience of the two latter cases the dosage was increased to 250,000 units eight-hourly for an average of six days. Of the seventeen cases so treated, thirteen were

classified as lobar pneumonia and four as bronchopneumonia. The predominating organisms were pneumococci and a mixed catarrhal flora. The patients' ages ranged from 16 to 87 years (two cases), with an average of 50 years. There were fifteen recoveries and two deaths. One of the two fatal cases, a man of 45, was admitted in a semi-conscious condition with severe toxæmia and congestive cardiac failure. He died within eighteen hours of admission after receiving two injections of 250,000 units of penicillin. The second fatal case, a man of 87, died on the seventh day of treatment from congestive cardiac failure, with auricular fibrillation and arteriosclerotic myocardial degeneration, after an initial apparent response to therapy. The fifteen patients who recovered all showed an excellent response to penicillin treatment. The temperature and pulse fell by crisis, and there was a great improvement in the clinical condition with loss of toxæmia in an average of thirty-six hours from the beginning of treatment. The average duration of stay in hospital of these patients was fourteen days.

My thanks are due to Dr. B. Gottlieb, senior resident physician at St. Alfege's Hospital, for the invaluable help he has given me in preparing this paper, and to many other members of the medical staff who have assisted in the treatment of these patients. I am grateful to Dr. E. N. Allott, of the Lewisham Group Laboratory, for his generous co-operation and advice, which have meant so much to us in developing penicillin treatment. Finally, I would thank Mr. White, the chief pharmacist, whose skill and ingenuity in dispensing this new and labile substance in all its forms have been a stimulating example of the high pharmaceutical technique we now expect from our pharmacists.

THE PLACE OF UNILATERAL RENAL DISEASE IN HYPERTENSION

BY

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Until recently hypertension has been the province of the physician and, apart from blood-letting, its treatment has been mainly rest and a restriction of activity. Now, however, there is a surgical approach to this very great problem, and attacks have been made along both direct and indirect lines. *Direct*: In cases in which unilateral renal disease has been found it may be assumed that this plays some part in the genesis of the hypertension, and the offending organ may be excised in an endeavour to remove this cause. *Indirect*: By interruption of the sympathetic nervous system a lowering of the blood pressure has been obtained. All operations of this type have their effect irrespective of the aetiology of the hypertension, and do not attempt to remove its cause.

This paper is concerned with the direct line of attack. It has been our routine to perform excretion pyelography in every case of severe or considerable hypertension which has come under investigation. If at this examination both kidneys do not show a normal contour of pelvis and calices, then further investigation by cystoscopy and retrograde pyelogram has been undertaken. The following cases of hypertension occurring in association with renal disease have been encountered, and it is desired to put them on record.

Case 1

A flight-lieutenant aged 38 noticed puffiness of the eyelids and swelling of the ankles in June, 1943. This persisted and became gradually worse. In September, 1944, he had an attack of acute tonsillitis, and at a medical board was found to have a raised blood pressure and albuminuria. For some years he had had frequency of micturition. He was admitted to an R.A.F. hospital on Jan. 12, 1945, and was seen to be a well-nourished man with no demonstrable oedema. The blood pressure was 215/140. The heart sounds were normal. Nothing abnormal was found in chest and abdomen. The blood urea was 33 mg. per 100 ml. Van Slyke: first hour 85%, second hour 92%. There was no albumin or deposit in the urine. A radiograph showed a calculus in the pelvis of the left kidney. He was given 21 days' leave, and returned to hospital on Feb. 13. A radiograph showed the calculus to be in the same position. Blood urea, 38 mg. per 100 ml. Blood pressure, 190/130.

On Feb. 18 the left kidney was exposed through a curved loin incision. It appeared normal in size and consistency, but was rather adherent to the perinephric fat. The pelvis was cleared and opened posteriorly, and the stone was removed. A bougie was passed down the ureter easily, and the opening in the pelvis was sutured. The wound was closed and a rubber drain inserted. He passed some blood-stained urine the following day, and there was a slight leakage from the drainage-tube for the first three days after operation. Convalescence was satisfactory. On March 14 the blood pressure was 180/120.

Case 2

A wireless operator aged 25, with 4½ years' service, began to have headaches about June, 1944. These became more frequent, and about the beginning of May, 1945, he noticed that the left side of his field of vision was blurred. His appetite was good, weight steady, and bowels regular. There were no urinary symptoms. Past history revealed nothing relevant.

On May 30 he was admitted to an R.A.F. general hospital overseas. His right vision was 6/6, left vision 6/6. The fundus of the right eye showed a cotton-wool-like horseshoe-shaped area, enclosing the macula nasally, and the disk was oedematous. There were one or two small haemorrhages and a patch of exudate in relation to the superior nasal vessel. The left fundus showed similar changes. The urine contained albumin +. The blood pressure was 210/160. Urea concentration was 78% of average normal. Two years previously he had been rejected for flying duties because his blood pressure was raised (amount not stated). On June 18 he was transferred to an R.A.F. hospital in England with a diagnosis of malignant hypertension.

On admission his general condition was good. The tongue was clean, pulse 100, blood pressure 260/180. The apex beat was in the fifth space, outside the mid-clavicular line, with a thrusting impulse but no bruits, and the artery walls were thickened. The lungs were normal. The liver, spleen, and kidneys were not palpable. Examination of the central nervous system revealed nothing abnormal; the jerks were brisk. The disks were substantially as above, with commencing papilloedema of the right eye. There was defect in the left upper outer quadrant of the visual fields.

Investigations.—Urine specific gravity 1020, albumin +. Urea clearance: first hour 2.26 g.; Van Slyke 133%. Second hour 2.3 g.; Van Slyke 129%. Blood urea: 33 mg. per 100 ml. Midstream specimen urine showed a moderate number of red blood cells, calcium oxalate crystals, epithelial cells, and several granular casts; culture was sterile. Blood count: R.B.C., 4,800,000; haemoglobin, 94%. Excretion urography showed a slight degree of hydronephrosis of the left side, with no excretion on the right side up to 60 minutes. (See Fig. 1.) Cystoscopy showed the bladder mucosa to be normal. Both ureteric orifices were normal. A catheter was passed up the right side without obstruction to 20 cm. and 35 ml. of sodium iodide 12% was injected. Radiographs revealed a small kidney with a marked hydronephrosis, and a diagnosis of hypoplastic kidney was made. (See Fig. 2.) Despite continued rest in bed the blood pressure remained raised; the lowest recorded was on June 29, when it was 235/145.

On July 10 the right kidney was exposed through a curved loin incision. It was represented by a shell of tissue only,