by Hall and Spink (1943), there was no relapse of temperature with the eruption.

Two women became confused during treatment. One has already been mentioned; she had had only 7 g. and her treatment was changed to penicillin. The other developed a psychotic state only after an adequate course of treatment had been given; the confusion cleared in four days and the pneumonia resolved rapidly. Drug psychosis has been reported by Flippin, Geftter, Domm, and Clark (1943), but both these cases had small doses of sulphonamide, and their condition may have been due to pneumonia rather than its treatment.

Drug fever occurs with all sulphonamides. Geftter *et al.* (1943) reported it in severe cases, most of which had over 40 g. of sulphamerazine. Two cases occurred in this series, the pneumonia responding according to expectation but fever persisting unexplained until a critical fall after stopping the drug incriminated the sulphonamide.

We have encountered no serious toxic manifestations in the use of this sulphonamide, and feel that they should be excessively rare provided that administration is not too prolonged.

Summary

A series of cases of primary pneumonia in adults is presented. No deaths occurred among 113 cases treated with sulphamerazine. Five deaths (7% mortality) occurred among 76 treated with other agents, including combined therapies. The total mortality was 3%.

It is claimed that sulphamerazine, which can be given in relatively small doses at eight-hourly intervals, is a satisfactory therapeutic agent for this disease. The results are such that pneumonia can be treated at home and be reduced to a "two-day fever." Should no response follow within 48 hours the case should be reviewed at once and the facilities provided by the hospital for further investigation and treatment be employed.

The need for radiological demonstration of complete resolution is emphasized, as is the need for adequate convalescence.

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Dr. Samuel Standard, the Associate Professor of Clinical Surgery at New York University, "has found that powder-puffs are a menace to health," reports B.U.P. "Anyone who has seen a powder-puff pulled out of a lady's handbag containing loose change, tobacco dust, and handkerchiefs, clean or otherwise, must have looked in awe as the perspired face and forehead were punished by swift, firm, hasty strokes smeared on fiercely by a deft, practised hand. Twenty-four hours later the owner of the face is surprised to find a crop of pimples spread over the cheek and forehead. In despair, she covers these again and again by the same method, and her wonder grows that her pimples multiply."

ORAL PENICILLIN IN TREATMENT OF PNEUMONIA IN THE ADULT

BY

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A comparative study (Anderson and Ferguson, 1945) of the efficacy of the sulphonamides and penicillin in the treatment of pneumonia showed that there was little to choose between the two methods. Although certain advantages could be claimed for penicillin on account of its lack of toxicity, its use had one great drawback, especially for the general practitioner—the need for repeated intramuscular injections. Early studies with regard to the route of administration of penicillin had suggested that the material was likely to have little effect when given by mouth because of its inactivation by the acid of the gastric juice (Abraham *et al.*, 1941) or because of penicillinase production by coliform organisms (Chain and Florey, 1944). This led different workers to try to combine penicillin with suitable antacids and buffers designed to counteract the stomach acids (e.g., Little and Lumb, 1945). Bunn and his co-workers (1945) used penicillin orally in the treatment of 45 cases of pneumonia and had only one fatality. The material was given in a gelatin capsule; in about half of the cases the capsule contained an oily suspension and in the remainder the ordinary powdered sodium salt was enclosed. However, Finland, Meads, and Ory (1945) came to the conclusion that elaborate buffering devices were unnecessary and that administration with saline or even water was equally valuable in procuring effective therapeutic blood levels. These authors obtained satisfactory results with oral penicillin in the treatment of seven cases of adult pneumonia. Bushby and Harkness (1946), who reviewed the conflicting reports on different methods of administration, used penicillin orally for the treatment of gonorrhoea and were satisfied with the results, which indeed were as good as those obtained with intramuscular penicillin. (It is important to realize that these results were obtained in adults, for Buchanan (1946) has since shown that oral penicillin can be used with excellent effect in infants whose normal achlorhydria was assumed to prevent inactivation of the antibiotic.)

In view of the great variations in the sensitivity of different organisms to the action of penicillin and because of the differences in severity between cases of the same infection, it was felt that there was a need to investigate the efficacy of penicillin administered orally to an unselected series of patients with pneumonia. In this infection, unlike gonorrhoea, the treatment must be capable of dealing with the bacteria not only in the tissues but also in the blood stream; it seemed possible that penicillin given by mouth might be unable to attain concentrations in the blood high enough to quell a bacteraemia.

Material and Methods

The patients comprised in the study were all adult males admitted to the wards of Knightswood Hospital during the winter of 1946–7 in whom the diagnosis of pneumonia was confirmed. They were divided into two groups, one group being given penicillin orally and the other penicillin intramuscularly as a control. There was no conscious selection of patients for either method; on admission they were allocated alternately to the two groups.

Intramuscular Penicillin.—The patients in this group were given an initial dose of 50,000 units, after which successive doses of 20,000 units were administered at four-hourly

intervals for a period of five days. Occasional severe cases received higher dosage in the early stages of treatment. The mean total dose of penicillin was 800,000 units.

Oral Penicillin.—Tablets of calcium penicillin with 0.5 g. of sodium citrate were used. They were made up to contain 20,000 and 25,000 units of penicillin, so that it was possible to vary the scheme of dosage. At first 40,000 units were given three-hourly, but it was soon apparent that this dose was too low, and thereafter for a considerable part of the trial the standard dose was 60,000 units three-hourly, at least during the early stage of treatment. Administration was continued for a period of five days. Towards the end of the trial further variations were made in the dosage, the principal one being that the three-hourly dose was reduced to 25,000 units after treatment had continued for 48 hours. The mean total dose given orally was 1,650,000 units. In order to avoid too much disturbance of the patient a double dose was given at midnight and the next dose at 6 a.m. Two measures were adopted in an endeavour to enhance absorption and to maintain effective blood levels: in the first place, the tablets were always administered along with a small amount (1–2 oz.: 28–56 ml.) of milk; and, secondly, the daily fluid intake was reduced to 2 pints (1.136 litres). Rather to our surprise this latter restriction was tolerated by the patients, and with adequate nursing supervision no difficulty was experienced in keeping the tongue moist and clean.

The bacteriological and clinical control was similar to that used in previous trials (Anderson and Ferguson, 1945). Pneumococcus typing from sputum was, however, somewhat restricted by the lack of adequate supplies of typing serum; the available supplies were kept for the examination of special cultures.

Results

The two groups of cases showed a fairly similar composition. The age distribution, duration of illness, and the presence of bacteraemia are shown in Table I. It will

TABLE I.—Composition of the Two Treatment Groups

	Intramuscular Penicillin	Oral Penicillin
Age distribution:		
0–20 years	0	3
21–40 "	14	13
41–60 "	22	18
61+ "	9	11
All ages	45	45
Bacteraemia:		
Pneumococcus Type I	2	2
" " II	5	7
" " V	0	2
Others	2	2
Staphylococcus	0	1
Total	9	14
Duration of illness on admission:		
0–2 days	18	23
2–4 "	13	13
5+ "	14	9
Mean duration (days)	3.5	3.2

be seen that in respect of the factors considered to have the greatest effect upon the prognosis there was little difference between the two groups. In so far as previous sulphonamide treatment was concerned routine estimations of the blood level on admission were not made during this trial. Of those who were given intramuscular penicillin 23 had received some sulphonamide before admission, but only seven had received more than 4 g. In the oral group the equivalent figures were 24 and 10, of whom two had received a single injection of penicillin intramuscularly.

The effect of treatment in the two groups has been compared in respect of the duration of fever, the occurrence of complications, and the number and causes of deaths. The average duration of fever in uncomplicated cases was: "intramuscular" group, 1.9 days; "oral" group, 1.4 days. A composite temperature chart (Fig. 1) shows little difference between the effect of the two methods of treatment.

FIG. 1.—Duration of pyrexia in uncomplicated cases of pneumonia treated with penicillin.

Complications developed in 12 of the patients given intramuscular penicillin and in 16 of those given oral treatment. The individual complications are listed in Table II. It shows that there is no appreciable difference between the two groups.

TABLE II.—Complications in the Two Treatment Groups

Complication	Intramuscular Penicillin	Oral Penicillin
Lung abscess	2	0
Empyema	1	1
Sterile effusion	2	1
Delayed resolution	7	13
Lobar collapse	0	1

The patients who died are recorded in Table III, which includes relevant details regarding their clinical condition. Study of the table throws light on the present status of pneumonia therapy, for it is apparent that in many of the patients the presence of some accompanying disease or degeneration was a contributory factor which weighed too heavily against effective treatment. Thus in four of the patients other conditions were present which were of themselves sufficient to have produced a fatal issue. The mortality rate for the series is 7.8%, and when it is recalled that 20 of the patients were over the age of 60 years such a low rate may be regarded with satisfaction.

TABLE III.—Deaths

Case	Age	Method of Treatment	Duration of Illness Before Admission	Extent of Consolidation	Blood Culture	Complicating Factors	Cause of Death
D. B.	41	Oral	5 days	L1 + 2	Positive (I); 624 col./ml.	Chronic bronchitis; pulmonary tuberculosis	Pneumonia
J. C.	55	"	6 "	R2 + 3	Positive (II); pour-plate, neg.	Severe anaemia; pulmonary tuberculosis (calcified)	—
J. G.	38	"	2 "	L2 R3	Positive (II); pour-plate, uncountable	Chronic bronchitis. Died within 11 hours of admission	Early abscess formation at necropsy
M. W.	64	"	6 "	R1 + 2 + 3	Positive (V); pour-plate, neg.	Auricular fibrillation	No necropsy. Cardiac failure
D. M.	61	Intramuscular	5 "	L1 + 2	Positive (XVI); pour-plate, 20 col./ml.	Cirrhosis of liver	Pneumonia, resolved at necropsy
J. M.*	68	"	4 "	L1 + 2	Sterile	—	Lung abscesses at necropsy
J. S.	58	"	3 "	R1 + 2 L1	Positive (II); 11 col./ml.	Gross spinal deformity	Pneumococcal meningitis

L1 and L2 = Left upper and left lower lobe. The figure in parentheses under "Blood Culture" refers to the type of pneumococcus.

* Received sulphonamide treatment before admission.

Clinical details are given of two typical cases, one in the younger age group and the other, a particularly severe case, in the older age group.

Case 1

Treatment: penicillin orally—60,000 units three-hourly for 54 hours, then 40,000 units for 75 hours: total 2,120,000 units (Fig. 2).

A man aged 27 was admitted on Dec. 11, 1946; temperature 102° F. (38.9° C.), pulse 120, and respirations 40. On Dec. 8 he had had a sudden attack of shivering, followed by severe

FIG. 2.—Chart of Case 1. Total penicillin, 2,120,000 units.

pain in the right chest anteriorly. Headache, troublesome cough, and rusty sputum were also noted. He had had several previous attacks of bronchitis. Sulphonamide had not been given before admission.

On admission the patient was acutely ill; his tongue was very dirty. Examination of the chest revealed a pneumonia involving the greater part of the right lung; this was later confirmed radiographically. Rales were numerous in both lungs, and there was a suggestion of spread of consolidation into the left lower lobe. The blood culture was sterile; sputum, pneumococcus Type II; W.B.C., 15,800 per c.mm. (polymorphs, 91%). Next day the temperature, pulse, and respirations fell and the patient's appearance improved, although there was no improvement in the chest signs. On the 15th, signs of consolidation were most pronounced in the middle third of the right lung. The general condition was much better. On the 23rd the chest was clear clinically and radiographically. The patient was discharged on Dec. 26.

Case 2

Treatment: penicillin orally—60,000 units three-hourly for 54 hours, then 40,000 units three-hourly for 57 hours: total, 1,840,000 units (Fig. 3).

The patient, a man aged 54, was admitted on Feb. 11, 1947, his sixth day of illness, having collapsed while at work. He

complained of shivering, pain in the chest, cough, and sputum. He had had no previous illnesses, and no treatment had been given before admission. His temperature was 100° F. (37.8° C.), pulse 96, and respirations 28.

Physical examination showed a poorly nourished man who was acutely ill, cyanosed, and dyspnoeic. The tongue was dry and coated. There were signs of consolidation in both lower lobes. A blood culture performed on admission proved to be positive, and Type V pneumococci were so numerous on the pour-plate as to be uncountable. The W.B.C. numbered 6,400 per c.mm. (polymorphs, 93%). Next day the physical signs in both lungs were unchanged, and the cyanosis and dyspnoea were not improved. Auricular fibrillation was now present. Recovery was slow and uneventful, except for an elevation of

FIG. 3.—Chart of Case 2. Total penicillin, 1,840,000 units.

temperature to 100.8° F. (38.2° C.) on March 1. At this time there was excessive prominence of old varicosities on the right leg, with surrounding redness. This subsided after 48 hours' rest in bed. When discharged after 36 days in hospital the chest had cleared except for a little basal rale.

Discussion

From the results recorded it is clear that the oral administration of penicillin is a satisfactory method of treatment for pneumonia. Our experience would suggest that treatment should start with a daily oral dosage equal to four times that required by the intramuscular route. After obvious clinical improvement (usually within 48–72 hours) this dose may be reduced by half. It is interesting that such a schedule is much smaller than that used by Bunn *et al.* (1945) and by Finland *et al.* (1945). When attention is directed solely to those patients who had bacteraemia at the beginning of treatment it may be noted that in nine of them the colony counts were between 4 and 624 organisms per ml. and that in two others the organisms were too numerous to count. The satisfactory recovery of seven of these cases (including one of the latter) is good evidence of the efficacy of the oral method of

presentation. With regard to the technique of administration it would seem desirable at present to give the antibiotic as we gave it—namely, in milk and with a maximum fluid intake of 2 pints a day.

The necessity for a larger dose of penicillin makes it apparent that destruction of the antibiotic must take place at some part of its course through the body. Even with this increased dosage high inhibition levels in the blood serum were not obtained and indeed inhibition was rarely found in dilutions of serum above 1 in 2. Whether the state of the stomach juices during an acute infection such as pneumonia is an important factor in diminishing the amount of destruction may be worth further examination. One of us (J. B. L., unpublished) has shown that there is a decided diminution in the hydrochloric acid content of the gastric juice in pneumonia, and that this hypochlorhydric or achlorhydric state does not disappear immediately upon clinical recovery. The significance of such a finding is not at once apparent, but it may be a contributory factor in preventing an excessive destruction of penicillin. It would seem of some importance to make test-meal studies in other acute infections to see if this loss of hydrochloric acid is a common feature.

It should perhaps be emphasized that the indications for penicillin therapy are not changed by the present report. The sulphonamides constitute an adequate method of treatment for the majority of cases, more especially in the younger age groups; but for those patients who require penicillin there may be some advantage in the use of the oral route. In the first place, the difficulties associated with continued injections are overcome and treatment of pneumonia with penicillin in the home becomes practicable. Secondly, it seems possible that therapy might be cheapened by the use of substandard penicillin, which would not require the careful sterilization and packing necessary when used by injection.

The tablets were supplied by Burroughs Wellcome, to whom we are indebted for the opportunity of conducting the trial. We wish to thank Dr. F. Prescott and Dr. G. Brownlee for their advice and help.

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Man Against Pain: The Epic of Anaesthesia (By Howard Riley Raper. Victor Gollancz, Ltd. 1947. 10s. 6d.) can hardly be regarded as a serious contribution to the literature of the history of anaesthesia, for it is written for the lay public in a journalistic style. For example, in analgesia "the patient is woozie but not unconscious," and "avertin is administered per rectum in the form of a nice little pink enema." On the title page is the quotation: "If America had contributed nothing more to the stock of human happiness than anaesthetics, the world would owe her an everlasting debt of gratitude." The author develops this theme to such an extent that the British reader becomes rather irritated by his depreciation of much outstanding European work. For instance, the introduction of ether anaesthesia, together with an account of the controversy about Morton, Long, Wells, and Jackson, occupies 88 pages, while he dismisses Simpson's discovery of the anaesthetic properties of chloroform in just over one page. He ignores the pioneer work of British anaesthetists done during and after the 1914-18 war in evolving the inhalation technique of endotracheal anaesthesia and blind nasal intubation, yet fully describes the relatively trivial modification of using a cuffed tube instead of a gauze pack in a chapter entitled "The Dunked Dog."

ORAL PENICILLIN IN YOUNG CHILDREN

BY

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We report here a clinical trial in which we treated 25 children, originally diagnosed as suffering from pneumonia, with oral penicillin. It is hoped that our modest contribution will induce others to try out on a bigger scale the oral administration of penicillin in sick children. No references to systematic experiments in the treatment of pneumonia in young children with oral penicillin could be found in the literature, and therefore the instructions given, especially those regarding the dosage, had to be modified after experience had been gained from the first few cases.

The original instructions given were as follows: (a) Pharyngeal swabs to be taken before treatment, and the isolated organisms to be tested for penicillin sensitivity. (b) The chest to be x-rayed as soon as possible after admission and again at the completion of treatment. (c) A record of the fluid intake to be kept; no extra fluids to be given unless specially ordered. (d) Oral penicillin to be given 4-hourly (later modified to 3-hourly) except for the last night dose, which may be doubled if a prolonged uninterrupted sleep is desirable. Dosage: Infants up to 6 months, 10,000 units (later increased to 20,000 units); between 6 months and 1 year, 20,000 units (later increased to 30,000 units); over 1 year and under 2, 30,000 units (later increased to 40,000 units). The treatment was continued for five days or less according to progress made by the child. Each tablet contained calcium penicillin 20,000 i.u. and sodium citrate 0.5 g. One or more tablets were crushed in water or milk and given preferably before feeds.

The dosage was originally calculated according to body weight in the proportion of 50,000 units per 24 hours for a 14-lb. (6.3-kg.) baby—say 8,000 units 4-hourly day and night. This dosage was based on that of 500,000 units per 24 hours for a 10-stone (63-kg.) adult, an amount of oral penicillin apparently effective against pneumonia in the adult (Prescott, 1947, personal communication). Buchanan (1946) considered 4,000 units per lb. (0.45 kg.) of expected body weight per 24 hours effective in young children. In the more severe cases, especially the later ones, and in view of the results of serum-penicillin estimations, these doses and sometimes larger ones were given at 3-hourly instead of 4-hourly intervals. At most oral penicillin was given for five days, and in several cases where clinical improvement was rapid the treatment was discontinued earlier than the fifth day.

Clinical Results

Of the 25 children treated 2 were under 6 months old, 9 between 6 months and 1 year, and 14 between 1 and 2 years old. The revised clinical diagnosis in 18 cases was bronchopneumonia, in 5 lobar pneumonia, and in 1 bronchitis. The remaining child developed measles the day after admission; treatment was stopped and she was removed to a fever hospital. The five cases of lobar pneumonia and 11 cases of bronchopneumonia were considered seriously ill on admission. In 15 cases the diagnosis was confirmed by radiography. Most of the children had a history of one to three days' illness before admission, but 2 had been ill for as long as seven days. In most of the cases pneumococci and streptococci (principally