A CLINICAL STUDY OF OXYTETRACYCLINE ("TERRAMYCIN") WITH SPECIAL REFERENCE TO THE GROWTH OF CANDIDA ALBICANS DURING ANTIBIOTIC THERAPY.

A Thesis submitted to the
University of Glasgow
for the degree of Doctor of Medicine by

JESSIE L. SHARP,
Bachelor of Medicine.

September, 1954.

PREFACE

I wish to record my gratitude to Dr Thomas Anderson who first suggested that I should undertake this investigation and whose encouragement has meant much to me.

To Mr C. McLean, Knightswood Hospital, Glasgow, I am indebted for the routine sputum examinations, the typing of the pneumococci and for the photographs.

J.L.S.

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INTRODUCTION

It is with some diffidence that I present a thesis on chemotherapy in 1954, the year which marks the centenary of the birth of Paul Ehrlich. It was he who coined the word chemotherapy to denote the use of a specific chemical substance for the treatment of human disease. He first used the term in connection with an attempt to treat malaria with methylene blue. Encouraged by the success of this experiment he went on to seek a remedy for trypanosomiasis. He conceived the idea of experimenting with a toxic substance like arsenic and so modifying it that it would kill the parasites and yet leave the host's tissues unharmed. This led to his discovery in 1910 of salvarsan, later called arsphenamine. The signal success of this drug in the treatment of both trypanosomiasis and syphilis laid the foundation of the modern science of chemotherapy.

The search for other chemotherapeutic agents continued but there was an interval until 1935 when clinical reports of a new drug, Prontosil Red, were published by Domagk in Germany. In the same year the two Trefouëls and Nitti and Bovet at the Pasteur Institute showed that the part of the Prontosil molecule which conferred its staining properties was not essential for its therapeutic powers. By removing this portion they produced

the chemically simpler substance, sulphanilamide, which was the active portion of Prontosil. Subsequently, derivatives of sulphanilamide were synthesised with greater antibacterial activity and less toxicity. In 1941 sulphadiazine was produced and the potency and freedom from toxic effects of this drug make it one of the most widely used sulphonamide compounds.

The next advance came with the introduction of antibiotics for the treatment of infection. The story of Fleming's discovery of penicillin is well known. In 1929 he noticed that a mould which had accidentally fallen on one of his culture plates was causing dissolution of the staphylococci in its neighbourhood. He realised that the mould, which he later identified as Penicillium notatum, was secreting a substance which was lethal to bacteria. This substance he called penicillin. It was not until eleven years later, however, that penicillin was sufficiently concentrated and purified by Florey and his co-workers at Oxford so that its curative properties in human infections could be demonstrated.

The success of penicillin led to an intensive search for other substances with antibiotic properties. The struggle for survival in the world of microscopic organisms had been recognised for many years. The term "antibiosis" to denote the opposition of one living organism to the life of another

organism had been introduced by Vuillemin in 1889 who called the active participator the "antibiotic". In 1941 Waksman re-introduced the word to designate the chemical substance produced by micro-organisms which could inhibit or even destroy other micro-organisms.

Antibiotic substances are produced mainly from three types of micro-organisms. These are, in ascending order in the biological scale, the bacteria, the actinomyces and the moulds. From bacteria, bacitricin, tyrothricin and polymixin have been obtained but, because of their high toxicity, they are of limited chemotherapeutic use. Penicillin is the only important antibiotic which has been discovered from the moulds. The first observation on the actinomyces was made in 1917 by Grieg-Smith in Australia. He noticed that some organisms grown from the soil had the power of inhibiting the growth of certain bacteria. Waksman chose the actinomycetes as being the most promising source of antibiotics. He examined a large collection of stock cultures and eventually found one species, the Streptomyces griseus, which had potent antibacterial activity. In 1944 he succeeded in isolating this new antibiotic which he called streptomycin.

This provided a great stimulus for the systematic screening of soils for other organisms with antibiotic

properties. In the post-war period extensive research programmes were drawn up and innumerable soil samples from all over the world were sent to laboratories for mycological investigation. Nowadays an elaborate routine precedes the introduction of a new antibiotic. Fungi grown from the soil are tested for antibiotic activity against various pathogenic organisms. In order to study the specific nature of the active agent, the fungi which seem promising are grown in quantity to get sufficient antibiotic in a semi-pure form. Should this substance not be already known it is studied for its toxicity in animals. If it passes this test satisfactorily the fungus is then grown in larger quantities for recovery and purification of the antibiotic substance. In its pure form the substance undergoes pharmacological testing in vitro and in animals before being used to treat experimental animal infections. Only after satisfactory results from these experiments is the antibiotic ready for clinical trials in human infections.

As a result of this system, over three hundred antibiotics have been discovered but only about a dozen are of clinical value. Three of the most outstanding ones, chloramphenicol, aureomycin and terramycin are used in the present investigations. Chloromycetin was isolated from Streptomyces venezuelae by John Ehrlich and his co-workers in 1947, and

aureomycin from Streptomyces aureofaciens by B.M.Duggar in 1948. In 1950 a team of workers led by Gladys L. Hobby found that Streptomyces rimosus produced a new antibiotic which they called terramycin.

Once an antibiotic has been discovered biochemists determine its chemical structure so that the substance can be synthesised. This leads to the development of methods suitable for its commercial production. In 1949 Controulis, Rebstock and Crooks discovered the chemical constitution of chloromycetin and described a method for its commercial production. The trade name Chloromycetin was registered by Park Davis and Co. and the name chloramphenicol was subsequently used as the generic name. In August 1952 the chemical structure of terramycin was elucidated and the descriptive chemical name given it was oxytetracycline. The corresponding name for aureomycin is chlortetracycline showing that these two drugs are closely related chemically. The chemical names are now the official designations for these antibiotics and their original names are the trademarks of the laboratories in which they were discovered. Thus the trade mark of Lederle Laboratories for chlortetracycline is Aureomycin and that of Charles Pfizer and Co. for oxytetracycline is Terramycin. For the sake of simplicity the familiar proprietary names are used for these two antibiotics

throughout this study.

In September 1951, when I was a house physician in Knightswood Hospital, Dr.Anderson, Consultant in Infectious Diseases to the hospital, was given by Dr.Hobby a supply of terramycin which at that time was the latest antibiotic. An attempt to evaluate this drug clinically forms the basis of the present work.

In the first place the value of a new drug must be proved in the treatment of human disease. Accordingly a controlled therapeutic trial of terramycin in pneumonia was carried out and this forms the first part of the study. If a drug is to establish a permanent place in therapeutics it must be relatively non-toxic to the patient. If a drug has serious toxic effects on the host then, irrespective of its efficiency in attacking and destroying the infecting organism, its use as a clinical agent will have to be abandoned. The side-effects of terramycin in the pneumonia patients were therefore carefully examined. Furthermore, to gain a wider experience of the side-effects of antibiotics the scope of the investigation was enlarged. While the therapeutic trial was in progress I was also in charge of a ward of patients suffering from pulmonary tuberculosis and three groups of these patients were given a course of chloramphenicol, aureomycin or terramycin. A study

of the clinical side-effects of the antibiotics in both the pneumonia and tuberculosis patients forms the second part of the work.

It is well known that chloramphenicol, aureomycin and terramycin have a wide range of antibacterial activity, hence the descriptive name "broad-spectrum" antibiotics. When such drugs are used for the treatment of infection, not only the specific organism responsible for the infection but all the sensitive organisms in the bacterial flora of the respiratory and alimentary tracts are eliminated. This effect on the microflora is another type of side reaction which antibiotics may produce. A study of the change in the microflora of the sputum, throat and rectum which occurred during antibiotic therapy forms the third part of the work. The usual relationship between man and his bacterial flora is one of commensalism, that is, the organisms live in equilibrium with the host without causing the deleterious effects characteristic of parasitism. Man may not live so equably, however, with the microflora left him by antibiotic therapy. In the fourth part of the study the significance of the alteration in the microflora is discussed, with special reference to its bearing on the clinical side-effects of the antibiotics.

The following chapter describes the therapeutic trial of terramycin.

In the first section the results obtained in the treatment of pneumonia are given and discussed. The pneumonia series of patients included two groups, one consisting of cases treated with terramycin and the other of the control cases.

In the second section the effect of terramycin on the course of the virus infection herpes simplex, which commonly accompanies pneumonia, is examined.

CHAPTER I.

THERAPEUTIC TRIAL OF TERRAMYCIN

Section 1. PNEUMONIA

The terramycin, it was considered, could best be used in treating patients suffering from pneumonia. Despite improved methods of treatment, pneumonia in the elderly patient remains a dangerous infection and consequently the majority of pneumonia patients seen in hospital belong to the older age group. Although modern therapy has reduced the gravity of this illness in younger persons to such an extent that most can be satisfactorily treated at home, in Glasgow the problem of overcrowding frequently renders the care of a sick person in the home impracticable. Many cases have to be removed to hospital and consequently, in the city fever hospitals, pneumonia patients account for a high proportion of cases admitted for treatment of an acute infection.

In estimating the value of terramycin in the treatment of pneumonia, the results of therapy in two groups of patients had to be compared. It was decided that one group would be treated with terramycin and the other, as similar to the first group as possible, would be the control group. In selecting the treatment for the control patients it was thought it would be helpful to compare this newest antibiotic with one of the

first of the chemotherapeutic agents, namely the sulphonamides.

When the sulphonamides came to be widely used in the treatment of bacterial infections, nowhere more than in pneumonia was their value more pronounced. They were indeed considered to be specific for pneumonia. Hitherto the recovery of a patient from lobar pneumonia had followed a typical clinical course. Fever continued and the patient was critically ill until the crisis which usually came on the seventh day of illness. At the crisis the temperature quickly fell to normal within 12 hours and this was accompanied by dramatic clinical improvement. Treatment by sulphonamides so greatly modified the course of the disease that classical cases were only rarely seen. At whatever stage of the illness sulphonamide was given, the temperature fell to normal in 24-48 hours by lysis, although the actual process of resolution was not accelerated. Sulphapyridine was accompanied fairly frequently by toxic effects, especially nausea, vomiting, headache, cyanosis due to methaemoglobinaemia and by haematuria. It was soon replaced by a much less toxic derivative, sulphathiazole. Sulphadiazine is even less toxic although not so potent an antibacterial drug as sulphathiazole. Because of its freedom from toxic effects sulphadiazine was chosen as the control drug in the present treatment trial.

Anderson (1948) showed that the sulphonamides were as beneficial in the treatment of pneumococcal pneumonia as penicillin and, from a study of 8,000 case records of lobar pneumonia, Norris (1953) came to the same conclusion. Nevertheless the action of sulphonamides is bacteriostatic while penicillin in large doses is bacteriocidal. Furthermore, sulphonamides are ineffectual in the presence of pus and a patient with a leucopenia often does not respond to this form of treatment. Consequently, whenever it was considered to be in the patient's interests, the cases in the control group were treated with penicillin in addition to sulphadiazine.

MATERIAL AND METHODS

The Cases. The patients included in the treatment trial were the routine admissions to the male pneumonia ward in Knightswood Hospital during the period September 1951 to December 1952. The series comprised 176 adult males over the age of fourteen years. The patients were allocated alternately in the order of their admission to the two treatment groups. Only patients whose pneumonia was confirmed radiologically have been included in the final analysis. Twenty-six patients in whom the pneumonia was not confirmed have been excluded. The

reasons for their elimination are shown in Table 1. This

TABLE 1. - REASONS FOR EXCLUSION OF CASES FROM THE FINAL ANALYSIS.

FINAL DIAGNOSIS	NUMBER OF CASES	
	Terramycin Group	Control Group
Bronchitis (chest X-ray clear)	4	5
Acute exacerbation of Chronic Bronchitis	1	3
Bronchiectasis	2	2
Pulmonary Collapse	2	1
Pleural Effusion	1	1
Bronchial Carcinoma	1	1
Pulmonary Tuberculosis	1	1
T O T A L	12	14

leaves a total of 150 cases in the pneumonia series of whom 75 were in the terramycin group and 75 in the control group.

Investigations. (a) Clinical: The patient was first seen

in the ambulance by the receiving doctor. If he was desperately ill resuscitation with oxygen and nikethamide was started at once on arrival in the ward. Otherwise he was given a blanket bath on admission and examined by the doctor half an hour later. The patient was first asked if he had been given any treatment prior to admission. A patient was considered to have had inadequate chemotherapy if he had had less than 6g of sulphonamide or only one injection of penicillin. Only patients who were in this category or who had received no previous chemotherapy were included in the series. Each patient was questioned about the mode of onset of the illness and the day on which the various symptoms appeared. A routine clinical examination of each system was then carried out. If the patient's history and clinical examination were in keeping with the diagnosis of pneumonia he was admitted to the trial series.

Each patient had an X-ray of chest taken on the day after admission and this was repeated at weekly intervals during his stay in hospital. When a patient was discharged before resolution was complete on radiological examination, he was asked to report at weekly intervals until the chest X-ray was clear or showed only residual pleural thickening.

(b) Laboratory: From each patient on admission a specimen of sputum was collected into a sterile petri dish and 10ml

of blood were withdrawn from the arm by venepuncture. Five ml were injected into a bottle containing sterile broth and 2ml were mixed with 20ml of melted agar to make a pour plate. All culture media contained 0.5% of paraaminobenzoic acid to counteract the inhibitory effect of any sulphonamide given before admission. The remainder was put in a small bottle containing heparin. These specimens were taken at once to the laboratory.

A direct film of the sputum was stained by Zeil-Neelsen's method and a search made for tubercle bacilli. The sputum was then emulsified with 5ml of sterile broth, a loopful inoculated on to a blood agar plate and 2ml injected into a mouse. The latter procedure was carried out with the purpose of rendering any pneumococci typable. The plate was examined at 24 hours and again at 48 hours for growth of organisms. When the mouse died, usually within 48 hours, its peritoneal fluid was examined for pneumococci. The blood culture bottle and the pour plate were incubated at 37°C and examined daily for ten days for growth of organisms. The pour plate was used for estimating the degree of bacteriaemia. Each colony on the plate was taken to represent a single organism originally present in the 2ml sample of the patient's blood. The number of colonies appearing on the pour plate were counted and half this figure gave the number of colonies present per ml of circulating blood.

As far as possible the serological type of the pneumococcus isolated from the sputum or blood of each patient was determined. The laboratory had a supply of typing srea for pneumococci types 1 to 42. From the heparinised blood a white cell count was done and films were made on which, after staining with Leishman's stain, a differential white cell count was done. The specimens of sputum and blood were collected by the receiving doctor who also did the white cell and differential counts. The subsequent examinations of the sputum and blood cultures were carried out by the senior laboratory technician.

Treatment. (a) Symptomatic: In the case of patients who complained of pleural pain, a hot kaolin poultice was applied to the chest. On the first night in hospital each patient was given 2dr of syrup of chloral and this was repeated on the following nights if the patient had insomnia. If the syrup of chloral proved ineffective 3gr of butobarbitone(Soneryl) were given. Delirium did not present a serious problem in any of the patients but the few who were confused and attempted to get out of bed were controlled with paraldehyde, 4-8dr orally or 2ml intramuscularly, repeated as necessary. Patients with cyanosis were given oxygen, either by a double nasal catheter or by a B.L.B. mask. Congestive cardiac failure was treated with digitalis leaf and other appropriate measures.

Nikethamide (Coramine) was reserved for the gravely ill whose pulse was almost imperceptible.

(b) Specific: Terramycin was given orally for a period of five days. The dosage was 1g six-hourly until the temperature had remained normal for 24 hours, followed by 0.5g every six hours. The total dose ranged from 11g to 21g, the mean being 14.2g. The patients in the control group were given 2g sulphadiazine at four-hourly intervals for the first 24 hours and if their clinical condition was satisfactory this was followed by 1g every four hours for a total period of five days. The total dose varied from 28g to 42g, the mean being 35g.

In the control group 23 patients were given additional chemotherapy. It was considered that a patient had failed to respond to sulphadiazine if his condition deteriorated after admission or it was felt that the duration of fever with its accompanying symptoms was becoming unduly prolonged. For this reason 16 patients were given penicillin at varying intervals after admission, as shown in Table 2. Penicillin was given intramuscularly in a dosage of 250,000 units or 100,000 units according to the severity of illness, at four-hourly intervals over a period of five days. The total dose of penicillin varied widely from 3 million to 15 million units. In addition, three patients who were seriously ill on admission were given

a single dose of 500,000 units before the course of sulphadiazine. The remaining four patients were given broad-spectrum antibiotics. Details of their treatment will be

TABLE 2. - REASONS FOR CASES IN SULPHADIAZINE GROUP RECEIVING PENICILLIN.

REASON	Number of Cases
Severely ill - single dose of penicillin on admission	3
No response to sulphadiazine in 24 hours	2
No response to sulphadiazine in 36 hours	6
No response to sulphadiazine in 48 hours	4
No response to sulphadiazine in over 48 hours	4
T O T A L	19

found in the section which describes the deaths.

I personally observed the clinical progress and had control of the treatment of each patient.

RESULTS

A. SERIES AS A WHOLE

Criteria. In assessing the results of therapy the following criteria were taken:

(a) Duration of fever: Fever was considered to be unduly prolonged if the patient's temperature continued to be elevated after the fifth day in hospital. Of the 150 patients 21 (14%) had fever continuing until or beyond the fifth day in hospital.

(b) Complications: None of the complications was serious. Only delayed resolution and sterile effusion were noted. Resolution was said to be delayed if the chest X-ray was not clear after four weeks in hospital. This occurred in 23 patients and 10 developed a sterile effusion, making a total of 33 patients (22%) with a complication.

(c) Deaths: There were nine deaths in the series giving a death rate of 6%.

Eleven patients had both prolonged fever and a complication. There remained 98 patients (65%) in the series whose temperature had subsided to normal by the fifth day and whose convalescence was uncomplicated. These patients are hereafter referred to as those who made a good recovery.

Prognostic Factors. In the first place I propose to examine the results of therapy in the light of the factors which are generally considered to determine the prognosis in pneumonia.

The standard error of the difference is applied to the results as a test of significance. When the actual difference is greater than three times its standard error it is regarded as significant.

(a) Age: There were 100 (67%) patients in the series who were over the age of 40 years. In this age group were 6 with prolonged fever, 28 who developed a complication and all the deaths. Forty-one patients, 82% of those under 40 years made a good recovery compared with 57, 57% of those over that age. This difference is more than three times its standard error of ±7.3 and is therefore significant. Thus, the age of the patient is an important factor in influencing the outcome of pneumonia.

(b) Duration of Illness: In the series 69 (46%) patients were admitted to hospital after the fourth day in the course of their illness. In this group were 11 with prolonged fever, 25 with complications and 6 of the deaths. Thirty-four patients, 49% of those admitted after the fourth day made a good recovery compared with 64 patients (79%) who were admitted before the fourth day. This difference (30%) of four times its standard error (±7.5) is significant. The length of time which elapses between the onset of infection and the beginning of treatment is therefore important, increasing as it does the chance of complications

and death.

It has been suggested (Flippin 1941) that, generally speaking, old people are admitted later in the course of their illness than younger patients. This is especially so if the patient is not a wage earner as there is less urgency in such a case. Also, old people, particularly those who live alone, tend to neglect their health and delay seeking medical attention. In the present series there were 39 patients over the age of 60 years of whom 21 (54%) were admitted after the fourth day of illness. This proportion is only slightly greater than the 46% of the series as a whole.

(c) Bacteriology of the Sputum: The organism most frequently found in the sputum of patients with pneumonia is the pneumococcus. There are many different serological types of pneumococci but types 1 to 8 are mainly responsible for pneumonia of sudden onset. Types 1, 2, 5 and 7 are most frequently associated with typical lobar pneumonia and were isolated from 71 patients in the present series, pneumococcus type 2 alone accounting for 43 cases. Pneumococci types 3, 4 and 8 are less prevalent and 17 patients in the series had pneumonia due to one of these organisms. Pneumococci of types higher than 8 may be present in the sputum of patients who do not have pneumonia. In the series there were 22 patients with one of these

organisms in the sputum and 7 patients whose sputum yielded a pneumococcus which could not be typed with the available typing sera. These 29 patients had pneumonia both on clinical and radiological examination and an inoculum of their sputum proved fatal to a mouse. The pneumococci which were recovered from the mouse were therefore regarded as the aetiological pathogens of pneumonia in these particular patients. There were thus 117 cases of pneumococcal pneumonia in the series. Bacillus friedländeri, Staphylococcus aureus and Haemophilus influenzae, organisms which may be commensals in the sputum, were considered to be the aetiological pathogens when they were predominant in the sputum and the clinical picture was in keeping with such a finding. There were 8 cases of non-pneumococcal pneumonia in the series.

Altogether, in 125 of the total 150 cases, bacteriological examination of the sputum revealed the organism regarded as responsible for the pneumonia. Of the remaining 25 cases, in 17 the sputum yielded a mixed bacterial flora in which either Streptococcus viridans, Neisseria catarrhalis or Staphylococcus albus was predominant, and from 8 patients a specimen of sputum was not obtained.

It is possible to make a broad distinction between two "bacteriological" groups of cases. Those with pneumococci

types 1 to 8 may be regarded as being infected with "pathogens" since these organisms are rarely found in the sputum apart from acute pulmonary infection. There were 88 patients in this group. The other group consisted of the 37 patients with pneumococci of types higher than 8, Bacillus friedländeri Staphylococcus aureus or Haemophilus influenzae. These, organisms, for purposes of comparison, are here labelled "non-pathogens" because, although pathogenic in the patients under discussion, they may also be present in the sputum without giving rise to symptoms and signs of pulmonary infection.

The group infected with pathogens included 10 with prolonged fever, 23 with complications and 2 of the deaths. In this group 61 patients (69%) made a good recovery compared with 21 (57%) of the group infected with non-pathogens. The difference (12%) has a standard error of ±9.5 and is therefore not significant. The group with non-pathogens contained 6 of the deaths. Thus, while a proportionate number of patients in each bacteriological group made a good recovery, two thirds of the deaths occurred as a result of infection with a non-pathogenic organism, and two thirds of the complications arose in those infected with a pathogen. The inference to be drawn from these facts is that in determining the recovery of a patient from pneumonia, the virulence of the infecting organism is of

subsidiary importance to the defence mechanisms of the host which enable him to overcome the infection. In those who recover, however, the majority of complications arise in those infected with a pathogenic organism.

(d) Bacteriaemia: There were 10 patients with a positive blood culture on admission giving a bacteriaemic rate of 6.7% for the series. The results in these patients were not good: 1 was febrile after five days, 3 developed a complication and 2 died; only 4 made a good recovery.

The degree of bacteriaemia is also important. In 7 patients the pour plate was positive and in 3 it was negative. These three made a good recovery. In two patients the colonies were so numerous in the pour plate as to be uncountable. Of those, one died and the other developed a sterile effusion. One patient with 90 colonies/ml had delayed resolution and one with 15 colonies/ml died. The remaining three patients had 5 colonies/ml, 4 colonies/ml and 2 colonies/ml and the outcome in them was good recovery, prolonged fever and delayed resolution respectively. In other words, while all the patients with a negative pour plate made a good recovery only one with a calculable number of colonies

in the circulating blood made a good recovery. It is of interest to note that the bacteriaemia in nine patients was due to a pathogenic organism, i.e. pneumococcus type 1 to 8 and in only one patient was it due to a non-pathogenic organism, in this case Bacillus friedländeri. This shows how the invasive property of the pneumococcus is closely linked with its pathogenicity. We may conclude that when the causative organism in pneumonia invades the blood stream in measurable quantities it influences the prognosis for the worse.

(e) Extent of Consolidation: The consolidation is usually confined to one lobe in pneumonia hence its name lobar pneumonia. This was true of 109 cases in the series and for the site of consolidation the right basal lobe was the commonest, followed by the left lower lobe, right upper lobe, left upper lobe and right middle lobe in descending order. In 15 patients the consolidation was localised to a part of a lobe; 26 had a broncho-pneumonic type of illness in which the consolidation was widespread but patchy in the lungs. The process of consolidation involved two or more lobes in 32 patients. Among those

were 5 with prolonged fever, 13 with complications and 4 who died. In those patients with extensive consolidation only 12 (37%) made a good recovery compared with 86 (72%) of those who had less than two lobes involved in pneumonic consolidation. This difference is almost four times its standard error of ±9.5 showing that the area of consolidation does have a bearing on the course of the disease.

(f) Treatment Prior to Admission: 55 patients (37%) in the series had received chemotherapy before admission to hospital. In this group were 6 with prolonged fever, 12 with complications and 4 who died. It is of interest to note that three patients with a positive blood culture were in this group. Thirty seven patients (67%) made a good recovery compared with 61 (64%) of those who reached hospital untreated. The close similarity of these figures indicates that the small amount of chemotherapy a patient was allowed to have received and still be admitted to the series had little effect on his ultimate recovery.

At this point the particular form of chemotherapy may be briefly considered. Of the 55 patients, 35 had received sulphonamide in an average amount of 4-5g, 16 had received penicillin either as a single intramuscular injection or a single dose of 2-3 oral tablets and 4 had received both sulphonamide and

penicillin. Of the 20 patients who had received penicillin one had a positive blood culture with a calculable colony count and one died; 15 (75%) made a good recovery compared with 22 (63%) of those who had received sulphonamide only. The similarity of these proportions suggests that penicillin has little advantage over sulphonamide.

(g) White Cell Count: If the white cell count was over 12,000/cmm and the differential count showed a preponderance of polymorphs the patient was considered to have a leucocytosis. This was present in only 81 patients (54%) of the series. Among the other 69 were 9 with prolonged fever, 17 with a complication and 7 who died. Of the leucopenic patients 58% made a good recovery compared with 73% of those with a leucocytosis. This difference is only twice its standard error of ±7.8 and is scarcely significant. Nevertheless, in those who died, a leucopenia on admission was a grave omen.

(h) The presence of associated disease: In the series 64 patients (43%) were handicapped by the presence of some other disease. Chronic bronchitis-45 patients, and cardio-vascular disease 13 patients, accounted for the majority. Of the remainder, 3 patients were chronic alcoholics, 2 had a severe anaemia and 1 had chronic nephritis. Twenty-nine (65%) of the chronic bronchitics made a good recovery compared with 69 (66%) of those

without chronic bronchitis, indicating that the presence of underlying chronic bronchitis made little difference to the progress of the pneumonia. In the group of 19 patients, i.e. excluding those with chronic bronchitis, 3 had prolonged fever, 7 developed a complication and 7 died. This group therefore fared badly; only 5 (26%) made a good recovery compared with 93 (71%) of the rest of the series. This difference is four times its standard error of ±10.8 and is therefore significant. Although chronic bronchitis is relatively unimportant, other associated diseases of which cardio-vascular disease is the commonest are of grave prognostic import.

TABLE 3. - COMPARISON OF THE TWO TREATMENT GROUPS.

PROGNOSTIC FACTORS	NUMBER OF CASES	
	Terramycin Group	Control Group
Age Distribution:		
14 - 20 years	5	2
21 - 40 years	23	20
41 - 60 years	28	33
61 years and over	19	20
ALL AGES	75	75
Duration of Illness on Admission:		
0 - 2 days	17	15
3 - 4 days	22	27
5 days and over	36	33
MEAN DURATION (DAY)	5.0	4.7

TABLE 3 (Continued) - COMPARISON OF THE TWO TREATMENT GROUPS.

PROGNOSTIC FACTORS	NUMBER OF CASES	
	Terramycin Group	Control Group
Bacteriology of the Sputum:		
Pneumococcus type 1	12	6
" " 2	21	22
" " 3	6	2
" " 4	1	1
" " 5	0	2
" " 6	0	0
" " 7	4	4
" " 8	3	4
Pneumococcus type 1 - 8	47	41
Pneumococcus type higher than 8	12	10
Untypable pneumococcus	4	3
TOTAL PNEUMOCOCCAL	63	54
Staphylococcus aureus	1	3
Haemophilus influenzae	1	2
Bacillus friedländeri	0	1
Mixed bacterial growth	7	10
No sputum obtained	3	5
TOTAL	75	75
Bacteriaemia:		
Pneumococcus type 1	1 cols. uncountable	1 90 cols/ml.
" " 2	1 p.p. negative	2 2 cols/ml. and p.p. neg.
" " 5	0	1 cols. uncountable
" " 7	0	1 4 cols/ml.
" " 8	1 5 cols/ml.	1 p.p. negative
Bacillus friedländeri	0	1 15 cols/ml.
TOTAL	3	7
Site of Consolidation:		
Lobar: Right Upper Lobe	7	12
Right Middle Lobe	4	4
Right Lower Lobe	22	15
Left Upper Lobe	4	9
Left Lower Lobe	15	17
TOTAL LOBAR	52	57
Localised to part of a lobe	10	5
Broncho-pneumonia	13	13
Extent of consolidation (av. no. of lobes)	1.3	1.2

p.p. = pour plate

TABLE 3 (Continued) - COMPARISON OF THE TWO TREATMENT GROUPS.

PROGNOSTIC FACTORS	NUMBER OF CASES	
	Terramycin Group	Control Group
Treatment prior to Admission:		
Sulphonamide	19	16
Penicillin	8	8
Sulphonamide + Penicillin	0	4
TOTAL TREATED	27	28
White Cell Count:		
Leucocytosis present	38	43
Associated Disease:		
Chronic bronchitis	21	24
Cardio-vascular disease	8	5
Chronic alcoholism	1	2
Anaemia	0	2
Chronic nephritis	1	0
TOTAL	31	33

RESULTS OF TREATMENT	NUMBER OF CASES	
	Terramycin Group	Control Group
Duration of Primary Pyrexia:		
Less than 24 hours	21	14
24 - 48 hours	30	25
2 - 5 days	12	22
5 - 7 days	6	4
1 - 2 weeks	2	7
Over 2 weeks	2	0
TOTAL	73 *	72 **
Average duration (hours)	60	70
Complications:		
Delayed resolution	11	12
Sterile effusion	5	5
Average time for resolution (weeks)	2.8	3.0
Deaths:	3	6

* 2 deaths omitted. ** 3 deaths omitted.

B. THE TWO TREATMENT GROUPS

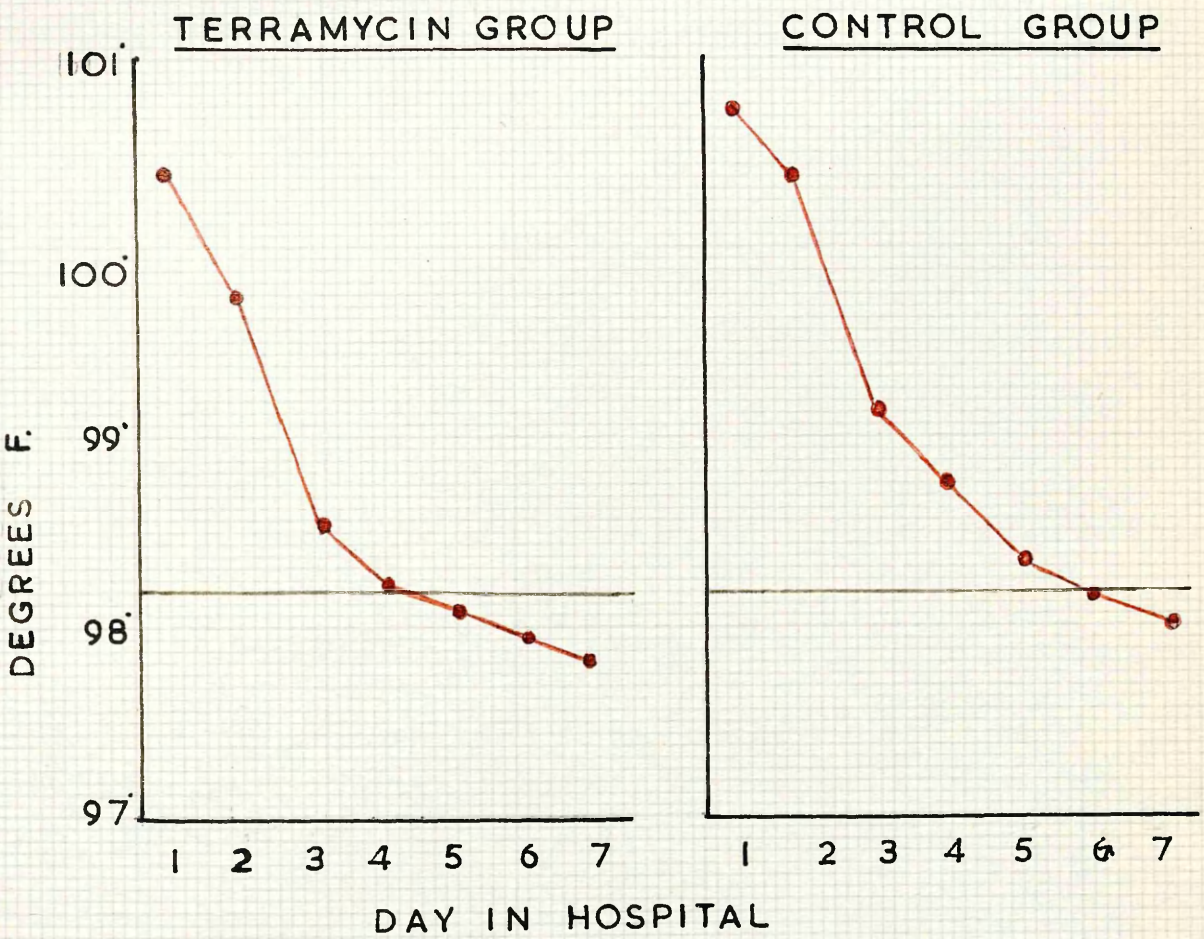
When the two treatment groups are examined to discover if these eight prognostic factors are equally represented in each it is found that the two groups were comparable in respect of age, duration of illness and extent of consolidation. Patients who had received chemotherapy before admission, who had a leucopenia and who had an associated disease were equally distributed in the two treatment groups (Table 3). As regards the bacteriology, however, the control group contained six of the eight non-pneumococcal pneumonias and seven of the ten cases with a bacteriaemia.

The results of the two methods of treatment may therefore with fairness be compared. Any difference which emerges may justifiably be attributed to the form of treatment rather than to a preponderance of poor prognostic factors in one group. The findings are summarised in Table 3.

(a) Fever: The temperature fell to normal within 48 hours of admission in 51 patients (68%) treated with terramycin and in 39 patients (52%) who received the control treatment. The difference (16%), only twice its standard error of ±7.9, is barely significant. A composite temperature chart (fig.1) was drawn for the two groups taking the mean of the highest temperatures recorded in each day during the first week in hospital.

FIG 1

COMPOSITE TEMPERATURE CHART



It shows a more sharply falling curve in the terramycin group. The average duration of the primary pyrexia was 60 hours in the terramycin group and 70 hours in the control group. Table 3 shows that of the 21 patients with fever prolonged beyond the fifth day 10 were in the terramycin group and 11 in the control group.

(b) Complications: The average time taken for resolution was 2.8 weeks with terramycin and 3.0 weeks with the control treatment. In the terramycin group there were 11 patients whose resolution was not complete after four weeks in hospital and 5 patients developed a sterile effusion. In the control group 12 had delayed resolution and 5 developed a sterile effusion. In this respect therefore the two methods of treatment gave similar results.

(c) Deaths: Of the 9 deaths 3 occurred in the terramycin group and 6 in the control group. The salient features of these patients are summarised in Table 4 and more details are given below.

Case 1. J.McL. 74 years, was admitted on the fourth day of illness. He had pneumonic consolidation throughout the right lung. He was allocated to the terramycin treatment group but died of peripheral circulatory failure 12 hours after admission. At autopsy areas of suppuration and necrosis were seen in the

TABLE 4. - DEATHS.

CASE	AGE (yrs)	D.of I.	EXTENT OF CONSOL.	BACTERIOLOGY	TREATMENT	P.M.	COMMENTS
1. J.McL	74	4	$R_1+R_2+R_3$	Nil	Terr. 2g.	Yes	Peripheral circulatory failure. Died in 12 hours.
2. J.O'H	62	3	R_1	B.C. pos. pneumo. type 1, p.p. uncountable	Terr. 1g. pen. $\frac{1}{2}$mill.u.	Yes	Peripheral circulatory failure. Died in 8 hours.
3. J.R.	74	7	Extensive patchy consol. both lungs	Sputum: pneumo. type 10	Terr. 13g. pen. 18 mill.u.	No	B.P. 180/100. Died of cardiac failure in 11 days.
4. P.M.	63	7	R_1+R_2	Sputum: and B.C. pos.B. fried. p.p. 15 cols/ml.	Pen. 3mill.u. aureo. 7g. strept. 9g.	Yes	Poor myocardium Died in 5 days.
5. P.P.	56	5	$R_1+R_2+R_3$	Sputum:Staph. aureus	S.D.34g.pen. 10 mill.u. terr. 20g.	No	Suppurative pneumonia. Died in 15 days.
6. H.B.	62	8	R_1+R_2	Sputum:Staph. aureus	S.D.24g.pen. 2 mill.u. chlor. 12g.	No	B.P. 170/120. Died in 6 days.
7. J.C.	54	3	R_1	Sputum: pneumo. type 12	S.D. 17g. pen. $2\frac{1}{4}$ mill.u.	No	B.P. 150/100. W.B.C. 3200/cmm. Died in 4 days.
8. C.D.	62	11	R_1+L_1	Sputum: untypable pneumo.	S.D. 6g. pen.1mill.u. chlor. 19g.	No	B.P. 180/100. Died of congestive cardiac failure.
9. G.W.	60	9	$R_2+R_3+L_2$	Sputum: pneumo. type 3	S.D. 30g. pen. $9\frac{1}{4}$ mill.u.	Yes	Poor myocardium Died in 12 days.

R_1 = R.U.L. etc. B.C. = blood culture p.p. = pour plate

D. of I. = Day of Illness.

right lung giving it a honeycomb appearance. There was moderate left ventricular hypertrophy. Blood culture was not carried out but a swab of the lung taken at post-mortem showed Gram positive diplococci on the direct film. These organisms, however, failed to grow on culture. This patient's extensive pneumonia had made him beyond hope of recovery on admission to hospital.

Case 2. J.O'H. 62 years. This patient, also in the terramycin group, was admitted on the third day of illness. He had a consolidation of the right upper lobe with a heavy bacteriaemia due to pneumococcus type 1. The white cell count was 4800/cmm. He was moribund on admission and died of peripheral circulatory failure 8 hours later. At autopsy the right upper lobe was firm with a yellowish consolidation and showed small areas of suppurative softening and local abscess formations. The heart showed no abnormality. Death was due to the overwhelming pneumococcal infection which had taken extensive hold on the patient before his admission.

Case 3. J.R. 74 years, was admitted on the seventh day of illness. X-ray of chest showed extensive patchy consolidation in both lung fields. B.P. was 180/100 and his pulse was soft and irregular. The white cell count was 25,000/cmm with 93% polymorphs and sputum grew pneumococcus type 10 on culture. He was treated with terramycin 1g six-hourly and after a slight

initial improvement his condition began to deteriorate. After a total dose of 13g terramycin his temperature which never rose above 100°F was normal but his general condition was very poor and he had numerous crepitations at both bases. A course of intramuscular penicillin was started and this was continued until his death six days later. There was no post-mortem and death was considered to be due to the massive pulmonary infection superimposed on an inefficient cardio-vascular system.

Case 4. P.M. 63 years, was admitted on the seventh day of illness with consolidation of the right upper and middle lobes. His heart sounds were of poor quality and irregular and B.P. was 160/90. The white cell count was 8400/cmm. Blood culture was positive for Bacillus friedländeri 15 colonies/ml and this organism was also cultured from the sputum. Although allocated to the sulphadiazine group his illness was of such severity that he was treated with intramuscular penicillin 250,000 units four-hourly from admission. When the bacteriology of the sputum became known treatment was changed to aureomycin 1g six-hourly. There was no improvement and streptomycin 1g four-hourly was started two days later. His general condition continued to deteriorate, however, and he died five days after admission. At autopsy the the right upper and mid lobes showed mucoid grey hepatisation. The heart was enlarged

and the left ventricle was hypertrophied. Death in this instance was due to the overwhelming Friedländer infection in a patient with cardio-vascular insufficiency.

Case 5. P.P. 56 years, was admitted on the fifth day of illness. He had extensive consolidation of the right lung. The heart sounds were soft but regular and B.P. was 130/70. The white cell count was 11,800/cmm with 93% polymorphs, sputum was negative for tubercle bacilli and grew Staphylococcus aureus on culture. Treatment was started with sulphadiazine but on the day after admission his condition was so poor that intramuscular penicillin 250,000 units four hourly was given. His temperature remained elevated around 100°F and he became breathless and cyanosed. The first X-ray of chest showed consolidation of the right lung and the second X-ray, taken only one week later, showed that cavitation had occurred in the right upper lobe. At this stage penicillin and sulphadiazine were discontinued and terramycin 1g six-hourly started. His general condition continued to deteriorate, temperature remained elevated and the right chest very moist. He died after 15 days in hospital. There was no autopsy but death was almost certainly due to a suppurating staphylococcal pneumonia.

Case 6. H.B. 62 years, also had an extensive pneumonia in the right lung and a heavy growth of Staphylococcus aureus

in the sputum. He was admitted on the eighth day of illness, was hypertensive (B.P.170/120) and the white cell count was 5600/cmm. He was allocated to the control group and treatment was started with sulphadiazine and penicillin. Three days later his general condition was fair but his tongue was still brown and dry. The Staphylococcus aureus had been shown to be sensitive to penicillin but because of the lack of clinical improvement treatment was changed to chloramphenicol, a drug to which also the organism was sensitive. His condition gradually deteriorated, however, and he died 6 days after admission. There was no post-mortem and death was considered to be due to an extensive pneumonia occurring in a patient with hypertension.

Case 7. J.C. 54 years, was admitted on the third day of illness with pneumonic consolidation of the right upper lobe. His general condition was fair, B.P. 150/100, white cell count 3200/cmm and sputum grew pneumococcus type 12 on culture. Treatment was commenced with sulphadiazine. Thirty-six hours later the temperature remained elevated at 102^{o}F and intramuscular penicillin 250,000 units four-hourly was given. On the following day the patient's general condition became worse, his colour dusky and there were crepitations throughout the right lung and at the left base. He died four days after admission. In the absence of an autopsy the only known factor which may have contributed towards

death was the leucopenia.

Case 8. C.D. 62 years, had a broncho-pneumonia on admission. His general condition was poor, pulse soft but regular and B.P.180/100. The white cell count was 32,000/cmm with 89% polymorphs and the sputum grew a pneumococcus which was untypable. Treatment was started with sulphadiazine and penicillin. On the following day he was cyanosed and breathless and chloramphenicol was given. This was done because the identity of the infecting organism was not certain and it was felt that a broad-spectrum antibiotic would be more effective in combating the infection. He responded well to treatment and his chest became clinically quiet. One week later he developed congestive cardiac failure. This was treated with digitalis leaf and mersalyl without benefit. The oedema gradually increased and he died after one month in hospital. Death in this case was attributable to congestive cardiac failure although the initial respiratory infection doubtless hastened the onset of cardiac failure.

Case 9. G.W. 60 years, was admitted on the ninth day of illness. He was sharply ill and had an impaired percussion note and crepitations at both bases. B.P. was 164/108 and pulse regular. The white cell count was 3000/cmm and sputum yielded pneumococcus type 3 on culture. He was treated with sulphadiazine

supplemented 24 hours later with intramuscular penicillin 250,000 units four-hourly. He developed a right sided pleural effusion, became dyspnoeic and cyanosed and died 12 days after admission. At autopsy the right mid and basal lobes and an area in the centre of the left lower lobe showed dense grey hepatisation. In these areas multiple abscesses had coalesced to produce gangrene of the lung with much thick, greenish pus. The heart showed considerable left ventricular hypertrophy and the myocardium, areas of fibrosis. In this patient both the type of pneumococcal infection and the poor myocardium contributed towards death.

From these case histories it will be seen that all the patients who died were over the age of 50 years. Cases 1 and 2 were moribund on admission and chemotherapy was instituted too late to be of any effect. Of the remaining seven, five had cardio-vascular insufficiency as well as the respiratory infection. Only in cases 5 and 7 was the sole cause of death a bacterial pneumonia which did not respond to chemotherapy.

Therapy and Prognostic Factors. The results of the two methods of treatment will now be examined with regard to some of the important prognostic factors.

(a) Age: In the terramycin group there were 28 patients under 40 years of whom 23, 82% made a good recovery, 28 patients between the ages of 41 and 60 years of whom 18, 64% made a good

recovery and 19 patients over 60 years of whom 12, 63% made a good recovery. Thus, while a higher proportion in the youngest age group had an uneventful convalescence there was no discrepancy in this respect between the other two age groups. There were 47 patients in the terramycin group and 53 in the control group who were over 40 years of age. Among these patients 30 (64%) in the terramycin group and 27 (51%) in the control group made a good recovery. This difference of 13% is not significant (its standard error is ±9.8) showing that terramycin was no more able than the control treatment to prevent prolonged fever and complications from occurring in the older patients.

(b) Duration of Illness: We have noted that the development of complications was influenced by the length of time which elapsed between the onset of infection and the start of treatment. In the terramycin group, 36 patients, and in the control group, 33 patients, were admitted after the fourth day of illness. An uneventful recovery took place in 19 (53%) of the terramycin patients and 15 (46%) of the control patients. Since this difference is less than its standard error of ±12.2 we may conclude that terramycin was not more effective than the control treatment in those who were admitted later in the course of their illness.

(c) Bacteriology of the Sputum: It is interesting to

compare the results of therapy in the light of the bacteriology of the sputum. Of the 117 pneumococcal pneumonias, 63 were treated with terramycin and 54 received the control treatment. Of these, 45 (71%) in the terramycin group and 34 (63%) in the control group made a good recovery. The difference (8%) is almost the same as its standard error (±8.7) and is not significant. Terramycin, therefore, although effective in pneumococcal pneumonia was not superior to the control treatment.

Infection with pneumococcus type 3 in an older person is generally regarded as being particularly dangerous. In them it often causes a severe broncho-pneumonia rather than lobar pneumonia. There were 8 patients in the series with pneumonia due to the pneumococcus type 3, 6 of whom were over 60 years of age. Six, including the two who were under the age of 60 years, were in the terramycin group and two in the control group. In the control group one patient died and the other had delayed resolution while in the terramycin group all the patients made a good recovery. Although the numbers are too small to justify a general conclusion these results do indicate that terramycin was of value in treating this form of pneumonia.

Staphylococcus aureus was responsible for 4 of the 8 cases of non-pneumococcal pneumonia. Pneumonia due to this organism has recently assumed greater importance. The increasing prevalence of staphylococci which are resistant to penicillin

make the newer antibiotics of great value in treating such infections. One of the staphylococcal pneumonias was in the terramycin group and three were in the control group. The one in the terramycin group made a good recovery. Two in the control group died, one after a course of terramycin and the other during a course of chloramphenicol; the third patient had a prolonged pyrexia and delayed resolution. These results show that staphylococcal pneumonia is a serious infection which is not always amenable to broad-spectrum antibiotic therapy. The three cases of pneumonia due to Haemophilus influenzae made a good recovery and the case of Friedländer's pneumonia died. In this small group of 8 patients the benefit of chemotherapy was not marked since 3 died and only 4 made a good recovery.

(d) Bacteriaemia: The grave significance of this factor has already been noted. There were 3 patients in the terramycin group and 7 in the control group who had a positive blood culture on admission. The two who died have been described; of the 4 with prolonged fever or a complication all were treated with sulphadiazine and penicillin; of the 4 patients who made a good recovery 2 were treated with terramycin, 1 with sulphadiazine and penicillin and 1 with sulphadiazine only. The specific form of treatment would seem to be of little import in determining the outcome in bacteriaemic patients.

(e) Associated Disease: With the exception of chronic bronchitis the presence of an associated disease diminished the likelihood of pneumonia patients making a good recovery. Of 10 patients in the terramycin group (8 with cardio-vascular disease, 1 with chronic nephritis and 1 chronic alcoholic) 2 had prolonged fever, 3 had complications and 3 died; while of 9 patients in the control group (5 with cardio-vascular disease, 2 with anaemia and 2 chronic alcoholics) 1 had prolonged fever, 4 had complications and 4 died. The results are similar in the two treatment groups showing that terramycin was not superior to sulphadiazine or penicillin in offsetting the disadvantage of associated disease.

Clinical details of two representative cases treated with terramycin are given in Appendix I.

THE PENICILLIN GROUP.

The results in the group of 19 patients who received sulphadiazine and penicillin therapy may briefly be mentioned. Only 5 (26%) made a good recovery; 2 patients died and the others either had prolonged fever, delayed resolution or a sterile effusion. It is impossible to compare these results with the results of those who received sulphadiazine only, because most of the seriously ill patients were given penicillin. The only exceptions were the 4 who received broad-spectrum antibiotics

instead of or along with penicillin. Since the 19 patients who received penicillin were all gravely ill one would expect this group to be weighted with most of the poor prognostic factors. This in fact was the case: 16 patients were over 40 years, 8 were admitted after the fourth day of illness, 5 had a positive blood culture and 4 had an associated disease which in 2 was cardio-vascular disease, 1 anaemia and 2 chronic alcoholism.

DISCUSSION

Prognostic Factors. The results are in agreement with the concept that certain factors are of prognostic import in pneumonia. Two thirds of the patients were over the age of forty years and this section contained all the deaths and most of the complications. This is in keeping with the generally accepted view that the age of the patient is the most important single factor in determining the outcome in pneumonia.

The longer the patient has been ill before he is admitted for hospital treatment the more liable is he to develop a complication. This is really the only factor over which we have any control. If patients could be persuaded to seek medical advice early in the course of their illness it would be possible to commence chemotherapy before the infection had gained a proper hold and before the tissues were extensively involved. This is particularly desirable in the older patient.

Bacteriaemia, another important prognostic factor, was present in 6.7% of the series. A previous therapeutic trial in pneumonia carried out in Knightswood Hospital was reported by Eadie, Grist and Landsman in 1951. In their series the bacteriaemic rate was 7.6%, a figure in keeping with that of the present series. Landsman (1952) showed that over the last twenty years there has been a progressive fall in the proportion of pneumonia patients who have a positive blood culture on admission to hospital. In different series of pneumonia patients investigated at Knightswood Hospital the bacteriaemic rate was 29% in 1933, 26% during the period 1938 to 1942 and 19% during the period 1943 to 1947. Landsman studied 500 bacteriaemic patients and found that the bacteriaemic rate in those who reached hospital untreated was almost twice that found in those who had been given sulphonamide prior to admission. In the present series the bacteriaemic rate in the treated patients was 5.5% and 7.3% in the untreated patients, a difference which is less marked.

It is impossible to judge the value of chemotherapy given to a patient before admission from a series such as this one. The patients in this trial who had received chemotherapy were not cases which had failed to respond to treatment at home but rather they were patients who had had treatment to tide them over until hospital admission could be arranged. It is unlikely

that the practice of giving chemotherapy before their admission to hospital has any bearing on the sharp fall in the bacteriaemic rate of the 1951 and the present series. The proportion of patients with previous treatment was 43% in the 1945 series, 52% in the 1947 series, 41% in the 1951 series and 37% in the present series. The corresponding bacteriaemic rates were 17.4%, 25.5%, 7.6% and 6.7%. Moreover, 3 of the present 10 bacteriaemic patients had received previous treatment. The fall in the bacteriaemic rate is not parallelled by any corresponding rise in the proportion of treated cases. One reason for the low proportion of treated cases in the present series was the small amount of chemotherapy a patient could have received and still be included in the therapeutic trial.

The importance of the white cell count is that it is an index of the adequacy of the patient's defence mechanism. It is significant that of the nine deaths in the series, seven had a leucopenia. This implies a failure of the protective reaction of the patient and it is such patients who are most likely to succumb.

Of the associated diseases, those affecting the cardiovascular system are the most important. An impaired cardiovascular system reduces the patient's ability to overcome infection. The presence of pneumonic consolidation throws a strain

on the right side of the heart. The longer this endures, the more likely is cardio-vascular insufficiency to become apparent. In the elderly arterio-sclerotic patient who has until then managed to remain in a state of cardiac compensation, the strain of acute pulmonary infection may be sufficient to tip the balance against him and precipitate cardiac failure. The circulation of blood through an area of consolidated lung is impeded and furthermore there is a reduction in the lung surface available for oxygenation of the blood. The main advantage of early treatment of the older patient is that the infection may be suppressed before it interferes with the circulation of blood through the lungs. In this way cardiac strain is reduced to a minimum.

Deaths. The death rate in pneumonia patients in hospital is higher than in the total number of patients suffering from pneumonia. This is due to the fact that many of the older patients and most of the seriously ill patients eventually come into hospital, while almost all pneumonia patients whose treatment is completed at home recover. Chemotherapy has dramatically reduced the mortality in pneumonia. The mortality rate in pneumonia was studied by Flippin (1943). In 1,635 cases during the period 1938-1942 the rate was 10.6% compared with 40.1% in 1,904 cases during the five year period preceding the

introduction of the sulphonamides. Norris (1953) from a study of 8,000 case records of pneumonia found that the death rate from lobar pneumonia during the period 1934-38 was 20% compared with 10% during the period 1944-48 but the mortality from broncho-pneumonia remained unaltered. In hospital it is unlikely that the mortality from pneumonia will ever fall much below 10%. The death rate in the present series was 6%, a figure similar to the 6.3% of the 1951 Knightswood series. The close similarity of these figures suggests that modern chemotherapy has brought the death rate down to what may be an irreducible minimum. The death rate of pneumonia patients in any treatment trial tends to be slightly lower than for all hospital patients with this condition. Patients who are sent into hospital because they failed to respond to adequate chemotherapy at home are excluded from such a trial and a certain number of them die.

Penicillin or one of the new antibiotics can in most instances rid the patient of the infecting organism but they do not cure his pneumonia. The process of resolution ultimately depends on the patient's own recuperative powers. The deaths of four patients in the control group despite treatment with antibiotics were due not so much to failure of the drug as to the inability of the patient to rally to his own defence.

Therapy. In terramycin we have an effective drug for

treating pneumonia. In the terramycin group the response to treatment was excellent as judged by the rapid fall in fever and the low incidence and mild nature of the complications. Only two patients in the series failed to recover after an adequate dose of terramycin and one of them had cardio-vascular insufficiency. Whether terramycin is more valuable than sulphadiazine or penicillin is doubtful. In preventing sterile effusions or in accelerating the process of resolution, terramycin had no advantage over the control treatment. On the other hand, the duration of the primary pyrexia was slightly shorter in the group treated with terramycin. The relief from the symtoms which accompany fever and the increased feeling of well-being of the patient might be considered to justify its use. Timpanelli (1950) found that terramycin caused a more rapid fall of temperature in pneumonia than penicillin. Composite temperature curves of 66 patients treated with terramycin and 48 patients treated with penicillin showed a difference in favour of terramycin of 0.9°F at 24 hours. The standard error of the difference is ±0.4 so that the difference, although interesting, is scarcely significant.

A less enthusiastic report was published by G.G.Jackson et al. (1951) who treated 91 pneumonia patients with terramycin. They estimated that the drug was of benefit in 68

(75%) and in the others the effect of terramycin was equivocal. In the present trial, an additional advantage enjoyed by the terramycin group was that they were receiving a powerful antibiotic in oral capsules which were easily swallowed, while in the control group, when a patient failed to respond to oral sulphadiazine he suffered the discomfort of intramuscular injections of penicillin.

Section 2. HERPES SIMPLEX

The introduction of the broad-spectrum antibiotics marked a great advance in the treatment of rickettsial infections which had hitherto been resistant to chemotherapeutic agents. The organisms of the rickettsia group are smaller than bacteria but are larger than the true viruses. Like viruses they have attained a high degree of parasitism and require living animal cells for their growth and multiplication. In the host cells both the rickettsiae and viruses enter closely into the metabolism of the cell and any agent which destroys them may easily damage the cell also. The best way of attacking viruses and rickettsiae is to prevent them from reaching a susceptible cell. During a viraemia or rickettsiaemia the organisms are extracellular. If an effective chemotherapeutic drug is also present in the blood stream the organism will be destroyed and the disease aborted.

Chloramphenicol, aureomycin and terramycin have a marked rickettsiostatic effect but are not rickettsiocidal. The antibiotics suppress the growth of rickettsiae while the patient builds up his own immunity on which his ultimate recovery depends. If the antibiotic is discontinued before the patient's immunity has developed there is a recrudescence of the disease. Relapses, however, can be prevented by giving

antibiotics for a long enough period so that control of infection by immunity takes over as the suppressive effect of the antibiotic wanes. In 1951 E.B. Jackson tested the rickettsiostatic activity of the three new antibiotics on a gravimetric basis in embryonated eggs infected with various rickettsiae. She judged their effectiveness to be terramycin, aureomycin and chloramphenicol in descending order. In treating human infections there is little to choose between the three antibiotics. Good results have been obtained with terramycin in the treatment of scrub typhus (Smadel, Jackson and Ley 1950), epidemic or murine typhus and Rocky Mountain Spotted Fever (Bauer et al 1950), and rickettsialpox (Rose, 1950). The newer antibiotics are in fact so effective as to be indeed specifics for rickettsial infections.

The viruses which are most closely related to the rickettsiae are the psittacosis-lymphogranuloma venereum group. These organisms also are highly susceptible to the antibiotics in experimental infections. Few reports on human infections have been published but satisfactory results have been obtained in the treatment with antibiotics of isolated patients suffering from psittacosis, ornithosis and lymphogranuloma venereum (Smadel, 1951).

The value of antibiotics in the treatment of infections

due to the smaller viruses is less certain. The virus which causes trachoma resembles those of the psittacosis - lymphogranuloma venereum group and aureomycin and chloramphenicol given locally and systemically have been reported to benefit patients with trachoma (Smadel 1951). Viral infections are frequently complicated by the intrusion of bacterial infection and it is difficult to say if the beneficial result of an antibiotic is due to its antibacterial effect or its action on the viral agent. This is especially true of viral or primary atypical pneumonia but Collins et al. (1950) found that patients with the clinical findings of primary atypical pneumonia, along with a rise in cold agglutinin substances and without conspicuous evidence of bacterial infection, responded well to aureomycin therapy. Antibiotics have no effect against the influenza viruses in experimental animal infections but in man they do have a place in the treatment of influenza. Their value lies in controlling the secondary bacterial invasion which is mainly responsible for fatal influenzal broncho-pneumonia.

In viral infections with dermatological manifestations the clinical response of a patient to any treatment cannot be properly assessed since these infections are of variable severity and irregular duration. Finland et al. (1949) found that 1g aureomycin q.i.d. gave beneficial results to patients with

herpes zoster. Of 24 patients treated there was rapid healing within 24 hours in 20 cases and in only 4 did new lesions develop after the start of treatment. The immediate effect on pain was striking and pruritus vanished in 4 days although postherpetic pain was not prevented in 6 patients. They tentatively suggested that aureomycin had a virustatic effect on the virus of herpes zoster.

Herpes febrilis is the most frequent virus disease of man. The primary infection normally occurs during childhood in the form of a herpetic stomatitis. The virus preferentially attacks the tissues of the embryonic ectodermal layers. These include the skin, mucous membranes, eye and central nervous system. The visible manifestations are characterised by the formation in the epithelium of vesicles which are scattered over the area surrounding the mouth. The primary infection is also a blood stream infection and the local lesion is usually accompanied by systemic illness which may be severe. Among human virus infections herpes simplex is unique in its life-long persistence in or near the site of the primary infection. The patient is liable to recurrent attacks of herpes throughout life. In these secondary outbreaks the vesicles are usually grouped closely together around the mouth and the patient remains free from symptoms of systemic upset. The lesions reappear

during various febrile illnesses and pneumonia is often the stimulus for such outbreaks.

It was decided to study the occurrence of herpes febrilis in the patients of the pneumonia series. If terramycin was effective against the virus of herpes simplex some difference in the two treatment groups would be observed. The purpose was to note the frequency, the duration and the extent of herpes febrilis in a group of pneumonia patients treated with terramycin and to compare them with a group treated with sulphadiazine, supplemented in a few cases with penicillin.

METHOD

After the treatment trial had been in progress for three months, the presence and extent of herpes febrilis in new admissions to the series was noted. The patient was asked about its day of onset and the symptoms. Both the terramycin and control treatment groups were thereafter inspected daily for new cases of herpes and for fresh spread in those who

already had the lesions. The activity of the herpes was determined by its appearance and the amount of pain and pruritus it was producing. Note was taken of the day on which crust formation began and on which healing was complete. Thirty-three patients were studied in this way, 16 of whom were in the terramycin group and 17 in the control group. The herpes was regarded as an incidental finding and at no time did it influence the prescribed treatment.

RESULTS

In the pneumonia series of 150 patients herpes febrilis occurred in 53 (35%) but in 20 of these only the fact of its presence was recorded. The patients were equally distributed in the two treatment groups and the findings in the

33 patients whose herpes was specially noted are summarised in

TABLE 5. - HERPES SIMPLEX (FEBRILIS) CASES.

	Terramycin Group	Control Group
No. of cases with herpes	24	29
No. with herpes specially noted	16	17
Mean day of illness on admission	3.9	4.2
Mean day of onset of herpes	3.3	4.4
Herpes at height (Day)	5.1	5.9
Start of crust formation (Day)	7.5	8.5
Healing complete (Day)	13	12
No. with spread of herpes during treatment	4	3
No. whose herpes appeared during treatment	5	10

Table 5. The average day of illness on admission was similar

in each group and it approximated closely to the day of onset of the herpes. Herpes appeared usually about the fourth day of illness and ran the same course in the two groups. It reached its height in 1-2 days; crust formation began in a further 2 days and healing was complete within 2 weeks.

The most significant findings appear at the foot of the table. In 5 of 16 cases in the terramycin group the herpes made its first appearance while the patient was on full doses of terramycin and in 4 the herpes which had been present before treatment extended during treatment. The proportion of cases in which this occurred in the control group is similar. Of 17 cases, 10 appeared and 3 extended during treatment. In the 5 patients whose herpes appeared during terramycin treatment the mean day of illness on admission was 2.2 which is rather earlier than the 3.9 for the whole group. The day of onset of the herpes in these 5 patients was 3.4 which is substantially the same as the 3.3 for the group as a whole. This shows that the early start of therapy did not even delay the appearance of herpes febrilis. The extent and duration of the herpes in those who first showed it during treatment was no less than in those who had the lesions on admission to hospital. Details of the individual cases are shown in Appendix II.

DISCUSSION

From the findings it appears unlikely that terramycin has a specific action against the virus of herpes simplex. The size of the infecting organism would seem to be a factor in determining whether an antibiotic can attack it. The new antibiotics are most effective against bacteria and rickettsiae. The rickettsiae are 475mμ in diameter and the psittacosis virus 450mμ. The herpes zoster virus against which the effect of antibiotics is doubtful is 210x260mμ in length and breadth but the herpes simplex virus is only 150mμ in diameter.

The other important factor is that the virus must be exposed to the action of the antibiotic at a stage in infection when it is extra-cellular. To stimulate antibody production the virus must be free in the blood stream. In all viral infections therefore which are followed by the presence of neutralising antibodies in the patient's blood stream, there must have been a viraemia. Herpes simplex is such an infection since the primary exposure leads to the development of antibodies. The antibody titre waxes and wanes with the first few subsequent outbreaks of herpes febrilis but once the host-virus relationship has been established the antibody titre remains static irrespective of the number of recurrent attacks (Scott 1954). Many people with antibodies in their blood have no history of ever

having had herpetic stomatitis so that the primary infection must often be subclinical. The recurrent attacks are manifestations of imbalance between the latent virus and the host and are not new infections. The close grouping of the vesicles in recurrent herpes suggests contiguous spread of virus from cell to cell. Blood spread is unlikely in the presence of circulating antibodies and this diminishes the opportunity for a drug to reach the virus. Nevertheless when local spread is taking place the virus must be extracellular just before the new epithelial cells are penetrated and at that time it is exposed to the action of the antibiotic. In the 5 patients whose herpes appeared during terramycin therapy the drug had a chance to prevent the infection from emerging. Perhaps also in the 4 patients who had a spread of herpes after terramycin treatment had been instituted there was a period when the virus was exposed to terramycin. Terramycin however did not prevent the outbreak of vesicles.

It is possible to argue that we do not know how many patients in the terramycin group might have developed a herpes had they not been given this form of treatment. Since the number of patients with herpes is approximately the same in the two treatment groups, which are comparable in other respects, it is unlikely that terramycin completely suppressed the infection in many, if indeed any, of the patients. In the 7 patients whose

herpes cleared up quickly after treatment was started, it is impossible to evaluate the part played by terramycin. Recrudescences of herpes are self-limiting and usually mild without any form of treatment. In any event, the findings in these cases are not significant because they constitute less than half the total number of patients with herpes in the terramycin group.

No claim has ever been made that antibiotics are effective in the treatment of infections due to the virus of herpes simplex. Quilligan et al.(1950) investigated the action of terramycin on the growth of herpes simplex virus in embryonated eggs. They found there was no difference in the final antibody titre in those treated with terramycin and in the untreated eggs. Furthermore, Finland et al.(1949) observed 4 patients in whom herpes febrilis appeared and extended during aureomycin therapy for acute bacterial infections. Perhaps it is only during the primary infection, when the virus is present in the blood stream that it will ever be successfully attacked by a chemotherapeutic agent yet to be discovered. In any case, the existing antibiotics are of great value in the primary infection in preventing and controlling secondary bacterial invasion. The ability of the herpes simplex virus to persist in human tissues makes it unlikely that it can be completely eradicated during one of its recrudescences.

In the following chapter the clinical side-effects usually attributed to antibiotics are reviewed. Details are given of the toxic reactions which were noted in the terramycin group of pneumonia patients. To accumulate more data on the side-effects of terramycin and to compare them with those of other broad-spectrum antibiotics, chloramphenicol and aureomycin, the series was enlarged. Patients who were available and to whom a course of antibiotic could be given with impunity were those in the two sanatorium wards for tuberculosis. Three groups of tuberculosis patients were studied, one given a course of chloramphenicol, one given aureomycin, and a third terramycin. The side-effects which occurred in these patients are described.

CHAPTER II.

CLINICAL SIDE-EFFECTS OF ANTIBIOTICS

The toxic effects of the broad-spectrum antibiotics are mainly limited to gastro-intestinal upset in the form of nausea, vomiting and diarrhoea. Heartburn, flatulence, epigastric pain and a bad taste in the mouth may also occur. Another type of side reaction is the development of a sore mouth, throat and tongue. Burning, soreness and pruritus of the anus and surrounding skin is known as the ano-rectal syndrome. Symptoms of mucosal irritation are in general more common in females in whom vaginal irritation may also occur.

In most patients the gastric upset is confined to a feeling of nausea with perhaps occasional vomiting. Sometimes the vomiting becomes persistent and necessitates stopping the drug. The diarrhoea is usually mild with the passage of 2-4 loose, bulky stools per day. The stools are often odourless with a green, mucoid appearance but in some patients the odour increases and becomes foul or sickeningly sweet. When the antibiotic is discontinued the stools generally return to normal but in a few patients the diarrhoea persists for some weeks. Sigmoidoscopic examination in these patients shows red bands or sharply defined areas of reddened mucosa with normal mucosa in

between.

Some of the diarrhoeas are unusually severe and intractable and are accompanied by dehydration and shock. In many of these Staphylococcus aureus is the predominant organism in the stool. It is usually resistant to the particular drug the patient is receiving and even although sensitive to another antibiotic, treatment with this drug does not always succeed in controlling the infection. The staphylococcal infections are contributory if not the actual cause of some deaths during and after antibiotic therapy. It was the possibility of this complication which prevented Jackson et al. (1951) from wholeheartedly advocating terramycin for the treatment of pneumonia. In their series of 91 cases, 37 had diarrhoea. Cultures of the stool were made in 18 of these and in 12 resistant strains of Staphylococcus aureus grew profusely. The staphylococcal diarrhoea may have contributed to the death of at least three of these patients. Finland, Grigsby and Haight (1954) found that the best cure for patients with secondary staphylococcal enteritis was to stop the antibiotic and instead treat the primary infection with intramuscular penicillin. This promptly restored the bowel flora to normal and the staphylococci, although resistant to penicillin, cleared from the stool.

Unfortunately this happy result is not always obtained and in their series of 520 patients treated with aureomycin or terramycin for various infections, mainly pneumonia, two died within 24 hours of the start of a severe staphylococcal enteritis. Other seven patients died after the diarrhoea had lessened or stopped but their general condition had failed to improve.

Oral symptoms occur more often when the antibiotic has been used to treat a sore throat or other local infection. Certain changes in the oro-pharyngeal mucous membrane accompany these symptoms. In the mouth, the classical picture of thrush is uncommon. More often there is a red vesico-papular eruption on the uvula extending to the hard palate, pharynx and buccal mucosa. When the lips also are involved the condition resembles perlèche or angular stomatitis. On the tongue an atrophic or a hypertrophic glossitis may develop, the former being more common. In this condition the normal white coating is lost leaving the tongue raw, red and smooth with a "beefy" appearance. The hypertrophic type of glossitis is due to the hypertrophy of the filiform papillae. The accumulation of matted hair-like processes gives the tongue the appearance of being brown or black and hairy.

The ano-rectal syndrome does not develop until the patient has been receiving an antibiotic for at least 5-7 days

and it may persist for some weeks afterwards. Proctoscopic examination in these patients shows perianal erythema with thickening and excoriation of the perianal skin. There may be superficial fissures at the margins of the anus. Allergic reactions are rare but drug rashes and drug fever may occur. With chloramphenicol, muscle fatigue with temporary ophthalmoplegia is a rare complication and, after prolonged administration, agranulocytosis has been reported.

SIDE-EFFECTS IN THE PRESENT SERIES

MATERIAL AND METHODS

Two groups of patients were studied. Firstly, the pneumonia group of 75 who received an average dose of 14.2g terramycin in five days. The selection of these patients has been described in Chapter I. Secondly, a series of 80 patients suffering from pulmonary tuberculosis were given a course of antibiotic. The only criteria used in selecting patients for inclusion in the tuberculosis series was that they should not be having a course of streptomycin therapy and should be well enough to be up to the toilet. The exposure of patients who were completely confined to bed with tuberculosis to the risk of toxic effects from antibiotics was not felt to be justified.

There were two wards of male tuberculosis patients and two patients from each were treated simultaneously. The two in one ward were given one antibiotic and the two in the other ward received another antibiotic.

Chloramphenicol was given to a group of 35 cases, aureomycin to a group of 20 cases, and terramycin to a group of 25 cases. The antibiotic was given in a dose of 1g every six hours for a total dose of 16g over a period of four days.

During the course of antibiotic I questioned the patients about subjective side-effects; inspected their mouths for mucosal changes and recorded daily the number and appearance of the stools.

RESULTS

In the pneumonia group, remarkably few patients had side-effects during terramycin therapy. A few complained of nausea but none had vomiting and only three had diarrhoea. Seven patients developed a raw, painful tongue. Other two complained of sore throat and one of these developed a black tongue. None had the ano-rectal syndrome.

In the tuberculosis series toxic reactions were more

common (Table 6); 46 patients (57%) had some disturbance. Of the 19 (24%) who complained of gastric upset, nausea was the usual feature and 4 had occasional vomiting. In 2 patients

TABLE 6. - SIDE-EFFECTS DURING ANTIBIOTIC THERAPY IN TUBERCULOSIS SERIES.

SIDE-EFFECT	CHLOR. GROUP	AUREO. GROUP	TERR. GROUP	TUBERCULOSIS SERIES	
Total	35	20	25	80	
Gastric Upset:	6	4	9	19	24%
Nausea	4	4	9	17	
Vomiting	1	2	3	6	
Bad taste in mouth	2	0	0	2	
Epigastric pain	1	0	1	2	
Diarrhoea:	17	8	16	41	51%
Average no. of stools per day					
Normally	1	1	1		
Day 1	1	1	1		
Day 2	2.3	2	2		
Day 3	2.3	2	2.5		
Day 4	2.3	2	2		
Oral Manifestations:					
Atrophic glossitis	3	4	2	9	11%
Black tongue	3	0	3	6	7%
Ano-Rectal Syndrome	1	1	2	4	5%

(1 on aureomycin and 1 on terramycin) vomiting was so severe that the drug had to be discontinued on the third day. Two patients had a bad taste in the mouth and two had epigastric pain. The highest proportion with gastric upset was in the terramycin group, 36% (9 patients), next in the aureomycin group, 20% (4 patients) and then in the chloramphenicol group, 17% (6 patients).

Diarrhoea occurred in 41 (51%) of the series. In none of the cases was the symptom severe. In the chloramphenicol and terramycin groups the patients had 2-3 stools per day and in the aureomycin group 4-5 stools was commoner in those with diarrhoea. Sixteen patients (64%) in the terramycin group, 17 patients (49%) in the chloramphenicol group and 8 patients (40%) in the aureomycin group had the symptom.

It seemed of interest to discover at what period of the antibiotic course abnormal stools appeared. Table 7 shows that of 80 patients, the stools were soft in 24, loose in 16 and green in 4 after 8g antibiotic, the number of green stools rising to 12 at the end of the course. Almost half the stools remained normal throughout the course of antibiotic. The frequency of the stools is shown in Table 6 from information given by the patients themselves. In the average there was a definite change in bowel habit from one motion each day to two.

In 9 patients (11%) the tongue became raw and painful

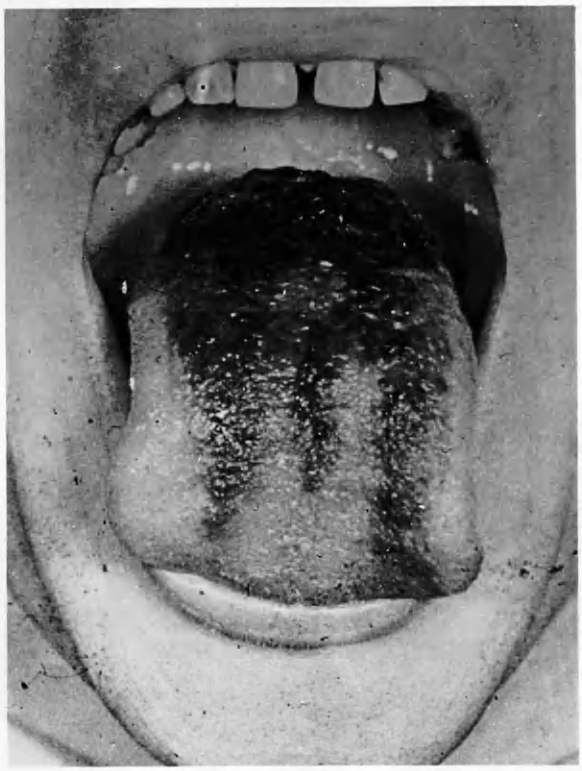
and in 6 patients (7%) it became black and hairy. A photograph

TABLE 7. - DOSE OF ANTIBIOTIC AND APPEARANCE OF STOOL.

ANTIBIOTIC	GROUP	TOTAL	APPEARANCE OF STOOL			
			NORMAL	SOFT	LOOSE	GREEN
Before	Chlor.	35	34	1	0	0
	Aureo.	20	18	2	0	0
	Terr.	25	22	3	0	0
	Series	80	74	6	0	0
After 8 g.	Chlor.	35	16	9	10	0
	Aureo.	20	12	3	2	3
	Terr.	25	8	12	4	1
	Series	80	36	24	16	4
After 16 g.	Chlor.	35	14	12	6	3
	Aureo.	20	10	3	0	7
	Terr.	25	14	8	1	2
	Series	80	38	23	7	12

of one of the black tongues is shown. Four patients (5%) complained of the ano-rectal syndrome. These particular

symptoms were more or less equally distributed in the three



Black Tongue.

treatment groups except that no black tongues occurred in the aureomycin group.

One patient complained of blurring of vision while on chloramphenicol and he was subsequently given another course of chloramphenicol. More details of this phenomenon will be found in Appendix III.

DISCUSSION

The comparative freedom from toxic effects in the pneumonia group treated with terramycin is the more remarkable when we consider that in the tuberculosis series terramycin caused more gastro-intestinal upset than either aureomycin or chloramphenicol. The dosage employed was relatively high. Willcox (1951) found that of 38 patients suffering from venereal disease and given 5-9g of terramycin in 5-7 days, 13% had gastric upset and 24% diarrhoea. In this tuberculosis series 36% had gastric upset with terramycin, a figure similar to the 32% of 87 patients treated by Finland et al. (1950) with terramycin for miscellaneous infections. Only 37% of their group had diarrhoea, however, compared with 64% in the present group.

Both Harris (1950) and Tomaszewski (1951) found gastric upset more common with aureomycin than chloramphenicol. In Harris's group of 110 patients, 34 who were unable to tolerate aureomycin were able to finish the course on chloramphenicol. The frequency of diarrhoea in the tuberculosis series tended to be higher than that found by other workers. In Harris's patients chloramphenicol caused only a mild diarrhoea in a few but the symptom was more severe with aureomycin. In Tomaszewski's patients the stools became soft or loose without increasing in number.

On the other hand, relatively few of the present patients had the ano-rectal syndrome compared with 13% of Willcox's patients. Oral complications occurred in similar degree to that found by Finland who noted stomatitis in 6% of his patients, while 10% of Tomaszewski's patients developed a black tongue.

The side-effects are discussed further in Chapters IV. and V.

In the next chapter the changes which occurred in the microflora of the respiratory and alimentary tracts during antibiotic therapy are studied.

In the first section attention is drawn to the growths of the yeast Candida albicans which were found in the sputum, fauces and rectum of the pneumonia series and in the sputum and faeces of the tuberculosis series. The results in the pneumonia series have already been published in the Lancet, February 20th. 1954, under the title "The Growth of Candida albicans during Antibiotic Therapy".

The second section deals with the effect of antibiotics on the growth of coliforms in the intestinal tract of both the pneumonia and the tuberculosis series.

CHAPTER III.

THE EFFECT OF ANTIBIOTIC THERAPY ON THE MICROFLORA

Section 1. THE GROWTH OF CANDIDA ALBICANS

INTRODUCTION

When a yeast is found in the human body it almost invariably proves to be the species known as Candida albicans. It belongs to the group of Fungi Imperfecti which are characterised by the formation of only asexual spores and in which the perfect or sexual stage is unknown. In the family Cryptococcaceae the yeasts reproduce by the budding off of daughter cells which in turn may bud to form a mass of spherical cells. These function as spores and are called blastospores. In the subfamily Candidoideae, the yeasts characteristically form a pseudomycelium. This is a structure produced by budding cells elongating and clinging together in chains, and so resembling a true mycelium. Some species also produce, by a process of disarticulation of the mycelium, yeast-like cells known as arthrospores. The forms which produce blastospores only are classified in the genus Candida. The species Candida albicans converts the terminal cells in the pseudomycelium into thick-walled, round, resting spores, called chlamydospores. These enable the fungus to exist during long periods of dormancy. Candida

albicans is not only the type species of the genus but it is the species of outstanding importance and interest. In 1931 Benham showed that all the pathogenic candida isolated from the human body were the same species, Candida albicans. The differences in the various isolates were unworthy, in her opinion, of being recognised by a distinctive name.

Yeasts were among the first micro-organisms to be described because their relatively large size made them more readily visible in the days before the compound microscope. There has been in the past some confusion in the nomenclature of Candida albicans. In 1839 Langenbeck first found a fungus in patches of thrush in the mouth and in 1847 Robin described the thrush fungus in detail. He gave it the name Oidium albicans but as it did not belong to the genus Oidium it was renamed Monilia albicans by Zopf in 1890. The disease caused by infection with this organism is still called moniliasis. For a century the term Monilia was used for many organisms but it should properly be restricted to a group of plant pathogens which cause brown rot of fruit. At the Third International Microbiological Congress in 1939 the delegates decided to use the name Candida for the genus and this name is now replacing the more familiar but invalid one, Monilia.

Although the human body is not the sole habitat for

the genus Candida the species Candida albicans has never been found unassociated with man or animals. In different surveys it has been isolated from 6 to 24% of healthy mouths and throats and in about 15% of normal faeces. The fungus is usually present in small numbers since the normal flora is predominantly bacterial. The disease it produces, moniliasis, is classified as one of the superficial mycoses because candida usually penetrates only the skin and mucous membranes. It can, however, invade the deeper tissues and become a deep mycosis. It is then that moniliasis becomes a serious and often fatal disease. Cases with blood-stream invasion (Wessler and Browne 1945), meningitis (Morris, Kalz and Lotspeich 1945), endocarditis (Pasternack 1942) and generalised visceral involvement (Gausewitz, Jones and Worley 1951) all due to Candida albicans have been reported. Many reports of broncho-pulmonary moniliasis have been published since the condition was first recognised as a clinical entity by Castellani in 1905.

A definite diagnosis of moniliasis is fraught with difficulty. To establish the diagnosis the causal organism, Candida albicans, must be demonstrated in large numbers in clinically typical lesions. These are:-

1. Oro-pharyngeal moniliasis. In the mouth the classical lesion is thrush. On the buccal mucosa, plaques of white or

cream exudate appear which coalesce to form a membrane. This is easily detached from the underlying reddened mucosa which is left dry and glazed. The soft palate and surrounding tissues become red and oedematous. The tongue becomes thickly coated giving a black hairy appearance. When this coating peels off the tongue is left red, swollen and tender. The patient complains of burning and soreness of the mouth, throat and tongue.

2. Oesophageal and tracheal moniliasis. The membranous plaque formation may spread down the oesophagus or trachea causing an oesophagitis or tracheitis. The symptoms are pain on swallowing, retro-sternal pain, huskiness and a dry non-productive cough. The membrane may also cause obstructive symptoms like dysphagia and dyspnoea. These are alleviated when the membrane becomes detached and is expectorated.

In all the lesions of these two groups the diagnosis depends on examination of a patch of membrane. Microscopically it is seen to consist of numerous yeast cells in a fibrinous matrix, and culture on Sabouraud's medium yields an almost pure growth of Candida albicans.

3. Cutaneous moniliasis. Typically the lesions here are circumscribed, erythematous and exudative patches with a papulo-squamous border. In these, candida is found in abundance. The condition most commonly occurs where two skin surfaces are in

contact, as an intertrigo, but generalised forms also occur. Onychia and paronychia due to candida may develop in people whose skin has become macerated from frequent immersion in water.

4. Broncho-pulmonary moniliasis. In the bronchial type the main symptom is cough with a mucoid, gelatinous sputum in which are grey flakes of budding yeast cells. The patient's health generally remains good, the physical signs are those of bronchitis and X-ray of the chest may show increase in the peri-bronchial markings.

The pulmonary type is less common but more serious. The patient has a pleural pain, cough with a gelatinous sputum which is often blood-stained and the temperature and pulse are elevated. It is a broncho-pneumonic type of illness and chest X-ray shows patches of consolidation, most marked at the bases of the lungs.

Broncho-pulmonary moniliasis is the most difficult type of all to diagnose with certainty. It is not practicable to examine the parenchyma of the lung for candida during life and finding the organism in the sputum does not warrant the diagnosis. Candida is a common secondary invader in patients with another primary lung disease, and many cases would be more accurately described as "secondary thrush of the bronchi". This,

occurring in patients whose general health is already poor, may hasten a fatal outcome. Ormerod and Friedman (1951) reported a case of moniliasis of the oro-pharynx spreading to the bronchi but the final cause of death was a staphylococcal pneumonia. In the diagnosis of cases of pulmonary moniliasis which have recovered reliance has too often been placed on finding candida in the sputum of a patient with obscure signs and symptoms of chronic chest disease (e.g. Barlass and Akyel, 1951). A very convincing case, however, was reported by Hiatt and Martin (1946) of a patient who recovered from pulmonary moniliasis after treatment with immune serum. The patient was given gradually increasing doses subcutaneously of serum from a rabbit which had been immunised against Candida albicans.

The occurrence of mycotic infections as a sequel to antibiotic therapy has recently brought moniliasis into greater prominence. The original infection for which the antibiotic is given clears up but the patient subsequently develops symptoms and signs of moniliasis. Woods, Manning and Patterson (1951) were among the first to give particulars of such cases. They described 20 cases of oro-pharyngeal, 3 of intestinal and 2 of broncho-pulmonary moniliasis and they considered that the yeasts had either increased in virulence or by sheer increase in numbers

had assumed pathogenic properties following antibiotic therapy. The frequency of moniliasis after antibiotic treatment is not known. Its rarity may be judged by the fact that the occurrence of a single case still warrants publication (e.g. Browne, 1954).

The difficulty in establishing a definite diagnosis of pulmonary moniliasis has already been mentioned. It is a common practice to give a course of antibiotic as a therapeutic test to a patient with symptoms and signs of chronic chest disease. Should the diagnosis of moniliasis subsequently be made, it might easily be attributed, although without justification, to the results of antibiotic therapy.

Most reports on the sequelae of antibiotic therapy mention overgrowths of candida only when they are found in association with a clinical lesion suggestive of moniliasis. In this investigation all the patients were examined for candida during their course of antibiotic whether or not there was reason to suspect the presence of yeasts.

PART I. PNEUMONIA SERIES

In conducting a therapeutic trial of terramycin in pneumonia an excellent opportunity was afforded for comparing a broad-spectrum antibiotic with sulphadiazine, a chemotherapeutic agent which was not bacteriocidal. The sputum, fauces and rectum were examined for candida in the two groups before, during and after treatment. In addition, the sputum was examined for candida in all patients who were admitted to hospital with a respiratory illness during the period of the investigation.

MATERIAL AND METHODS

During the period September 1951 to December 1952, in all cases where the sputum was examined routinely on admission to confirm or refute a diagnosis of pneumonia or tuberculosis, the specimen was also examined for yeasts. A total of 367 admission sputa accrued. This figure includes sputa from males and females in whom the diagnosis of pneumonia was confirmed, those who were found to have some other respiratory disease, those whose symptoms were attributable mainly to cardiac failure and 57 males who were notified by the chest clinic as having tuberculosis requiring hospital treatment.

Of those, the 176 patients in the treatment trial were

used to study the growth of candida during chemotherapy. The 26 patients whose pneumonia was not confirmed radiologically are included as each had the full course of treatment. Of the 19 patients who had penicillin, the 3 who had a single dose of penicillin before the course of sulphadiazine are included in the sulphadiazine group. Six patients who died before the series of examinations was complete have been excluded and thus the totals are: terramycin group 85 patients, and sulphadiazine group 69 patients. The group of 16 patients who had a course of penicillin are considered separately.

In the pneumonia series, in addition to the specimen of sputum, a post-nasal swab and a rectal swab were taken on admission. After the first 51 patients had been investigated a throat swab was substituted for the post-nasal swab because of the infrequent isolation of candida from post-nasal swabs. (v.infra). From all patients, rectal and post-nasal or throat swabs were again taken on the third, fifth, seventh and ninth days in hospital. Further specimens of sputum were obtained from 61 of the patients (28 in the terramycin group and 33 in the sulphadiazine group) on the third to fifth days during treatment and again on the second to fourth day after the end of treatment.

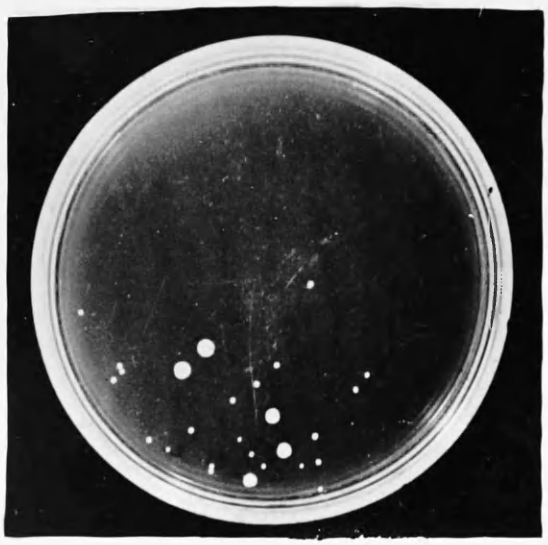
After being collected from the patient, all specimens

were taken to the laboratory at once for examination for yeasts. When this was impossible the specimen was immediately put in the refrigerator until the examination could be made.

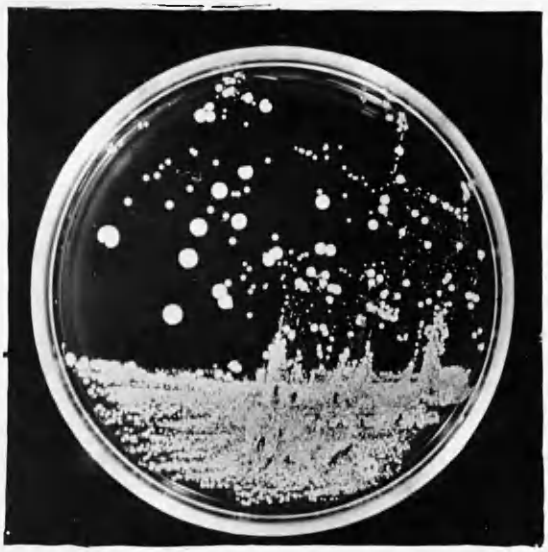
Isolation of yeasts. From each specimen of sputum, after emulsification with 5 ml. of sterile broth, a loopful was inoculated on to a plate of Sabouraud's medium. Post-nasal, throat and rectal swabs were inoculated directly on to this medium. The plates were incubated at 37°C. for 24 hours before being examined for growth of yeasts. All plates which at this stage were regarded as negative were kept at room temperature for a further 3 days before they were finally examined and discarded. The amount of growth was recorded as "absent"; "scanty" when discrete colonies of yeasts were present over the site of the original inoculum, "heavy" when colonies of yeasts appeared over the whole of the area inoculated or were densely packed over the site of the original inoculum. The photographs show typical examples of the different growths obtained.

The following criteria were used to identify Candida albicans:

1. Morphology: Typically, colonies are large, smooth, white or cream in colour with a pasty consistency. The presence of yeast cells was confirmed by microscopic examination of films made from representative



Scanty growth of Candida albicans



Heavy growth of Candida albicans

colonies.

2. The ability to grow at room temperature. This served to emphasise their differentiation from cocci which remained static.

3. Sugar reactions: From each patient, but not from each specimen, a representative colony was grown in sugar media and found to give the reactions of Candida albicans: namely, formation of acid and gas in glucose and maltose; acid only in sucrose; and no acid or gas in lactose.

I personally carried out the examinations for yeasts.

RESULTS

A. ADMISSION SPUTA.

Candida was isolated from 49% of the 367 sputa examined on admission, and a heavy growth was obtained from 32%. The patients were analysed with respect to age, presence of chronic chest disease and their final diagnosis.

Age of the patient. It seemed possible that the changes in the lungs associated with ageing might increase the liability to candida infection. Table 8 shows however that candida was present in 52 (47%) of 110 patients under the age of 40 years

compared with 127 (49%) of 257 patients over this age.

TABLE 8. - PREVALENCE OF CANDIDA IN ADMISSION SPUTA.

GROUP	TOTAL	NO. OF SPUTA WITH CANDIDA		
		ABSENT	SCANTY	HEAVY
All groups	367	188	60 17%	119 32%
Aged less than 40	110	58	22 20%	30 27%
Aged more than 40	257	130	38 15%	89 34%
With chronic bronchitis	138	66	25 18%	47 34%
With tuberculosis	57	26	7 12%	24 42%
Total with chronic chest disease	195	92	32 17%	71 36%
Without chronic chest disease	172	95	30 17%	47 28%
With pneumonia	208	113	33 16%	62 30%
With cardiac failure	33	18	6 18%	9 27%

Presence of chronic chest disease. The table shows that of 195 patients with a history of chronic chest disease 103 (53%)

harboured candida in the sputum, whereas of 172 patients without such a history there were 77 (45%) whose sputum yielded the organism.

An attempt was made to correlate these two factors by dividing the patients into the following groups:-

(a) under 40 years without a history of chest disease - 70 patients.
(b) under 40 years with chronic chest disease - 40 patients.
(c) over 40 years without a history of chest disease -102 patients.
(d) over 40 years with chronic chest disease -155 patients.

The numbers of patients in these groups from whose sputa candida was isolated were respectively 30, 22, 44 and 84. When a chi square test is applied to these figures we find that P = 0.1. This result indicates that such a distribution might have arisen by chance. It appears therefore that age and chronic pulmonary infection bear no relation to the presence of candida in the sputum.

46% of the patients with pneumonia and 45% of those with cardiac failure had candida in the sputum.

B. ISOLATION OF CANDIDA BEFORE TREATMENT.

The distribution of candida in the various admission specimens of the pneumonia series is shown in Table 9. It will be seen that the highest proportion of positive results was obtained from the sputa. Of these 48% were positive compared

with 26% of the throat swabs and 3% of rectal swabs. Since 150 patients were suffering from an acute pneumonia and almost

TABLE 9. - DISTRIBUTION OF CANDIDA IN SPECIMENS BEFORE ANTIBIOTIC THERAPY.

(Both Treatment Groups)

SPECIMEN	NUMBER EXAMINED	NO. OF SPECIMENS WITH CANDIDA		
		ABSENT	SCANTY	HEAVY
Post-nasal swab	51	51	0	0
Throat swab	103	76	11 11%	16 15%
Sputum	149*	78	22 15%	49 33%
Rectal swab	154	149	1 0.5%	4 2.5%

* 5 cases with no admission sputum.

half had candida in the sputum, it seemed necessary to compare the results of routine bacteriology of the sputum with the results of examination on Sabouraud's medium. Of the 88 patients with "pathogenic" organisms (see Chapter I.) 39 (44%) had also candida in the sputum. In the group of 37 patients infected with "non pathogens" 18 (49%) had candida in the sputum. The

similarity of these proportions suggests that the presence of candida in the sputum could not be regarded as bearing any relationship to the acute disease.

C. ISOLATION OF CANDIDA DURING AND AFTER TREATMENT.

The growth of candida during and after treatment in the two groups is shown in Table 10.

TABLE 10. - GROWTH OF CANDIDA IN THROAT SWABS, SPUTA, AND RECTAL SWABS DURING TREATMENT.

SPECIMEN	GROWTH OF CANDIDA	DAY IN HOSPITAL										TOTAL	
		Admission		Third		Fifth		Seventh		Ninth			
		Terr.	S.D.	Terr.	S.D.	Terr.	S.D.	Terr.	S.D.	Terr.	S.D.	Terr.	S.D.
Throat Swab	Absent	44	32	42	35	31	29	30	32	30	28		
	Scanty	4	7	3	7	2	9	5	6	10	10	57	46
	Heavy	9	7	12	4	24	8	22	8	17	8		
Sputum	Absent	14	13	*8	18			**6	11				
	Scanty	5	8	3	5			7	6			28	33
	Heavy	9	12	17	10			15	16				
Rectal Swab	Absent	85	67	70	67	34	65	34	58	33	55		
	Scanty	0	0	1	0	1	0	3	1	1	0	85	69
	Heavy	0	2	14	2	50	4	48	10	51	14		

* on third to fifth day

** on seventh to ninth day

Post-nasal Swabs. It has been mentioned that post-nasal swabs were taken from 51 patients, 27 of whom were receiving terramycin and 24 sulphadiazine. Of those 51 swabs only two in the sulphadiazine group (both taken on the ninth day) grew candida. As post-nasal swabs did not seem to be a fruitful source of candida, throat swabs were taken from the subsequent cases.

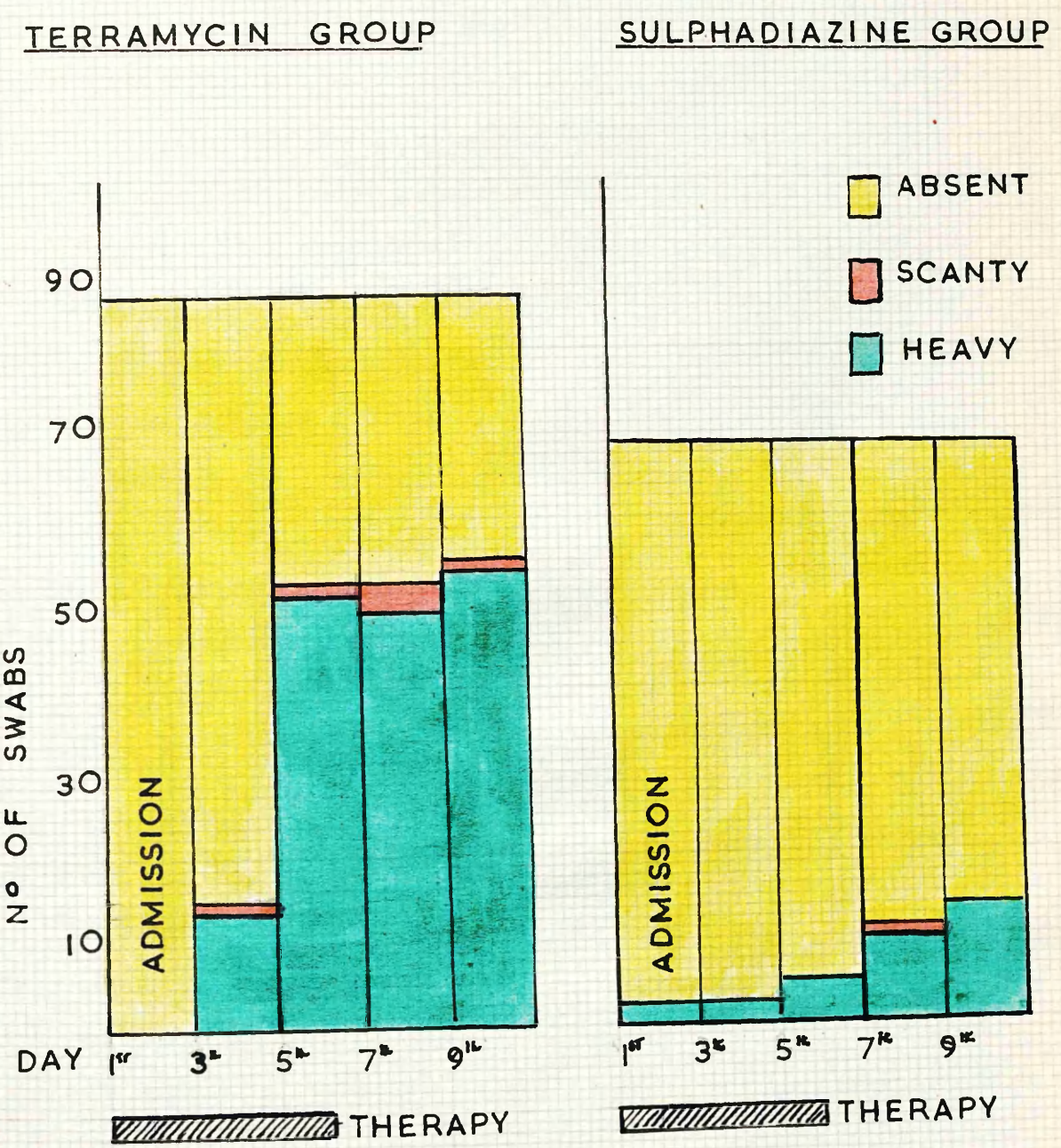
Throat Swabs. The number of patients in the terramycin group with heavy growths of candida rose from 9 (16%), the figure on admission, to 24 (42%) on the fifth day, falling again slightly to 17 (30%) on the ninth day. At similar periods in the sulphadiazine group the figures were 7 (15%), 8 (17%) and 8 (17%).

Sputa. In the terramycin group the number of patients with a heavy growth of candida rose from 9 (32%) on admission to 17 (61%) during treatment, while, over the corresponding period in the sulphadiazine group there was no increase. It may be observed, however, that 2-4 days after sulphadiazine had been stopped, the number with heavy growths rose from 10 (30%) to 16 (49%).

Rectal Swabs. Perhaps the most striking difference in the two treatment groups emerges when the results of the rectal swabs are compared (see also fig.2). In the terramycin group, the number of patients showing a heavy growth of candida had risen from nil prior to treatment to 50 (59%) on the fifth day.

FIG. 2

GROWTH OF CANDIDA IN RECTAL SWABS



On the ninth day in hospital i.e. 4 days after treatment had been discontinued, this high figure persisted. On the other hand, in the sulphadiazine group, the corresponding figures were 2 (3%) prior to treatment, 4 (5%) on the fifth day and 14 (20%) on the ninth day. Again it will be observed that after treatment had been stopped, there was a rise in the number of positive results in the sulphadiazine group.

Correlation of Throat Swabs and Sputa. The presence of candida in both the throat swab and sputum collected on the same day was studied and it was found that out of 118 patients showing candida in the throat swab and/or sputum, both specimens were positive in 52 (44%). The throat swab only in 5 (4%) and the sputum only in 61 (52%) was positive. In other words, of 57 cases whose throat swab was positive, the sputum was positive in 52, whereas of 113 cases whose sputum was positive, the throat swab was positive in only 52. Such a finding might support a view that the yeasts were actually in the sputum and not merely present as a result of throat contamination.

Penicillin Group. The growth of candida in the penicillin-treated group is shown in Table 11. As the total number is small (16), percentages are apt to be misleading but they are given here to allow comparison with the other groups. The number having a heavy growth of candida in the throat swab

rose from 1 (6%) on admission to 4 (25%) on the fifth day, and in the rectal swab from nil to 1 (6%) and then to 3 (19%) on the ninth day in hospital. The behaviour of this group with regard

TABLE 11. - GROWTH OF CANDIDA IN THE PENICILLIN GROUP.

SPECIMEN	GROWTH OF CANDIDA	DAY IN HOSPITAL			TOTAL
		Admission	Fifth	Ninth	
Throat Swab	Absent	13	8	7	16
	Scanty	2	4	6	
	Heavy	1	4	3	
Sputum	Absent	6	5	4	11
	Scanty	1	1	1	
	Heavy	4	5	6	
Rectal Swab	Absent	15	15	13	16
	Scanty	1	0	0	
	Heavy	0	1	3	

to the throat swabs is similar to the terramycin group but with regard to the rectal swabs the figures are more closely related to those in the sulphadiazine group.

DISCUSSION

The foregoing findings show that, in patients with respiratory illness Candida albicans may be isolated from a considerable proportion of admission sputa (49% of 369 sputa). Although these patients belong to a small and specialised group of the population they are fairly representative of that section of the community who have a productive cough. The presence of candida in the sputum was shown not to be related to the age of the patient, the presence of chronic chest disease or the particular form of chest disease from which the patient was suffering. This would suggest that in the sputum candida is usually a harmless saprophyte. This is true, moreover, even when it is present in large quantities in the sputum, since 32% of the sputa had heavy growths of candida. Skinner (1947) cited different series of patients with known or suspected tuberculosis in whom candida was isolated from 9-36%. He considered that the wide difference in the findings was due to the varying techniques employed by the workers in the isolation of candida. According to Castellani, candida may be present in the sputum under three circumstances, - (a) as saprophytes, (b) as secondary invaders in other primary diseases of the lungs, and (c) as the real agents of broncho-pulmonary disease. Candida in the sputum only acquires significance when it is found constantly

and in large numbers from a patient who presents a typical clinical picture of pulmonary moniliasis. Care must first be taken to exclude tuberculosis, the disease which moniliasis most closely resembles.

It is interesting to compare the throat swab results with those of other workers. In America, Todd (1937) reported the isolation of candida from the throat in 3.9% of 1,000 healthy adults, while Marples and di Menna (1952) in New Zealand recorded a figure of 6.3% from the throat swabs of 351 normal persons. The present figure of 26% is more in keeping with those of Fisher (1936) who found that 25% of throats of 48 children and 21% of 28 adults had candida. It must be noted, however, that my series differed from those reported above in that all the patients had a respiratory infection at the time of examination.

When the mouth also is examined for candida by rubbing the swab over the gums and tongue a higher proportion is generally found to harbour the organism than when the swab is rubbed on the fauces only. Todd found 14% and Marples and di Menna 18.3% of their series positive for candida by this method. An even higher proportion of positive results may be obtained by culturing the saliva. In this way Marples and di Menna found 41% of their series positive for candida. Lilienthal (1950)

examined the mouths of 109 healthy boys for yeasts. Examination by gum swabs showed 37% to be positive and by culturing the saliva 47.7% were positive. In a group of adults, he found no relationship between the presence of yeasts and obvious dental caries but their presence was affected by whether or not the person had teeth. Persons with their own teeth were more likely to harbour yeasts than the edentulous but when dentures were worn the yeasts reappeared. Marples and di Menna actually found the incidence of candida was greatest in those with dentures. Of 80 persons with natural teeth 45% had candida in the mouth compared with 68% of 19 persons with artificial teeth.

The present findings would indicate that the rectal swab may not be as sensitive an indicator as faeces in detecting the presence of yeasts in the lower bowel. The findings of many workers in different surveys are closely similar in indicating that about 15% of normal faeces yield candida on culture. Schnoor's figure (1939) was 14% of 314 normal persons and Benham and Hopkins' (1933) was 18% of 100 normal persons while I found only 3% of rectal swabs to be positive in patients admitted to hospital. As my purpose was to compare the effect of two kinds of treatment and the method used was the same in both groups, the examination of rectal swabs proved satisfactory in this study.

During the course of treatment comparison of the two groups elicited a marked difference in the frequency with which candida was obtained. With sulphadiazine there was no increase in the proportion of patients with candida in throat swabs, sputa and rectal swabs, whereas with terramycin there was a significant increase of candida in all these specimens.

The nearest approach to the present investigation was reported by Lipnik, Kligman and Strauss in 1952. Mouth swabs and rectal swabs from three groups of hospital patients were cultured on Sabouraud's medium. In the control group the patients had received no antibiotics and in the therapy groups swabs were not taken from persons unless they had received antibiotics for at least four days. The control group numbered 67 patients, a group treated with aureomycin or chloramphenicol, 63 patients and a group treated with penicillin, 42 patients.

Lipnik's control group of patients were selected at random from the hospital wards and it is permissible to compare his findings there with the admission findings in the present series since neither group of patients had received chemotherapy. 7.5% of his mouth swabs, 26% of my throat swabs; 1.5% of his rectal swabs and 3% of mine yielded candida. The incidence of candida in throat and mouth swabs tends to be less constant in different surveys. In the faeces, on the other hand, the

figure is fairly constant but Lipnik's results confirm the contention that rectal swabs give fewer positive findings.

It is interesting to compare the presence of candida in the two broad-spectrum antibiotic groups of patients i.e. those of Lipnik's who received aureomycin or chloramphenicol and those of mine on the fifth day of terramycin treatment. In the former 60% of the mouth swabs were positive, and in the latter 26 (46%) of the throat swabs. The difference here is probably due to the fact already pointed out that the mouth is in general a more fruitful source of candida than the throat. By rather a remarkable coincidence the 60% of his positive rectal swabs and the 51 (60%) of mine were the same. In the two penicillin groups of patients 5% of Lipnik's rectal swabs and 1 (6%) of mine were positive for candida. These figures are in alignment but there is a gross discrepancy between the 7% of his mouth swabs, and the 8 (50%) of my throat swabs which were positive, although only 4 (25%) of the throat swabs yielded heavy growths of candida.

To revert to the present series, the increase of candida in the sputa and rectal swabs of the sulphadiazine group after the cessation of therapy is rather surprising. A similar finding emerged in the rectal swabs of the penicillin group. It seems possible that these patients were cross-infected by others in the terramycin group who were excreting large

quantities of yeasts. It is noteworthy that this increase after treatment was found in the groups which had shown little or no increase in candida during treatment. It would be impossible to detect when a patient who already harboured a large number of candida was re-infected by another patient. In the straightforward case of pneumonia which responded well to treatment the patient got up to sit in a chair in the afternoons of the sixth and seventh days in hospital and thereafter was allowed up to the toilet and to walk for gradually increasing periods. Consequently when the last two swabs of the series were taken, on the seventh and ninth days in hospital, the patient was more in contact with his fellow patients. Mingling with them increased the opportunities for cross-infection. It would appear therefore that a person with a heavy growth of candida in the sputum, throat or rectum may act as a source of infection for others.

A review of the findings from the present series of patients indicates that overgrowths of candida occurred most frequently during terramycin treatment, less frequently during penicillin treatment and least often during sulphadiazine treatment. It is of interest that this effect of terramycin was most marked in the rectal swabs and suggests that a high local concentration of the drug may be an important factor. After oral

administration Kraus, Casey and Johnson (1951) showed that antibiotics are excreted in appreciable quantities in human saliva so that the throat is constantly exposed to the action of antibiotics. Terramycin is readily absorbed from the alimentary tract of man and presumably a therapeutic concentration in the lungs, the source of the sputum, is obtained. The greatest concentration of the drug, however, is found in the faeces. Linsell and Fletcher (1950) in the first report on terramycin in this country found that on a dose of 1g six-hourly, up to 4,000μg/g could be recovered in the faeces, but the average was around 1,250μg/g. This would account for the effect of terramycin being more pronounced in the rectum than in the sputum or throat.

The concentration of drug in the site of origin of the specimen, however, is not the sole factor in determining whether or not yeasts will overgrow. The other and equally important factor appears to be the type of bacterial flora which is normally found in the areas from which the specimens were taken. In the throat and sputum the bacterial flora is predominantly Gram positive while in the lower intestine it is predominantly Gram negative. Terramycin being effective against both Gram positive and Gram negative organisms was able to inhibit the growth of most of the organisms normally present in the throat,

sputum and rectum. Penicillin, on the other hand, by its effectiveness against Gram positive but not Gram negative organisms was able to exert its fullest effect on the bacteria of the throat and sputum. Irrespective of the degree of local concentration obtained in the lower intestine, penicillin could not eliminate most of the organisms normally found there. Although sulphadiazine acts against both Gram positive and Gram negative organisms it is a much less potent drug. Consequently it causes less upset in the normal microflora of the throat, sputum or rectum.

The extent to which the normal bacterial flora is suppressed is faithfully reflected in the frequency with which candida overgrew during the different methods of treatment. During terramycin therapy there was an increased proportion of patients with overgrowths of candida in the throat, sputum and rectum; during penicillin therapy the increase was noted in the throat but not in the rectum; finally, during sulphadiazine treatment no increase occurred in any of the three sites. These findings support the theory that an antagonism exists between the bacteria and the yeasts in the microflora of the throat, sputum and rectum. Normally the bacteria are dominant but when they are exposed to drugs which have the power to inhibit or even destroy them, their growth is suppressed. It is

then that the yeasts which are insensitive to terramycin, penicillin or sulphadiazine are allowed to flourish and become dominant in the flora.

PART II. TUBERCULOSIS SERIES

The extension of the investigation to patients in the tuberculosis wards enabled a comparison to be made of the effects of the three antibiotics, chloramphenicol, aureomycin, and terramycin on the microflora. The tuberculosis patients, unlike the pneumonia patients, usually had regular bowel movements which made practicable the examination of actual specimens of faeces rather than rectal swabs. This was of special interest because of the discrepancy between the positive findings for candida in admission rectal swabs and those of other workers who had sampled faeces. McVay and Sprunt (1951) reported that the administration of parahydroxybenzoic acid (paraben) along with aureomycin prevented the overgrowths of yeasts. The substance is used as a preservative in foods and drugs, the methyl ester being effective against moulds and the propyl ester active against yeasts. To repeat their experiments a supply of capsules containing aureomycin and paraben esters was given by the manufacturers, Lederle Laboratories. These were given to a small

group of patients.

MATERIAL AND METHODS

The series of 80 adult males suffering from pulmonary tuberculosis was studied. Chloramphenicol was given to 35, aureomycin to 20 and terramycin to 25. The supply of aureomycin hydrochloride which contained 90 mgs. methylparaben and 22.5 mgms propylparaben incorporated in each 250 mg. capsule was sufficient to treat 5 patients. Concurrently, other 5 patients were given ordinary aureomycin to act as controls. In the aureomycin group there were thus 15 patients who received ordinary aureomycin and 5 who received paraben aureomycin. Because of the possible effect of paraben on the growth of candida, when this factor alone is under examination, the patients who received paraben aureomycin are excluded from the analysis leaving a total of 75 cases in the tuberculosis series. The patients were not receiving streptomycin treatment and were allowed up to the toilet. In the paraben experiment the additional criterion was imposed that no patient with a heavy growth of candida beforehand was given paraben aureomycin or used as a control.

Each patient received a total dose of 16 g. antibiotic over a period of 4 days. Before the drug was given a specimen of sputum was collected into a small, greased cardboard container and

a specimen of faeces into a larger carton. Similar specimens were again taken on the morning of the third day of the course i.e. after 8g of the drug, and on the morning after the day treatment stopped, i.e. after 16g of the drug. The specimens were taken to the laboratory where a note was made of the naked-eye appearance of the sputum and of the stool. After the sputum had been emulsified with 5 ml. of sterile broth a loopful was inoculated on a plate of Sabouraud's medium and another loopful rubbed on a glass slide to make a film. A loopful of faeces was also inoculated on a plate of Sabouraud's medium then mixed with a drop of saline on a glass slide to make a film. The plates were dealt with in the same way and the same criteria used to identify Candida albicans as in the pneumonia series. The films were examined microscopically for yeast cells after staining by Gram's method and yeasts were recorded as "absent"; "scanty" when only a few were seen in the whole of the stained area; "heavy" when numerous cells were seen.

RESULTS

A. ALL ANTIBIOTICS.

Growth of candida before and during course of drug.

Table 12 shows that, of the 75 patients in the series as a whole, the proportion with a heavy growth of candida in

the sputum rose from 12% before an antibiotic course to 32% after 8g and to 41% after 16g. The corresponding results from

TABLE 12. - GROWTH OF CANDIDA IN THE SPUTUM OF TUBERCULOSIS SERIES.

ANTIBIOTIC	GROUP	TOTAL	NUMBER OF SPUTA WITH CANDIDA					
			ABSENT		SCANTY		HEAVY	
			D/F	SAB.	D/F	SAB.	D/F	SAB.
Before	Chlor.	35	33	15	2	14	0	6
	Aureo.	15	14	8	1	7	0	0
	Terr.	25	25	17	0	5	0	3
	Series	75	72	40	3 4%	26 35%	0	9 12%
After 8 g.	Chlor.	35	25	11	7	14	3	12
	Aureo.	15	13	8	2	3	0	4
	Terr.	25	19	13	5	4	1	8
	Series	75	57	32	14 19%	21 28%	4 5%	24 32%
After 16 g.	Chlor.	35	22	9	9	12	4	14
	Aureo.	15	12	6	3	5	0	4
	Terr.	25	18	10	6	2	1	13
	Series	75	52	25	18 24%	19 25%	5 7%	31 41%

D/F. = Direct Film.

SAB. = Culture on Sabouraud's Medium.

the examination of faeces, shown in Table 13 are more striking.

Here the percentage of specimens showing heavy growths rose from 3 before the drug to 40 after 8g, then to 51 after 16g.

TABLE 13. - GROWTH OF CANDIDA IN THE FAECES OF TUBERCULOSIS SERIES.

ANTIBIOTIC	GROUP	TOTAL	NUMBER OF FAECES WITH CANDIDA					
			ABSENT		SCANTY		HEAVY	
			D/F	SAB.	D/F	SAB.	D/F	SAB.
Before	Chlor.	35	32	29	2	4	1	2
	Aureo.	15	15	11	0	4	0	0
	Terr.	25	17	22	8	3	0	0
	Series	75	64	62	10 13%	11 15%	1 1%	2 3%
After 8 g.	Chlor.	35	15	17	16	7	4	11
	Aureo.	15	8	6	6	6	1	3
	Terr.	25	5	8	11	1	9	16
	Series	75	28	31	33 44%	14 19%	14 19%	30 40%
After 16g.	Chlor.	35	13	14	17	8	5	13
	Aureo.	15	2	3	6	3	7	9
	Terr.	25	4	3	8	6	13	16
	Series	75	19	20	31 42%	17 23%	25 33%	38 51%

D/F. = Direct Film.

SAB. = Culture on Sabouraud's Medium.

When we look again at the sputum results we find that

35 were positive for candida before the drug and 31 had heavy growths after 16g. One might argue that if the heavy growths developed from these 35 patients, then no patient who was negative beforehand developed a heavy growth of candida as a result of the antibiotic and only 15 who were negative before developed a scanty growth of the organism. It must be noted, however, that the chloramphenicol group alone contained 20 of the positive sputa before therapy so that in the other two groups, 15 were positive before, but 17 had heavy growths of candida at the end of the course. Applying a similar argument to the results in the faeces we find that while only 13 were positive before the drug, 38 had heavy growths after 16g. This means that 25 patients who were negative before developed heavy growths of candida as a result of the antibiotic. All this is based on inference, but a re-examination of the results in each individual patient would reveal whether or not patients who were negative were less likely to show overgrowths of candida during a course of antibiotic than those who already harboured the organism. This was accordingly done and the findings are shown in Table 14. It will be seen that 19 patients whose sputum was negative for candida became positive during antibiotic therapy; moreover in 14 of these the growth was heavy; in 21 patients the sputum remained negative throughout the

course. Thirty-five patients whose faeces were negative became

TABLE 14. - DEVELOPMENT OF CANDIDA IN TUBERCULOSIS SERIES.

GROWTH OF CANDIDA DURING COURSE OF ANTIBIOTIC	NUMBER OF	
	SPUTA	FAECES
BEFORE - AFTER 8 g. - AFTER 16 g.	(TOTAL IN SERIES 75)	
Negative - Negative - Scanty	1	4
Negative - Scanty - Scanty	4	4
Negative - Negative - Heavy	4	6
Negative - Scanty - Heavy	3	4
Negative - Heavy - Heavy	7	17
Negative becoming positive	19 25%	35 47%
Scanty - Scanty - Heavy	2	3
Scanty - Heavy - Heavy	6	6
TOTAL with increased growth	27 36%	44 59%
Negative - Negative - Negative	21	27
Scanty - Scanty - Scanty	18	2
Heavy - Heavy - Heavy	9	2
TOTAL with growth unchanged	48 56%	31 41%

positive and in 27 the growth of candida was heavy; in 27 patients the faeces remained negative. In other words, of 31

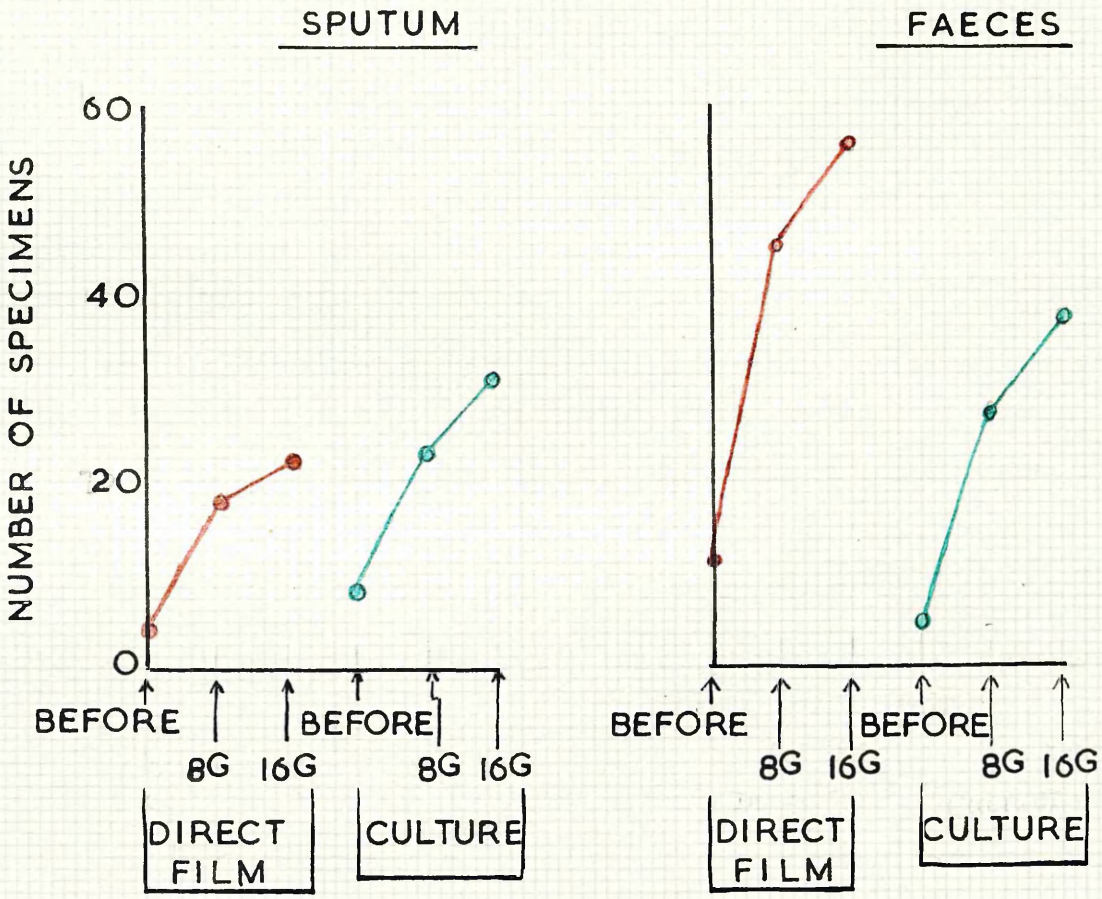
sputa with heavy growths of candida at the end of a course of antibiotic 14 had been negative beforehand, 8 had had scanty growths and the remaining 9 had had heavy growths from the start. Similarly in the faeces, of 38 with heavy growths of candida at the end of the course of the drug, 27 had been negative beforehand, 9 had had scanty growths and the remaining 2 had had heavy growths from the beginning. In short, of the 75 patients whose sputa and faeces were examined, in 36% of the former and 59% of the latter, the growth of candida either appeared or became more profuse as a result of giving an antibiotic.

The additional point emerges from Table 14 that after 8g antibiotic 13 patients, and after 16g 22 patients, had a heavy growth of candida in the sputum. In the faeces, after 8g antibiotic 23 patients, and after 16g 36 patients, had a heavy growth. In the sputum, therefore, 13 (59%) and in the faeces 23 (64%) of the heavy growths of yeasts developed mid-way through the antibiotic course.

Comparison of direct film and culture for detection of candida. Table 12 shows that the number of times yeasts were seen in the direct film was smaller than the number of times candida was grown on Sabouraud's medium from the same specimen. When the frequency with which the direct film was positive is compared with the number of times a heavy growth of candida was obtained from culture of the same specimen of sputum, the

FIG 3

COMPARISON OF POSITIVE FINDINGS FOR CANDIDA ON DIRECT FILM AND HEAVY GROWTH OF CANDIDA ON CULTURE



figures approach one another (see fig.3) although the direct film positives still fall below the culture ones. This indicates that if the film of a specimen of sputum is positive on microscopic examination then a heavy growth of candida will probably be obtained when the same specimen is cultured. With regard to the faeces, Table 13 shows that after 8g antibiotic the direct film was positive in 47 patients and culture in 44 patients. After 16g antibiotic the figures again are closely similar - in 56 patients the direct film and in 55 culture was positive for candida. When the number of times the film was positive is compared with the number of times a heavy growth of candida was obtained on culture and the results charted (see fig.3) we find that, although the curves are closely parallel, the direct film figures are actually higher. In the faeces, therefore, the film may show yeasts cells when only a scanty growth of candida is obtained on culture of the specimen.

Comparison of the two methods of examination indicates that culture is the more sensitive, especially for the sputum.

Appearance of the sputum and growth of candida. Seeking some explanation for the absence of yeasts in the film when they appeared on culture, I wondered if candida was more likely to be present in one type of sputum than in another. Often a mucoid or purulent sputum was not completely homogeneous after stirring it with broth and the film made from it may not have been representative of the specimen as a whole. On the other hand, a salivaceous sputum was easily emulsified with broth and the resultant film more truly represented the specimen. The

sputa were divided into groups according to their naked-eye appearance and considered along with the presence of candida in them.

TABLE 15. - APPEARANCE OF SPUTUM AND GROWTH OF CANDIDA.

APPEARANCE OF SPUTUM	NUMBER OF SPUTA (Total 93)	NUMBER OF SPUTA WITH CANDIDA					
		ABSENT		SCANTY		HEAVY	
		D/F	SAB	D/F	SAB	D/F	SAB
Salivaceous	27	18	14	4	6	5	7 26%
Mucoid	26	19	10	7	10	0	6 24%
Muco-Purulent	16	14	9	1	5	1	2 13%
Purulent	24	19	16	3	3	2	5 21%

D/F. = Direct Film.

SAB. = Culture on Sabouraud's medium.

Table 15 shows that in a total of 93 sputa candida grew heavily in a similar proportion of each type, indicating that the consistency of the sputum has little to do with its content of

candida. On comparing two kinds of sputum, one consisting mainly of saliva which was produced from the throat, with the other types which were produced from the lungs, we find 13 of 27 (48%) of the former and 31 of 66 (47%) of the latter were positive for candida on culture. Thus, material from the lungs yielded candida as often as material from the throat. This finding corroborates the point already made that candida found in the sputum comes from the lungs and is not present solely as a result of throat contamination. When the appearance of the sputum is compared with the finding of yeasts in the direct film, it is seen that the number of positive findings decreases with increasing tenacity of the sputum. Of the 8 occasions when yeasts were numerous on the film, 5 occurred in a sputum consisting mainly of saliva. Examination of a direct film of a mucoid or purulent sputum was therefore a less satisfactory means of detecting the presence of candida than culture of the specimen on Sabouraud's medium.

Appearance of stool and growth of candida. Correlation between the appearance of the stool and its growth of candida is shown in Table 16. It is at once apparent that, unlike the sputum, the appearance of the faeces is related to its growth of candida. Only 15% of normal stools had heavy growths of the

organism compared with 57% of soft stools, 72% of loose ones

TABLE 16. - APPEARANCE OF STOOL AND GROWTH OF CANDIDA.

APPEARANCE OF STOOL	NUMBER OF STOOLS (Total 287)	NUMBER OF STOOLS WITH CANDIDA		
		ABSENT	SCANTY	HEAVY
Normal	181	124	30	27 15%
Soft	63	14	13	36 57%
Loose	25	3	4	18 72%
Green	18	3	2	13 72%

and 72% of green ones.

B. INDIVIDUAL ANTIBIOTICS.

The results in each group of patients will now be considered separately. The following figures refer to patients with a heavy growth of candida in the specimen.

In the sputum the figure rose from 6 (17%) before treatment to 14 (40%) after 16g chloramphenicol, from nil to 4 (27%) after 16g aureomycin and from 3 (12%) to 13 (52%) after 16g terramycin (Table 12). There was an increase, therefore, of 23% in the chloramphenicol group, 27% in the aureomycin group and 40% in the terramycin group.

In the faeces the increase is more striking in the aureomycin and terramycin groups (Table 13). Here the figure rose from nil before treatment to 9 (60%) after 16g aureomycin and from nil to 16 (64%) after 16g terramycin. In the chloramphenicol group, although 2 (6%) had heavy growths before treatment the figure rose to only 13 (37%) after treatment.

That there was an undue proportion of patients positive for candida, particularly in the sputum, prior to the course of chloramphenicol, was already evident after the first 23 patients had been studied. The succeeding 12, therefore, were chosen so that 6 should be under 30 years and 6 over that age. Separate analysis of these cases (see Table 17) shows that 7 were positive at the first examination and that they

were equally distributed in the two age groups. Consequently, this attempt at selecting patients was of no value in reducing

TABLE 17. - GROWTH OF CANDIDA IN A SUB-SECTION OF THE CHLORAMPHENCOL GROUP.

	6 CASES OVER 30 YEARS			6 CASES UNDER 30 YEARS		
	NUMBER OF SPECIMENS WITH CANDIDA					
	Absent	Scanty	Heavy	Absent	Scanty	Heavy
SPUTUM						
Before chlor.	3	2	1	2	3	1
After 8 g.	1	2	3	1	1	4
After 16 g.	1	0	5	1	1	4
FAECES						
Before chlor.	5	1	0	4	2	0
After 8 g.	1	0	5	4	0	2
After 16 g.	1	0	5	3	0	3

the proportion of positive sputa in this group.

The development of candida in the 5 patients treated with paraben aureomycin together with the five patients given ordinary aureomycin as controls is shown in Table 18. With such a small series it would be unwise to generalise but it appears that the addition of paraben did have an inhibitory effect on the growth of yeasts. In the sputum, two patients

had scanty growths before, and remained scanty during the course of paraben aureomycin; while in the controls, where none had

TABLE 18. - PARABEN EXPERIMENT.

ANTIBIOTIC	BEFORE			AFTER 8 g.			AFTER 16 g.		
	NUMBER OF SPECIMENS WITH CANDIDA								
	Absent	Scanty	Heavy	Absent	Scanty	Heavy	Absent	Scanty	Heavy
SPUTUM:									
Paraben Cases (5)	3	2	0	4	1	0	3	2	0
Controls (5)	5	0	0	3	2	0	3	0	2
FAECES:									
Paraben Cases (5)	4	1	0	2	0	3	3	0	2
Controls (5)	4	1	0	1	0	4	1	0	4

been positive before, two had heavy growths of candida at the end. The occurrence of candida in the faeces was the same in the two groups before treatment, one in each having a scanty growth, while at the end, two of the paraben group and four of the controls had heavy growths.

C. COMPARISON WITH PNEUMONIA SERIES.

Before treatment, candida was present in the sputa of 48% of the pneumonia series and 47% of the tuberculosis series. Candida appears to be associated with each of these illnesses

to a similar degree. This also is borne out by the subsequent increase in the number of patients with heavy growths of yeasts during antibiotic therapy. In the terramycin group of pneumonia patients the percentage with a heavy growth of candida in the sputum rose from 32 before to 61 after an average of 14.2g, while in the tuberculosis series the rise was from 12 to 41 after 16g. This increase of 29% in both groups indicates that whether the illness is acute or chronic makes little difference to the growth of candida.

It is interesting to compare the results of the rectal swabs of the terramycin-treated pneumonias with the faecal examinations of the tuberculosis patients. In the former the rise was from none to 59% with heavy growths of candida after 14.2g and in the latter from 3% to 51% after 16g. The difference here is slight and suggests that, in fact, the rectal swab is just as sensitive an indicator as culture of the faeces for detecting heavy growths of candida. This would appear to be at variance with the previous supposition that culture of a rectal swab was the less satisfactory method. Perhaps the answer to this problem is to be found when we consider the positive findings i.e. when those with scanty as well as heavy growths before antibiotic therapy are included. In the pneumonia series as a whole the proportion of positive rectal swabs was 3%, while in

the tuberculosis patients, culture of the faeces was positive in 13 (17%.) This latter figure is comparable to the 18% found by Benham and Hopkins and the 14% found by Schnoor. We may conclude that if a heavy growth of candida is obtained on culture of a specimen of faeces, then the rectal swab from that patient will also be positive but if only a scanty growth is obtained from the faeces, then the rectal swab will probably be negative.

DISCUSSION

The proportion with candida in the sputum of this series of 75 tuberculosis patients was 47%. This figure is fairly high compared with that of Schwarting and Skinner (1949) who found candida in the sputa of 20% of 500 patients in a tuberculosis sanatorium. They found that the degree of tuberculosis had no influence on the incidence of candida nor was there any evidence of disease due to candida in any of the patients. In their series, 28 sputa of 100 newly admitted patients to the sanatorium were positive, a figure which was higher than the 20% of the larger series. In this present investigation, from the admission sputa of 57 patients with tuberculosis, 54% were found to be positive. This is also a slightly higher figure than the 47% of the tuberculosis series. An explanation for the discrepancy in their own figures is put forward by Schwarting and

Skinner. They suggest that on admission to hospital, a tuberculosis patient is "regressing" and his resistance to candida infection is low. After a period in hospital, his resistance gradually increases with rest in bed and good food, and thus he is able to overcome candida infection. They admit, however, that the difference is hardly big enough to justify drawing definite conclusions.

The proportion with candida in the present series of patients who suffered from chronic chest disease is almost the same as in the group of patients with no history of previous chest illness on admission (45%). This, together with the absence of negative sputa in the younger patients in the chloramphenicol group, bears out a statement previously made that chronic chest disease and age bear no relation to the presence of candida in the sputum. To this we may add that the presence of a chronic debilitating disease like tuberculosis does not raise the susceptibility of the patient to candida infection. It seems unlikely therefore that the improvement in a tuberculosis patient's general condition after admission will influence the presence of candida in his sputum.

From culture of the faeces, 17% of the series had candida before antibiotic was given and in 3% the growth was heavy. This is in keeping with the results of Schnoor (1939)

who found candida in 14% of 314 normal stools but a significant number of colonies on each plate in only 1%.

During the course of antibiotic it was observed that heavy growths of candida could develop in those in whom the organism was not demonstrated beforehand. There are two explanations for this. Either the yeast was originally present but its growth on culture plates was suppressed by the growth of the other organisms or the patient became cross-infected from another patient with candida. The constant presence of candida in the ward was maintained by the admission of new patients who harboured the organism. Many of the patients were ambulant and there was therefore ample opportunity for cross-infection.

When candida is the casual agent of pulmonary disease the typical sputum is mucoid. In the tuberculosis series there was no undue preponderance of patients with this type of sputum nor was broncho-pulmonary moniliasis considered a likely diagnosis in any of the cases. This would indicate that the yeasts which were present were saprophytes, or at the most, secondary invaders in these patients. Heavy growths of candida were most frequently associated with a soft, loose or green

stool. The relationship between candida and abnormal stools is discussed more fully in the next chapter.

The results show that the three antibiotics, chloramphenicol, aureomycin and terramycin were each of them associated with an increase in heavy growths of candida. The sputum findings show that this increase was most marked with terramycin. Consideration of the faecal results shows that the greatest proportion of heavy growths of candida appeared during terramycin treatment, next with aureomycin, and the lowest with chloramphenicol. In a study of the absorption of the three drugs, Werner, Knight and McDermott (1950) found that after a single dose of 50mg/Kg of body weight, maximum serum concentrations of antibiotic in man occurred in 4 hours. These were, 25-50μg/ml for chloramphenicol, 12-16μg/ml for terramycin, and 3.3-12.5μg/ml for aureomycin, showing that chloramphenicol was the drug most fully absorbed from the gastro-intestinal tract. Welch (1950) found that relatively large amounts of all three antibiotics were inactivated in the body but this was especially high with chloramphenicol. In faecal excretion, terramycin had the greatest concentration

in μg/g of faeces; aureomycin came next, and chloramphenicol had the lowest. This might explain why the increase in heavy growths of candida in the faeces was less marked in the chloramphenicol group than in the other two.

In view of the close chemical kinship between aureomycin and terramycin, one would expect their effects in the human body to be very similar. It has, however, been suggested that certain antibiotics actually stimulate the growth of candida and aureomycin especially has been incriminated. It is on record that this antibiotic directly stimulates fungus metabolism and thereby increases its rate of growth. The evidence, however, is conflicting. In an in vitro experiment Moore (1951) found that aureomycin hydrochloride in solution of 0.2mg/ml stimulated the growth of candida on Sabouraud's medium. Pappenfort and Schnall (1951) demonstrated a marked in vitro growth enhancement of candida by a solution of aureomycin made up from the contents of the aureomycin capsule normally used for oral administration. Crystalline aureomycin failed to give this effect. On the other hand, Huppert (1953) who compared the effect of various antibiotics on the growth of candida, found that both the oral and parenteral preparations of aureomycin caused a definite increase in growth while penicillin, streptomycin,

chloramphenicol and terramycin had no effect. Seligmann (1952) experimenting with mice, found that the antibiotic activity of aureomycin solutions was parallelled by their faculty for enhancing the growth of candida. In 1953 he reported that the same was true of terramycin solutions. Lipnik, Kligman and Strauss (1952), repeating Pappenfort and Schnall's experiment, confirmed that aureomycin solutions from the oral capsules had a stimulant effect on the growth of candida which none of the crystalline preparations had. The inert diluent or carrier in aureomycin capsules contains dibasic calcium phosphate. When Lipnik and his co-workers used this relatively insoluble salt alone, it increased the growth of candida. They concluded that the agent responsible for this was the phosphate ion and not aureomycin. Furthermore, they pointed out that Sabouraud's medium is deficient in phosphorus, an element required by the fungi. The addition of the phosphate salt merely corrected this deficiency. When 1% dibasic sodium phosphate was incorporated in Sabouraud's medium, there was no longer any stimulant effect from the capsule form of aureomycin. It is doubtful, therefore, if the overgrowths of candida in man are the result of direct growth stimulation by aureomycin. In the patients which I studied during antibiotic therapy, the aureomycin group did not have an excessively high proportion of persons with

overgrowths of yeasts.

There was an increase from nil to 60% with heavy growths of candida in the faeces during a course of aureomycin. McVay and Sprunt (1951) found an increase from nil to 67% with candida in the faeces in a group of 30 patients given aureomycin for seven days. On the other hand, in a group of 15 patients given aureomycin with paraben, only 13% became positive for candida. In keeping with this is my finding that the addition of paraben to aureomycin tended to inhibit the growth of candida in the sputum and faeces. When McVay and Sprunt gave 800mg of both esters of paraben daily for 4 days to patients who had overgrowths of candida as a result of aureomycin therapy, they found that the yeasts persisted. Paraben therefore cannot remove yeasts once they are established in the microflora. Siegel (1953) found that paraben inhibited the growth of candida in vitro in low concentrations. It had a low toxicity and did not interfere with the antibacterial action of aureomycin. Paraben, therefore, has a place as a prophylactic agent against the overgrowth of candida during antibiotic therapy. In developing this idea McVay and Sprunt (1953) showed that the long term administration of the broad spectrum antibiotics was both practicable and profitable to certain patients. Using aureomycin to which paraben had been added they gave 500mg

daily for an average of eleven months to 21 patients with chronic bronchitis. In these patients the frequency of fresh respiratory infections was greatly reduced. Moreover, in the 4 patients whose sputum yielded candida, the growth did not become heavier.

Even if aureomycin is a growth factor for candida, it does not explain the growth of the organism which appeared during chloramphenicol or terramycin therapy. It has not so far been demonstrated that chloramphenicol encourages the growth of candida. The reason for the overgrowths must lie in some property common to all three antibiotics. An experiment was carried out by Paine (1952) in which when equal quantities of coliforms and candida were mixed in a flask, culture of the mixture resulted in a heavy growth of coliforms and yeasts were suppressed. On addition of antibiotic to the mixture, culture showed that the coliforms were eliminated and candida grew abundantly. In this experiment the effects of chloramphenicol, aureomycin and terramycin were more or less identical. The three drugs have a similar antibacterial spectrum and are essentially the same in pharmacological behaviour. It is more likely that herein lies the explanation for the overgrowths of yeasts. They are the result of the suppression of antibiotic sensitive organisms. The present investigation strengthens

the previous argument. When adequate concentrations of antibiotic are maintained in an area where the normal microflora contains susceptible organisms, then candida may overgrow.

Section 2. THE GROWTH OF COLIFORMS

For the surgeon one of the advantages afforded by modern chemotherapy is the increased safety with which he can undertake major operations. Antibiotics are widely employed as prophylactic agents against post-operative infection. In this connection it must be borne in mind that the antibiotic is a two-edged weapon. Antibiotics do not always entirely suppress post-operative infection and the infection may pursue such a mild course that its familiar signs and symptoms are not only modified but even quite absent. This low grade infection may be the result of the bacteriostatic rather than the bactericidal effect of the antibiotic on highly virulent organisms or the infection may be due to resistant organisms of low pathogenicity. In 1952 Lake drew attention to the masking effect by antibiotics of the appearance of post-operative sub-phrenic abscess. There may be a collection of pus under the diaphragm even when abdominal palpation reveals no abnormality and of course ill-health persists in the patient until the pus is evacuated.

The other sphere in which the surgeon uses antibiotics prophylactically is in the preparation of patients for surgery of the bowel. The intestinal organisms are not pathogenic as long as they remain in the bowel but if they gain access to

other tissues in large quantities they can cause an infection. This is particularly liable to happen during and after resection of part of the bowel when the peritoneum may be soiled by many intestinal organisms resulting in peritonitis. The broad-spectrum antibiotics by their effectiveness against Gram negative as well as Gram positive organisms are peculiarly suitable as pre-operative antiseptics.

The organism most numerous in the colon and pathogenic when it gains access to the peritoneal cavity in large numbers is Escherichia coli. In 1886 Escherich isolated the organism from normal faeces and named it Bacterium coli commune. The name Escherichia coli (E.coli) is now replacing the older name Bacterium. The organisms in the coliform group are characterised by the fact that they are Gram negative bacilli which ferment lactose broth with the production of acid and gas. The group includes both E.coli and Aerobacter aerogenes. This latter organism was first described in 1885 by Escherich who found it in souring milk. It is also a common intestinal organism but, unlike E.coli, is not uncommon in nature outside the alimentary tract. It differs from E.coli in its total absence of flagellae i.e. it is non-motile and it is almost never pathogenic in man.

In both the pneumonia and tuberculosis series the

disappearance of coliforms from the faeces was noted during therapy. Since no attempt was made to distinguish between E.coli and Aerobacter aerogenes, these organisms are referred to as coliforms.

METHOD

Each rectal swab from the pneumonia series and a loopful of faeces from each specimen from the tuberculosis series were inoculated on to MacConkey's medium, incubated for 24 hours at 37°C and coliform colonies were identified by their morphology and microscopic appearance. Typically the colonies were moist, pink and opaque. In the Gram film of the faeces of the tuberculosis patients Gram negative bacilli were recorded as "absent", "scanty" or "heavy".

I personally carried out the examinations for coliforms.

RESULTS

A. PNEUMONIA SERIES. The findings in the two treatment groups are shown in Table 19. The figures include the patients admitted to the series but in whom a diagnosis of pneumonia was not

confirmed; patients who died before the full series of swabs

TABLE 19. - PNEUMONIA SERIES - DISAPPEARANCE OF COLIFORMS FROM RECTAL SWABS.

	GROWTH OF COLIFORMS	ADMISSION	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
TERRAMYCIN GROUP (85 cases)	Absent	0	24	36	37	27
	Scanty	9	2	3	1	0
	Heavy	76	59	46	47	58
SULPHADIAZINE GROUP (69 cases)	Absent	0	15	20	16	22
	Scanty	7	2	1	0	2
	Heavy	62	52	48	53	45
PENICILLIN GROUP (16 cases)	Absent	0	2	2	5	3
	Scanty	0	1	2	2	1
	Heavy	16	13	12	11	12

were taken are excluded. In the terramycin group coliforms disappeared from the intestinal tract in 36 (43%) of the cases by the fifth day compared with 20 (29%) in the sulphadiazine group. Two days after treatment had been stopped, i.e. on

the seventh day in hospital, coliforms were absent in 37 (44%) of the terramycin group and in 16 (23%) of the sulphadiazine group. In the small group receiving penicillin in addition to sulphadiazine, in 2 cases (12.5%) on the fifth day, 5 (30%) on the seventh day and 3 (19%) on the ninth day coliforms failed to grow. As penicillin has no effect on Gram negative organisms one would not expect this group to differ from the group receiving sulphadiazine only.

B. TUBERCULOSIS SERIES. Table 20 shows the findings of microscopic and culture examinations for coliforms in 35 patients during a course of chloramphenicol; 20 patients during a course of aureomycin (the 5 patients who received paraben aureomycin are included here), and 25 patients during a course of terramycin.

In the series of 80 patients, no coliforms grew on MacConkey's medium in 21 (26%) after 8g of antibiotic nor in 17 (21%) after 16g of antibiotic. Coliforms were reduced or absent on culture of the faeces in 32 (40%) after 8g and in 31 (39%) after 16g. This indicates that no advantage was gained by prolonging the course beyond 8g of antibiotic. In the direct film examination, coliforms were reduced or absent in 42 (52%) after 8g and 39 (49%) after 16g. These figures are all slightly higher than those obtained on culture of the

specimen.

TABLE 20. - TUBERCULOSIS SERIES - DISAPPEARANCE OF COLIFORMS FROM THE FAECES.

ANTIBIOTIC	GROUP	TOTAL	NUMBER OF FAECES WITH COLIFORMS					
			ABSENT		SCANTY		HEAVY	
			D/F	McC	D/F	McC	D/F	McC
Before	Chlor.	35	0	0	0	0	35	35
	Aureo.	20	0	0	0	0	20	20
	Terr.	25	0	0	0	0	25	25
	Series	80	0	0	0	0	80	80
After 8 g.	Chlor.	35	1	2	7	4	27	29
	Aureo.	20	8	5	6	2	6	13
	Terr.	25	15	14	5	5	5	6
	Series	80	24	21	18	11	38	48
After 16 g.	Chlor.	35	2	4	4	6	29	25
	Aureo.	20	7	2	7	3	6	15
	Terr.	25	15	11	4	5	6	9
	Series	80	24	17	15	14	41	49

D/F. = DIRECT FILM.

McC. = CULTURE ON MacCONKEY'S MEDIUM.

Comparison of the three antibiotics shows that in

eliminating coliforms from the bowel, terramycin was most effective, aureomycin next and chloramphenicol least effective. After 8g of terramycin, coliforms were reduced in 19 (76%) and absent in 14 (56%); the corresponding figures for aureomycin were 7 (35%) and 5 (25%) and for chloramphenicol 6 (17%) and 2 (6%).

In considering the results in the pneumonia series together with those in the tuberculosis series, it must be remembered that cultures from rectal swabs are being compared with culture of actual specimens of faeces. In the two terramycin groups the proportions in which coliforms disappeared from the lower bowel are similar. In the pneumonia group after 14.2g, the figure was 36 (43%) compared with 11 (44%) after 16g in the tuberculosis group. Comparison of sulphadiazine, aureomycin and chloramphenicol shows that sulphadiazine was indeed a more active drug against coliforms than either of these two antibiotics. After 35g sulphadiazine, coliforms were absent in 20 patients (29%); after 16g aureomycin in 2 patients (10%) and after 16g chloramphenicol in 4 patients (11%).

DISCUSSION

The finding that coliforms may not be seen on microscopic examination of a Gram stained film of faeces, even although these organisms may be grown on culture of the same specimen, is of interest. It is well known that bizarre forms of coliforms appear during antibiotic therapy. The bacilli become elongated and curving with swellings along their course. It may be that some which undergo this change lose their staining properties and become indistinguishable as organisms in the Gram negative debris of the faeces and yet are capable of growing in favourable media.

The use of any one of the four drugs was not dramatically effective in reducing the numbers of the intestinal flora. Although terramycin was the best, in about half of the patients coliforms persisted. The probable reason for the poor results lay in the fact that as the patients were not being prepared for surgery, no adjuvants in the sterilisation of the bowel were used. The reduction of the total number of bacteria in the large intestine greatly enhances the effectiveness of terramycin. When terramycin is given in adequate dosage to patients with a smaller concentration of bacteria in the intestine its action becomes bacteriocidal. Baker and Pulaski (1950) gave 11 patients a low residue diet and aided the mechanical emptying of the colon

by the use of saline purgatives or enemata. When terramycin was subsequently given in a dosage of 2g followed by 0.5g six-hourly for 5 days, coliforms were eliminated in all but 1 patient, maximal suppression occurring in 72 hours.

The conclusion on the superiority of terramycin is in keeping with that of Di Caprio and Rantz (1950) who claimed that terramycin was the best drug in the preparation of patients for surgery of the bowel. They gave 7 patients 3g of terramycin daily, in 5 of whom coliforms were eliminated in 48 hours and in the other 2, diminished. Linsell and Fletcher (1950) found that on a dose of 1g terramycin six-hourly coliforms were diminished within 24 hours and absent by the third day. Less enthusiastic reports have been published concerning the efficacy of aureomycin. Metzger and Shapse (1950) giving 5 patients 1g aureomycin t.i.d. for 5 days, found that the degree of suppression of coliforms obtained was inferior to results using sulphonamides or streptomycin. Pulaski and Connell (1949) obtained similar results on giving 2g aureomycin daily to their patients. E.coli was reduced but less so than with sulphonamides or streptomycin and other organisms were not at all affected. They concluded that aureomycin held no promise as an intestinal antiseptic.

The reason for the differences in results from the use

of the three antibiotics may lie in their pharmacology. After a single dose of 1g all three antibiotics are excreted in large amounts in the faeces in the following descending concentrations - terramycin 550μg/g; aureomycin 400μg/g and chloramphenicol 450μg/g (Welch, 1950). Again, greater amounts of chloramphenicol are inactivated in the body and consequently the concentration of active drug in the faeces may be even lower. Herrell, Heilman and Wellman (1950) pointed out that the concentration of antibiotic in the urine bears no relation to its therapeutic efficacy in urinary infections. A similar principle may govern the concentration in the faeces. Although chloramphenicol is very effective in the treatment of typhoid fever, the causative organism here is not confined to the intestinal tract. Chloramphenicol was found by Woodward, Smadel and Ley (1950) to be ineffectual in treating typhoid carriers.

Sulphadiazine is a drug readily absorbed from the intestine and is excreted in small amounts in the faeces. Hawking (1942) found that the concentration of sulphadiazine was 5.7mg/100ml of faeces compared with 900mg/100ml for sulphaguanidine after the same dosage. Sulphadiazine, by its greater potency, can overcome to some extent the disadvantage of its low concentration in the faeces. The relatively insoluble sulphonamide derivatives such as sulphaguanidine and sulphasuxidine,

however, have a higher degree of local activity against intestinal coliforms even although they have less intrinsic antibacterial activity (Poth, 1944). Possibly these sulphonamides should be preferred even to terramycin for reducing the bowel flora pre-operatively. Finland (1953) emphasised the importance of choosing as a prophylactic a drug other than the one which may have to be relied on in the treatment of the infection should it arise. The development of organisms which are resistant to the less potent prophylactic drug allows the more potent drug to be used with greater effectiveness later.

In the following chapter an attempt is made to estimate the significance of the overgrowths of candida, especially in those patients who had toxic reactions from antibiotic therapy.

CHAPTER IV.

THE RELATIONSHIP BETWEEN THE CLINICAL SIDE-EFFECTS OF ANTIBIOTICS AND THE GROWTH OF CANDIDA ALBICANS

Table 21 shows how often overgrowths of candida were found in association with the side-effects noted in the patients.

TABLE 21. - RELATION OF SIDE-EFFECTS OF ANTIBIOTICS TO GROWTH OF CANDIDA.

	SIDE EFFECT	TOTAL	GROWTH OF CANDIDA			
			Absent	Scanty	Heavy	Site
Pneumonia Series Terramycin Group (75 cases)	Diarrhoea	3	0	0	3	Rectum
	Atrophic Glossitis	7	4	0	3	Throat
	Black Tongue	1	0	0	1	Tongue
Tuberculosis Series (80 cases)	Gastric upset	19	3	3	13	Faeces
	Diarrhoea	41	3	8	30	Faeces
	Atrophic Glossitis	9	5	3	1	Tongue
	Black Tongue	6	0	2	4	Tongue
	Ano-Rectal Syndrome	4	1	2	1	Anus

It is unlikely that gastric upset was in any way related to the overgrowth of candida. The high acidity of the normal gastric contents does not permit the establishment of a microflora either of bacteria or yeasts. When the covering of the oral capsule dissolves in the stomach the antibiotic is liberated in high concentrations. The direct irritant effect of the antibiotic on the gastric mucosa seems the most reasonable explanation

for the nausea, vomiting and epigastric pain. In support of this is the finding by Finland, Grigsby and Haight (1954) that there was less gastro-intestinal upset during terramycin and aureomycin therapy if smaller individual doses were used. Furthermore, gastro-intestinal upset was less frequent in patients on a six-hourly than on a four-hourly dosage regime.

Antibiotics are excreted in fairly high concentrations in the faeces and here again, irritation of the intestinal mucosa by the antibiotic may result in diarrhoea. Most of the drug, however, has been absorbed and the remainder thoroughly mixed and diluted with the intestinal contents by the time it reaches the lower bowel. Also, many of the patients with diarrhoea did not have gastric irritation, suggesting that some other factor contributes towards the diarrhoea. Table 21 shows that 38 patients (93%) with diarrhoea in the tuberculosis series had candida in the stools, in 30 (73%) of whom the growth was heavy and in the three patients in the pneumonia group with diarrhoea heavy growths of candida were obtained from the rectal swabs.

Woods, Manning and Patterson (1951) considered that the diarrhoea during antibiotic therapy was due to the over-growths of yeasts in the bowel. The connection between yeasts and diarrhoea has long been recognised. In 1924 Fleisher and

Wachowaik investigated the stools of 32 patients with diarrhoea and found yeasts in 63%. They tentatively suggested that the yeasts were the cause of the diarrhoea and in 1929 Ashford considered that infection with Monilia psilosis, now known to be identical with Candida albicans, was the cause of tropical sprue. Yeast extract is believed to increase the functional activity of the intestine and people taking brewer's yeast medicinally often complain of diarrhoea.

More recently, Merliss and Hoffman (1951) suggested that the yeasts were the result rather than the cause of diarrhoea, which was due to the rapid passage of the intestinal contents through the lower bowel. This resulted in organisms normally found higher up in the alimentary canal being excreted in large quantities in the faeces and candida may have been such an organism.

The third possibility is that candida in the stool is merely an incidental finding and of no significance. In support of this is the fifty pneumonia patients in the present investigation who had heavy growths of candida in the rectum as a result of terramycin therapy, yet only three had diarrhoea. It cannot be disputed, however, and my findings are in agreement with this, that a person with diarrhoea is more likely to have candida in the stools than a normal person. Whether candida has any

aetiological relationship to the diarrhoea has by no means been established.

Among the other side-reactions found, the one with which candida is associated in the minds of most physicians, is black tongue. Even here, the relationship is not thoroughly clear, although in five of the seven patients with black tongue, heavy growths of candida were obtained from culture of tongue swabs. Tomaszewski (1953) examined microscopically tongue scrapings from patients with black tongues after antibiotic therapy and found candida in 60%. In all cases the antibiotic had diminished the bacterial flora and in 40% it was absent. His investigation showed that there was no special type of flora associated with black tongue and he considered that the presence of candida was merely incidental.

Even if infection with candida is not the aetiological factor in black tongue it is possible that it is the factor which keeps the condition going after antibiotic therapy is stopped. Unlike diarrhoea which usually ceases when the antibiotic is discontinued, black tongue does not clear up so quickly. In the present seven patients, the tongue eventually reverted to normal but the process was slow and gradual over a period of one to four weeks. Rubbing the tongue four hourly with a swab soaked in Collute Thymol Co B.P.C. improved the

condition. A special mouth wash of paraben esters dissolved in 50% glycerine and water was prepared for these patients and this also was found to be of benefit.

Tomaszewski examined tongue scrapings from people with idiopathic black tongues and again found candida in 60%. He made the interesting observation that antibiotic lozenges or troches can actually be a cure for black tongue. By their local action they denude the surface of the tongue of the accumulated debris. It seems reasonable that it is the same local action which causes the atrophic type of glossitis. Even after swallowing the capsules, sufficient antibiotic is excreted in the saliva (Kraus, Casey and Johnson, 1951) to cause this local irritant effect. Fisher and Leider (1951) found that patients given troches containing as little as 15mg of antibiotic were more liable to have oral symptoms of mucosal irritation than patients who swallowed the full dose in capsules. In the present series no relation was found between atrophic glossitis and the growth of candida in tongue swabs.

The ano-rectal syndrome is possibly a result of the overgrowth of candida within the rectum but the relationship is not constant. In 3 of the 4 patients with this syndrome, candida was present in the skin round the anus and all of them had heavy growths of candida in the stools. Harris (1950) and Tomaszewski

found candida in the exudate or skin round the anus in some of their patients with symptoms of anal irritation and Willcox (1951) in 2 of his 5 patients with the syndrome. They thought that local infection with candida might be responsible for the symptoms but Lipnik, Kligman and Strauss (1952) considered that the symptoms could be more readily attributed to local irritation by the antibiotic. Its high concentration in the rectum caused rectal irritation and leakage of small amounts of fluid laden with antibiotic caused irritation of the surrounding skin.

In the mouth, only the appearance of typical thrush is diagnostic of monilial infection. None of the present cases showed this but Woods, Manning and Patterson found it in their 20 cases of oro-pharyngeal moniliasis following antibiotic therapy.

Another side-effect which I did not observe and which is possibly related to candida is perlèche. It occurred in 11% of Harris's patients and in 2 of them he found candida in the lesion. He considered, however, that the alteration by antibiotics of normal intestinal life interfered with the synthesis of vitamin B. Although the mucous membrane lesions developed too rapidly to be due to avitaminosis he thought that candida was a secondary invader in patients, the resistance of whose tissues had been lowered by vitamin B deficiency.

The clinical course of candida infection appears to be governed, not by any property of the organism itself but by the general state of health of the host. Many people harbour small numbers of yeasts in the respiratory and alimentary tracts and in them the organism has been incorporated in the commensalism typical of the normal microflora. The finding that candida is the predominant organism in the microflora implies that the other components have been eliminated and the agents most often responsible for this are the antibiotics. Even these overgrowths of candida seldom give rise to signs of clinical infection.

Patients who are heavily infected with candida may be classified as falling into one of three categories. In the first the overgrowths of candida remain harmless saprophytes and are only known to be present when they are deliberately sought. This is by far the commonest and in it fall most of the patients in the present investigation. In the second category, candida gives rise to symptoms and signs of a superficial mycotic infection which does not endanger the patient's life. Into this fall the seven patients with black tongue. The third category is one where the superficial moniliasis goes on to become a deep mycosis which may be fatal. This rare occurrence did not befall any of the present patients.

In conclusion, it must be admitted that I found little evidence that candida has a significant bearing on the side-effects of antibiotics. We are on fairly firm ground in believing that candida in the mouth plays an important role in maintaining the condition of black tongue. The mere isolation of candida from the lesions of patients with other side-effects does not establish it as the cause of the symptoms and signs. We must take into account the patients with toxic reactions from whom candida was not obtained and also, the other patients with overgrowths of candida who did not have side-effects. Lipnik, Kligman and Strauss believed that the local maintenance of a fairly high concentration of antibiotic was the main factor in causing side-effects. That it does this through the medium of candida infection is very doubtful. It appears that candida, even when it overgrows during antibiotic therapy, remains for the most part a harmless saprophyte.

In the first section of the next chapter the symptom of diarrhoea is investigated. Since it did not appear to be the result of candida infection of the intestinal tract and it was the most constant side-effect of antibiotic therapy, it seemed possible that it was due to some other change in the intestinal tract wrought by antibiotic therapy. The effect of antibiotics on fat absorption and then on intestinal transit time is studied.

In the second section the effect of antibiotic therapy on the pH of the saliva is examined. The pH findings are then examined further to discover if any relationship exists between the pH of the saliva or sputum and the growth of candida in the throat or sputum.

CHAPTER V.

FURTHER INVESTIGATIONS ON THE SIDE-EFFECTS OF ANTIBIOTICS

Section 1. THE CAUSE OF DIARRHOEA

The occurrence of diarrhoea in 51% of the tuberculosis series was the more surprising since so few of the pneumonia patients on terramycin treatment had complained of it. Admittedly their dose of terramycin was smaller, 14.2g in five days, compared with the 16g in four days which the tuberculosis patients received. The difference, however, was not felt to be sufficiently great to account for the absence of diarrhoea in the pneumonia patients.

One disparity in the two groups lay in the diet. For the first 48 hours, the pneumonia patients were mainly on fluids and then on light diet while the tuberculosis patients were on a generous full diet. It was possible that during antibiotic therapy there was defective absorption of food from the bowel thus accounting for the bulky stools. Since fat absorption is a good indication of absorption of foodstuffs generally, it was decided to control the fat intake in a group of tuberculosis patients and measure the fat output before and during a course of antibiotic.

MATERIAL AND METHODS

Six patients were studied. With the help of the College of Domestic Science a diet containing 90g fat was made up. This rather generous amount of fat was allotted because the patients were suffering from pulmonary tuberculosis, but nothing outside the diet was allowed. The patient was on the diet for 24 hours before the collection of stools was begun. A commode containing a lid-covered tin was used by the patient and at the end of each 24-hour period, the tin was removed and a fresh one substituted. The diet and collection of stools were continued for 14 days. After the first four days, terramycin 1g six-hourly was given for a further four days up to a total dose of 16g. Accordingly the duration of the test can be divided into three periods:-

D1-4	...	before terramycin
D5-8	...	during terramycin
D9-14	...	after terramycin

The appearance of each collection of stool was noted and a loopful inoculated on to Sabouraud's medium for the detection of yeasts.

Estimation of Faecal Fat. The total higher fatty acids in the faeces were estimated by the method described by van de Kamer et al. (1949). The details of the method which I followed were adapted from van de Kamer by Professor A.C. Frazer,

Department of Pharmacology, Birmingham University.

On a mechanical mixer (Kenmix) of just under 1 litre capacity the level reached by 750ml of water was marked. The 24-hour collection of stool was poured into the empty mixer and the volume made up to the mark 750ml with tap water from a measuring cylinder. The volume of faeces was estimated by the difference. The lid was screwed on tightly and the mixer run at full speed for one minute. Before sedimentation or creaming occurred, a 10ml aliquot of the emulsified faeces was transferred with a 10ml syringe fitted with an enlarged exit tube into a 250ml ground glass stoppered conical flask. To this was added 47ml of alcoholic 3% potassium hydroxide containing 0.4% amyl alcohol. A few chips of porous pot were placed in the flask which was fitted with a reflux condenser and the mixture was boiled on a steam bath for twenty minutes. The flask was cooled under running tap water and 15ml of aqueous hydrochloric acid (2 water:1 concentrated acid) added. The digest was well cooled before the addition of the hydrochloric acid to prevent esterification of the fatty acids. The flask was cooled again and 50ml petroleum ether were added. The mixture was shaken vigourously for one minute and allowed to settle. Using a pressure pipette a 10ml aliquot of petroleum ether was transferred into a 50ml flask and, after the addition of 2ml of

neutral absolute alcohol, this was titrated with N/50 tetra methyl ammonium hydroxide. The neutral absolute alcohol was added to improve the mixing of the two solutions and thus enable direct titration to take place in the petroleum ether. The alkali was standardised against a known solution of benzoic acid. The indicator used was thymol blue and if any hydrochloric acid had been carried over with the petroleum ether aliquot the indicator first showed red. Allowance was made for the quantity of alkali needed to change the colour from red to yellow as this was only titration of mineral acid. The end point was taken as the first change of the solution after shaking from yellow to green.

Calculation

Daily excretion of fatty acid (as stearic acid M.Wt. 284) =

$$v \times \frac{(284 \times N \times V \times 50)}{(1{,}000 \times 10 \times 10)} \text{ in grams}$$

$$= v. \frac{284 \times 1 \times 750 \times 50}{1{,}000 \times 50 \times 10 \times 10}$$

$$= v. \ 2.13g$$

v = titration figure

N = normality of standard alkali

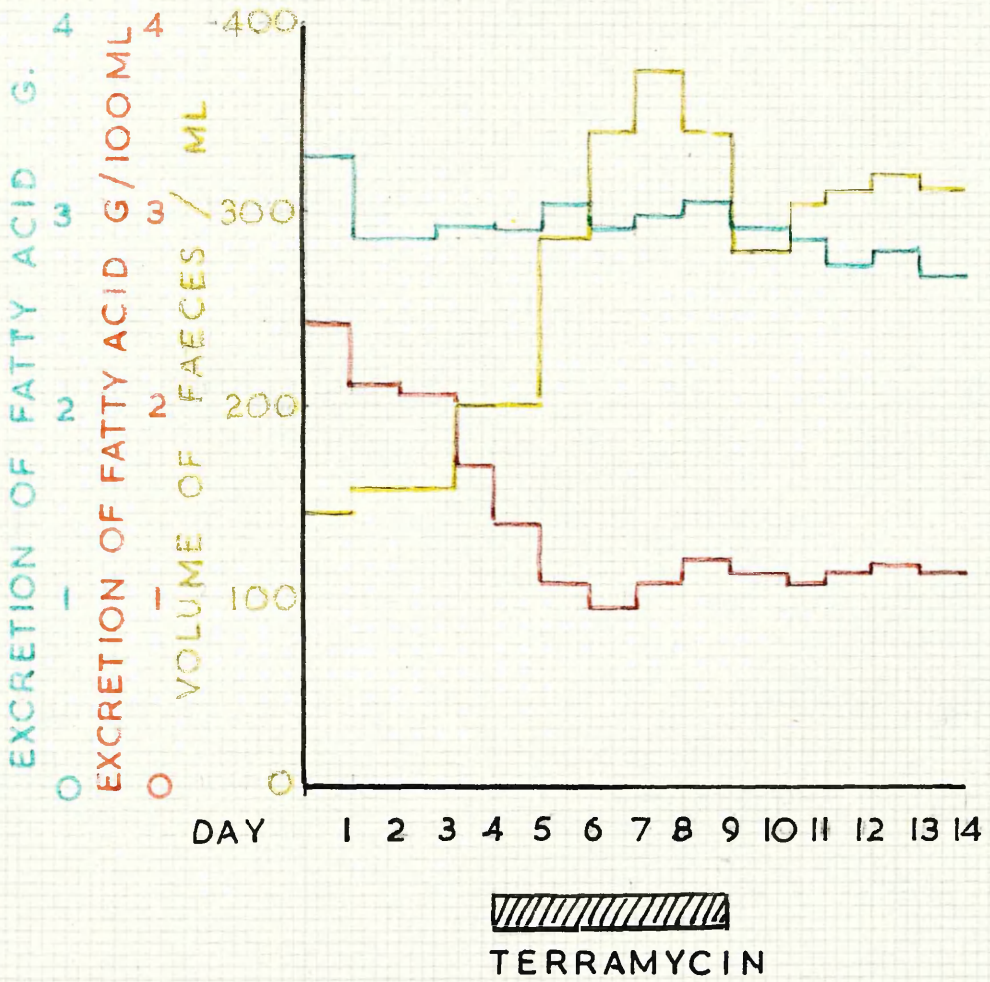
V = total volume of emulsified faeces.

For ten days the amount of fat in samples of ordinary milk was estimated and then in three 24-hour collections of stools from patients on ordinary diet. When I was satisfied

FIG 4

ESTIMATIONS OF FAECAL FATS

RESULTS FOR SIX PATIENTS EXPRESSED AS THREE-DAY MEANS



that the method was giving accurate results and when titration figures could be duplicated within 0.5ml of each other, the patients, two at a time, were started on the controlled diet.

RESULTS

For each of six patients a daily record for 14 days was obtained of the volume of faeces, the excretion of fatty acid in g, thence the excretion of fat in g per 100ml of faeces, the appearance of the stools and their growth of candida. These records are given in full in Appendix IV. but the findings have been summarised in Table 22 which shows the mean readings for one day for each patient during the three periods, before, during, and after terramycin. Each patient conformed to the same pattern; the daily output of faeces increased in volume during the terramycin period and remained high until the end of the two weeks; the daily excretion of fatty acids remained fairly constant but it followed that the excretion of fat in g per 100ml of faeces fell when terramycin was started. The mean daily results for the six patients expressed as three-day averages to give a sliding graph are shown in fig.4.

The stools became abnormal and although individual findings are not shown in the table many became green, odourless

TABLE 22. - RESULTS OF FAECAL EXAMINATIONS
(six cases)

PERIOD	MEAN DAILY VOL. OF FAECES (ml.)	MEAN DAILY EXCRETION OF FATTY ACIDS (g.)	EXCRETION OF FAT g./100 ml.	APPEARANCE OF STOOL	GROWTH OF CANDIDA
D1 - 4	110	3.6	3.4	Normal	Absent
	130	2.3	2.0	"	Scanty
Before	220	3.4	1.55	"	Absent
	170	2.3	1.4	"	"
Terramycin	210	4.4	2.2	Soft	"
	80	2.6	3.25	Normal	"
Mean	152	3.1	2.3	Normal	Absent
D5 - 8	210	3.1	1.6	Loose	Heavy
	270	2.9	1.25	Soft	"
During	295	3.0	1.1	"	"
	270	2.2	0.8	"	Scanty
Terramycin	552	5.0	1.6	Loose	Heavy
	248	2.6	1.1	"	"
Mean	308	3.1	1.24	Soft-Loose	Heavy
D9 - 14	217	3.7	1.7	Soft	Scanty
	282	2.0	0.74	"	Heavy
After	303	3.0	1.28	Normal	"
	202	2.0	1.34	"	Scanty
Terramycin	548	4.1	0.8	Soft	Heavy
	298	2.5	0.97	Normal	Scanty
Mean	309	2.9	1.14	Soft-Normal	Scanty-Heavy

and contained excess mucus. All the patients but one had heavy growths of candida during the course of terramycin.

The results indicate that the absorption of fat remained normal during terramycin therapy but the volume of faeces did increase and candida flourished in the abnormal stools. Accordingly, it was concluded that the increase in bulk of the stools was not due to unabsorbed foodstuffs.

.....

It seemed advisable to ensure that the diarrhoea was peculiar to the tuberculosis patients and was not occurring unobserved in the pneumonia patients. In an attempt to measure the symptom objectively, the faeces excreted during the first week in hospital, i.e. including the five days of therapy, were weighed in the case of ten pneumonia patients receiving terramycin and, as controls, in the case of ten patients receiving sulphadiazine.

METHOD

This was carried out by the ward sister or staff nurse during the day and by the nurse in charge during the night. Each bed-pan, after use, was drained of any urine and weighed on scales. By subtracting the weight of the bed-pan, the weight of faeces was obtained and recorded in a book. At the end of a

week these were added to give the total weight of faeces excreted during the week.

RESULTS

Table 23 shows that the mean weight of faeces for one week was more or less the same whether the patient was on terramycin or sulphadiazine therapy. Increased output of faeces

TABLE 23. - WEIGHT OF FAECES
(10 cases)

	TERRAMYCIN GROUP	SULPHADIAZINE GROUP
Weight of faeces excreted during first week in hospital (oz.)	56	82
	59	23
	62	16
	37	30
	17	27
	17	40
	28	23
	34	30
	18	20
	26	24
MEAN (Oz.)	35.4	34.8

therefore seemed to occur only in patients who were well enough to be on full diet and who did not have to contend with such constipating factors as fever, low residue diet and complete confinement to bed.

.....

If the bulky stools were due to an irritant effect of the antibiotic on the intestinal mucosa, it was hoped that intestinal hurry might be demonstrable in the patients with diarrhoea. The only method of measuring transit time in the small intestine is radiological (French, 1952). The time after swallowing in which the head of a simple barium meal reaches the caecum is observed. Although there are wide variations, about 2 hours is considered normal in adults. If the barium reaches the caecum in less than an hour, the intestine may be regarded as hypermotile but if the barium with the stimulus of food has not reached the caecum in 5 hours then hypomotility is present. This investigation was carried out in six of the tuberculosis patients.

METHOD

Six patients, two at a time, who had been starved for 12 hours were given a small barium meal of 2 oz. at 8.30 a.m. and X-ray films were taken at $\frac{1}{4}$ hour intervals starting at 9.30 a.m. until the barium appeared to have reached the caecum. No food was given during this time. The films were scrutinised by the hospital radiologist and the time taken for the meal to reach the caecum noted.

The patients were then given terramycin 1g six-hourly. If they had an increase in number or bulk of stools, then after

the last dose at 6 a.m. to complete the course of 16g, a further 2 oz. of barium were given at 8.30 a.m. and the time when it reached the caecum noted as before.

RESULTS

Table 24 shows that there was little alteration in the small intestine transit time before and after 16g of terramycin.

TABLE 24. - SMALL INTESTINE TRANSIT TIMES
(six cases)

	BEFORE TERRAMYCIN	AFTER 16 g. TERRAMYCIN
Time after swallowing for 2 oz. Barium to reach Caecum (Hours)	$2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ $3\frac{1}{4}$ $2\frac{3}{4}$ $2\frac{1}{2}$	$2\frac{3}{4}$ 2 $3\frac{1}{2}$ $3\frac{1}{2}$ 4 2
MEAN (Hours)	$2\frac{3}{4}$	3

Intestinal hurry, if present, must then occur in the large intestine but unfortunately it was not practicable to measure the large intestine transit time in the patients.

.....

DISCUSSION

The foregoing results indicate that diarrhoea during antibiotic therapy is not associated with decreased absorption of fat, nor presumably with defective absorption of any other foodstuffs. I was also unable to demonstrate any evidence of intestinal hurry when measured by the transit time of a barium meal through the small intestine.

These findings are in disagreement with those of Merliss and Hoffman (1951) who investigated diarrhoea subsequent to antibiotic treatment in four patients. They found an increased amount of fat in the stools and a tendency for the diarrhoea, which was of a mild nature, to be aggravated by fat ingestion. All are features of steatorrhoea and they considered that the diarrhoea closely resembled that of the sprue syndrome and might even be identical with it. Since this condition arises from dysfunction of the small bowel, they concluded that the cause of diarrhoea following antibiotic therapy lay there. X-ray films of the small bowel in their four cases showed a deficiency pattern in one and considerable hyperactivity in another. This, together with the increased excretion of fat led them to believe that the origin of the diarrhoea was acute steatorrhoea. They postulated that the steatorrhoea resulted from deficiency of vitamin B complex due to destruction by antibiotics of the

intestinal bacteria which normally synthesise the vitamin. In Chapter III. it was shown that antibiotics were not very efficient in destroying coliforms in the intestine. It is therefore unlikely that the synthesis of vitamin B was disturbed to any extent in the present cases. Altogether and particularly in view of the normal fat absorption findings in these patients, it is difficult to believe that the diarrhoea is in any way related to that of the sprue syndrome.

An irritant effect of the antibiotic on the intestinal mucosa causing intestinal hurry still seems the most likely explanation for the bulky and frequent stools. Although measurement of the transit time in the small intestine did not show evidence of this, the artificial barium meal of small bulk was perhaps not such an effective stimulus to peristalsis as normal food.

Section 2. THE pH OF THE SALIVA

From the study it has emerged that patients treated with the newer antibiotics frequently had heavy growths of candida in the fauces and sputum. Some incidental change within the body secondary to antibiotic therapy may have encouraged the growth of yeasts.

It has been postulated that the unusually acid secretion in the mouth of the young infant may be the principal reason for the high incidence of oral thrush in infancy (B.M.J. 1950). In an investigation of neo-natal thrush, Ludlam and Henderson (1940) found that the pH of the saliva of the new-born infant was around 5.2 which, they said, was the optimum pH for the growth of the thrush fungus. Lilienthal (1950) showed that some synergistic activity occurred between lacto-bacilli and Candida albicans in experimental conditions and that this resulted in increased acid formation. A similar conclusion was reached by Fosdick and Hansen (1936) who incubated a mixture of saliva and powdered dental enamel. They found that saliva containing Lactobacillus acidophilus alone did not dissolve the enamel but when "a yeast isolated from the mouth" was added, sufficient acid was produced to dissolve it.

It was decided to find out if the pH of the saliva changed during antibiotic therapy and if there was any relationship

between the salivary pH and the presence of candida in the fauces. In the pneumonia patients, along with taking 391 throat swabs, I estimated the pH of the saliva with B.D.H. indicator papers and the results were correlated with the growth of candida from the corresponding throat swab. In the 112 swabs which were taken from patients on terramycin therapy, the salivary pH was correlated with the amount of terramycin the patient had received and, for purposes of comparison, the 113 swabs taken from patients on sulphadiazine therapy were dealt with in the same way.

TABLE 25. - pH OF SALIVA AND DOSE OF TERRAMYCIN.

PERIOD	NUMBER OF pH READINGS	MEAN SALIVARY pH
Before Terramycin	26	6.4
Before Sulphadiazine	31	6.4
After 10 g. Terramycin	41	6.3
After 25 g. Sulphadiazine	42	6.3
After 14.2 g. Terramycin	45	6.3
After 35 g. Sulphadiazine	40	6.3

The results show that the saliva did not become more

acid during terramycin (Table 25). Furthermore, there was no undue prevalence of candida with any particular pH (Table 26). The slight differences noted are not statistically significant (P = 0.1). In the pH range 5.5 to 6.1, 57 (30%) of the 189 throat swabs furnished a heavy growth of candida while in the pH range 6.4 to 7.0, only 35 (17%) of 202 swabs had heavy growths. Since this

TABLE 26. - pH OF SALIVA AND CANDIDA IN THROAT SWABS.

SALIVARY pH	NUMBER OF THROAT SWABS (Total 391)	NUMBER OF THROAT SWABS WITH CANDIDA		
		Absent	Scanty	Heavy
5.5	44	26	4 9%	14 32%
5.8	99	60	8 8%	31 31%
6.1	46	29	5 11%	12 26%
6.4	63	45	9 14%	9 14%
6.7	75	49	13 17%	13 17%
7.0	64	37	14 22%	13 20%

difference is only 1½ times its standard error of ±9 it is not significant.

On 185 occasions the estimation of the salivary pH coincided with the collection of a specimen of sputum from a patient. Table 27 shows that the presence of candida in the

TABLE 27. - pH OF SALIVA AND CANDIDA IN SPUTUM.

SALIVARY pH	NUMBER OF SPUTA (Total 185)	NUMBER OF SPUTA WITH CANDIDA		
		Absent	Scanty	Heavy
5.5	19	5	7 36%	7 36%
5.8	51	26	13 26%	12 23%
6.1	21	10	5 24%	6 28%
6.4	29	9	11 38%	9 31%
6.7	36	15	11 31%	10 28%
7.0	29	15	6 21%	8 27%

sputum was not associated with any particular salivary pH. In the pH range 5.5 to 6.1 25 (27%) of 91 sputa yielded a heavy growth of candida compared with 27 (29%) of 94 sputa in the pH range 6.4 to 7.0. In the passage of sputum through the mouth one would not expect the saliva to affect its content of candida.

The pH of the sputum itself, however, might have varied

according to the presence of candida. The pH was estimated directly in 48 sputa whose yield of candida was then compared with its pH. These pH readings extended into a more alkaline range than those of the saliva, 32 (67%) of them being higher than 7.0. As the numbers of sputa were rather small, the results have been grouped in pH ranges as shown in Table 28. In the pH

TABLE 28. - pH OF THE SPUTUM AND CANDIDA IN SPUTUM.

SPUTUM pH RANGE	NUMBER OF SPUTA (Total 48)	NUMBER OF SPUTA WITH CANDIDA		
		Absent	Scanty	Heavy
5.5 - 6.1	4	2	0 0%	2 50%
6.4 - 7.0	12	3	1 8%	8 67%
7.3 - 7.9	16	9	4 25%	3 19%
8.2 - 8.8	16	8	4 25%	4 25%

range 5.5 to 7.0, 10 (63%) of 16 sputa had heavy growths of candida while in the range 7.3 to 8.8, only 7 (22%) of 32 sputa had heavy growths. Thus more than half the sputa with heavy growths of candida had a pH which fell within the range of that found in the saliva in the mouth. As no salivary pH was found above 7.0, it suggests that a change occurred in the pH of some of the sputa after

their collection. Perhaps it was the presence of large numbers of yeasts which prevented the pH of the other sputa from becoming alkaline also.

The foregoing results indicate that the pH of the saliva is not altered by oral terramycin and also that heavy growths of candida may be obtained over a considerable range of salivary pH. The range of salivary pH in the patients was from 5.5 to 7.0. Young, Resca and Sullivan (1951) found that the pH of the saliva in 584 normal persons ranged from 5.0 to 7.5 and that most were between 6.0 and 7.0. They found, too, on culture of the saliva that 248 (48.6%) were positive for candida and the percentage of positive yeast cultures was higher in those with more acid salivas. The present findings are more in keeping with those of Karnaky (1946) who investigated 41 cases of monilial vaginitis and found that alteration of the vaginal pH had no effect on the growth of candida. He also demonstrated that candida grew well at any pH on Sabouraud's medium. It seems unlikely that the pH of the body fluids has any influence favourable or adverse on the growth of candida.

Diarrhoeic stools which are acid are a feature of tropical sprue and large numbers of yeasts are frequently found in these stools. In this condition the stools are acid because of unabsorbed fatty acids but in this series of patients the

excretion of fatty acids did not increase during antibiotic therapy. The relationship, therefore, between acid stools and their yield of candida is probably incidental rather than direct.

CONCLUSION

In the short space of 44 years since Ehrlich's discovery of salvarsan the scope of chemotherapy has expanded tremendously. The most recent impact on it has been the discovery of the broad-spectrum antibiotics. The field of antibiotic therapy alone is now so vast that it is impossible for any one person to do more than scratch its surface.

The present investigation has shown that in terramycin we have a valuable addition to the list of chemotherapeutic agents. It is an effective drug in the treatment of pneumonia. Its action is reliable; it can be administered easily in oral capsules and beneficial results are obtained in all age groups. Its main advantage over treatment with sulphadiazine and penicillin is that it produces a more rapid subsidence of fever. The low incidence of complications, the low death rate and the length of time taken for the pneumonic consolidation to resolve were all satisfactory, although equally satisfactory results in these respects were obtained with the control treatment.

The results have shown that adequate therapy alone, however, does not ensure recovery from pneumonia. Certain factors which influence the outcome in pneumonia are more important than the specific drug used in its treatment. These prognostic factors are, the age of the patient, the length of time

which elapses between the onset of infection and the institution of chemotherapy, the presence of a bacteriaemia, the extent of the consolidation and the presence of associated disease, particularly the degree of efficiency in the cardio-vascular system.

One disadvantage of treating patients with terramycin is the high cost of the drug compared with that of sulphonamides or penicillin. Another objection is that a straightforward case of pneumococcal pneumonia scarcely warrants the use of such a potent drug as terramycin. Sulphadiazine, supplemented by penicillin where necessary, is perfectly adequate for the majority of cases. Terramycin, however, with its wider range of antibacterial activity is preferable when the identity of the infecting organism is in doubt.

Terramycin, from the experience of this study, is free from serious clinical side-effects. In the pneumonia series toxic reactions were uncommon but comparison of the side-effects in the tuberculosis series during an antibiotic course showed that terramycin was rather more toxic than either chloramphenicol or aureomycin. Gastric upset occurred in about one third and diarrhoea in two thirds of the terramycin group of tuberculosis patients. The gastric upset was usually limited to a feeling of nausea and the diarrhoea, which was mild, cleared in all cases within a few days of discontinuing the drug.

One effect which arises from the very efficiency of the newer antibiotics against both Gram positive and Gram negative organisms is the frequency with which the normal microflora of the respiratory and alimentary tracts is replaced by overgrowths of Candida albicans. Elimination of the sensitive bacteria allows the insensitive yeasts to grow freely in the microflora. The growth of candida in the patients was shown not to be related to the age of the patient or to the presence of chronic chest disease. During and after antibiotic therapy overgrowths of yeasts were most marked in the rectum where before treatment it was rare to find a heavy growth of candida. Although heavy growths of candida were not unusual in the sputum and throat before treatment, the proportion of patients with such growths was greater after a course of antibiotic.

Secondary infection with resistant staphylococci, still another example of the results which may follow a disturbance of the normal microflora by antibiotic therapy, did not appear in any of the patients.

In diminishing the growth of intestinal coliforms terramycin was found to be more effective than either chloramphenicol or aureomycin but its action was not constant. This may have been due to the fact that the patients received none of the adjuvant measures which reduce the concentration of bacteria in

the intestine and thereby increase the effect of antibiotics.

The significance of overgrowths of candida in the patients who had side-effects to the antibiotics is a matter for speculation. The development of black tongue is probably the result of candida infection. Diarrhoea is related to yeasts but in view of the many pneumonia patients who had large quantities of yeasts in the rectum yet did not complain of diarrhoea, it is unlikely that the overgrowth of candida has any aetiological bearing on diarrhoea.

Fat absorption from the intestine was not defective during antibiotic therapy. Although unable to prove it, a direct irritant effect of the antibiotic itself seems the most reasonable explanation for its clinical side-effects. This effect on the mucosa of the alimentary tract would account for the gastro-intestinal upsets. A similar effect on the tongue and pharynx would explain the sore tongue and sore throat, and the irritation caused by fluid containing antibiotic could cause the ano-rectal syndrome.

The investigation has shown that a short course of a single antibiotic is unlikely to be followed by any serious clinical effects, even when it leaves Candida albicans as the predominant organism in the microflora. In a total of 160 patients who received a course of antibiotic, the only clinical evidence

of infection with candida was black tongue which occurred in 7 (4.5%). After the course of antibiotic heavy growths of candida, however, were present in 24 (42%) of the 57 throat swabs examined, 48 (47%) of the 103 sputa and 88 (55%) of the 160 rectal swabs or specimens of faeces. Moreover, 75 of those patients suffered from the debilitating disease, pulmonary tuberculosis, which might have been expected to render their tissues more susceptible to invasion by candida.

It is one of the principles of medical mycology that a fungus which is endogenous like candida is of low pathogenicity and only invades the tissues of the host when his resistance to infection is lowered by some other factor. Thus thrush is found particularly in premature or marasmic infants, in adults with an underlying disease and in the elderly and debilitated.

In the more widespread manifestations of moniliasis the same principle generally holds. Before the days of chemotherapy, patients with a fatal illness such as cancer commonly succumbed to a bacterial infection like pneumonia. Nowadays the practice of giving an antibiotic to a patient with signs of infection whether or not he already has a fatal illness, makes it unlikely that he will die of a bacterial infection. The newer antibiotics eliminate the infecting organism but the yeasts which remain may cause the terminal infection to be fungal rather than

bacterial. A close parallel to this type of illness is the infection with Gram negative organisms which occasionally follows penicillin treatment. The Gram positive organisms responsible for the primary infection are eliminated by penicillin but the resistant Gram negative organisms which remain cause a secondary infection. This form of re-infection occurred in four patients reported by Sommer and Favour (1949) and resulted in the death of two of them.

Similarly, moniliasis is rarely a sequel to a straightforward case which has been treated with antibiotics. A recent report was published by Brown et al.(1953) on three cases of fatal moniliasis after antibiotic therapy. These patients were typical of those who die of moniliasis in that they did not suffer from a simple bacterial infection in the first place and all had received several courses of antibiotic treatment. The first patient had aplastic anaemia and the second had a perinephric abscess secondary to a perforation of the duodenum which was found at autopsy. The third patient had suffered chronic ill health for thirty years and was admitted in coma. In establishing conditions favourable for the overgrowth of candida, the antibiotics no doubt contributed towards the fatal issue. The main responsibility for death, however, must lie with the primary disease which antibiotic therapy alone could not have been

expected to cure. The patient with a grave underlying disease and with overgrowths of candida in the microflora is unable to resist invasion of the tissues by the fungus. In them, moniliasis merely hastens a death which was already inevitable.

In conclusion, it may be stated that candida rarely becomes a pathogenic organism. Nevertheless, the continuing widespread use of the antibiotics must result in an increasing prevalence of antibiotic resistant organisms such as Candida albicans. Many of the present pneumonia patients were dismissed from hospital as early as the fourteenth day when they must still have been heavily infected with candida. Although the organism appears to be generally harmless, the exposure of young children in the home to candida infection is not without risk. Perhaps in them, and especially in debilitated children, candida could more readily assume its invasive properties.

The broad-spectrum antibiotics are extremely powerful weapons with which to combat disease. In their beneficent potency lies also their potential danger and consequently the administration of these drugs should be restricted to infections which warrant their use. The mere possibility of moniliasis should be a warning against their indiscriminate use as prophylactics or for minor infections.

APPENDIX I.

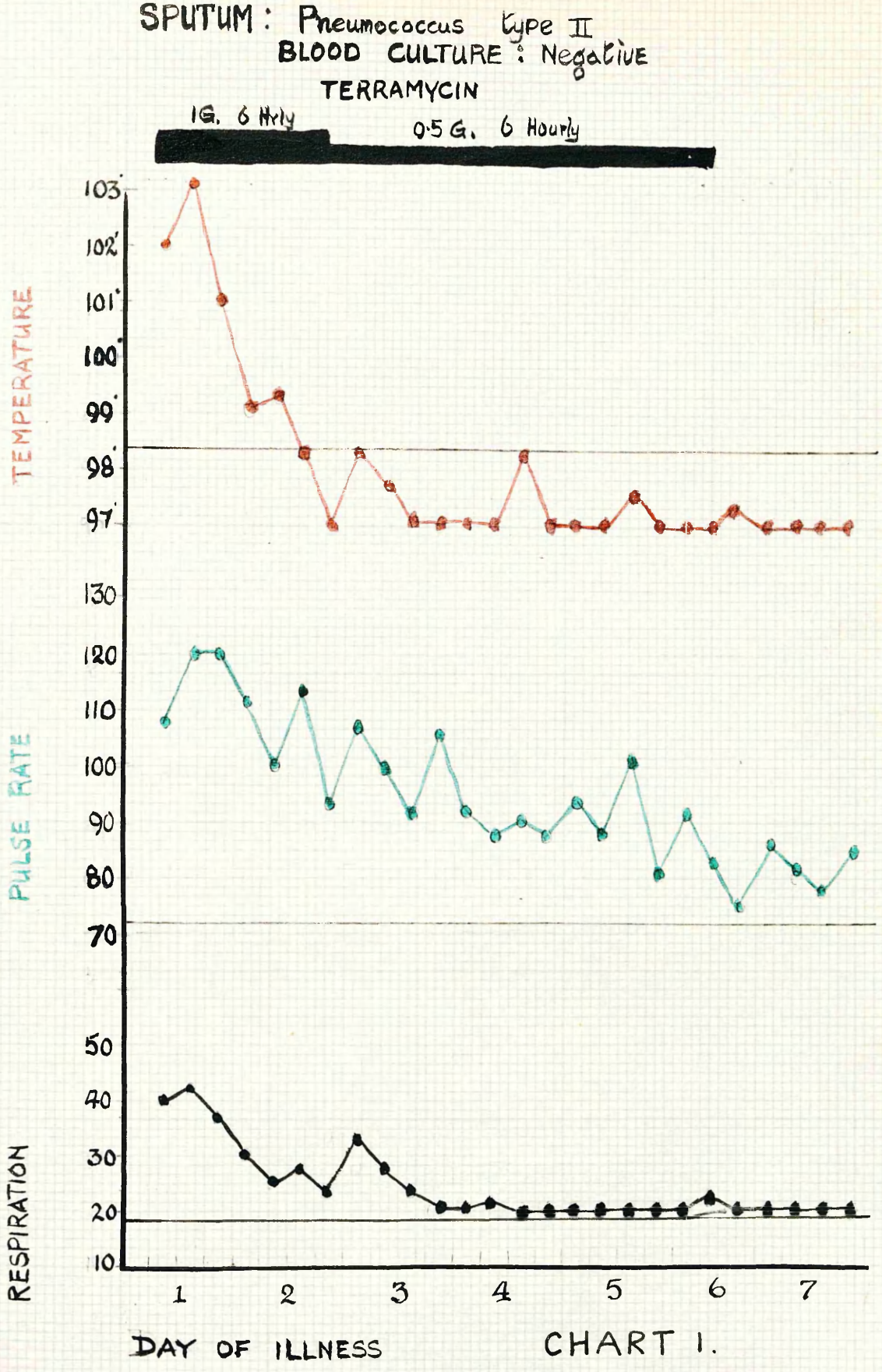
DESCRIPTION OF TWO CASES OF PNEUMONIA

Clinical details are given of two typical cases of pneumonia treated with terramycin.

Case 1. The patient was an electrical engineer of 23 years who was admitted on the first day of illness. He complained of a sudden onset of pleural pain, headache and rigors and had vomited twice. He gave no history of previous chest illness and had received no treatment prior to admission.

On admission his temperature was 102°F, pulse rate was 108 and respirations 40 (Chart 1). He was sharply ill and his tongue was dry and coated. Examination of the chest revealed signs of consolidation at the right base. X-ray of chest showed pneumonic consolidation of the right basal lobe. Sputum culture yielded pneumococcus type 2. Blood culture was sterile. White blood cells numbered 19,000/cmm with 94% polymorphs. Treatment was commenced with 1g terramycin six-hourly. After 6g the dose was reduced to 0.5g six-hourly, the total dose being 13g.

After 24 hours his temperature had fallen to 99°F and he felt much better. By the third day his tongue was clean, cough was loose and the pleural pain had almost gone. On the sixth day he got up to sit in a chair and on the eighth day he was allowed up to walk. By the eighth day his chest was


SPUTUM : Pneumococcus type II
BLOOD CULTURE : Negative
TERRAMYCIN
1G. 6 Hrly
0·5 G. 6 Hourly
TEMPERATURE
103
102
101
100
99
98
97
PULSE RATE
130
120
110
100
90
80
70
RESPIRATION
50
40
30
20
10
1
2
3
4
5
6
7
DAY OF ILLNESS
CHART 1.

clinically clear and he was discharged on the fourteenth day. X-ray of chest, however, did not show resolution to be complete until three weeks after the onset of the pneumonia.

.....

Case 2. A retired ship's carpenter aged 69 years was admitted on the third day of illness. Two days previously he had developed an unproductive cough and had had several rigors. He had suffered no previous chest trouble and had been given two tablets of oral penicillin before admission.

On admission his temperature was 100.2°F, pulse rate was 84 and respirations 24 (Chart 2). He appeared to be fairly ill and his tongue was lightly coated. Clinical examination of the chest showed signs of an early consolidation in the left upper zone. Consolidation of the left upper lobe was confirmed on radiological examination. Pneumococcus type 8 was grown from the sputum and blood culture was also positive for this organism; the pour plate showed 5 cols./ml. The white cell count was 5,000/cmm, 60% of which were polymorphs. He was given terramycin 1g six-hourly for 8g then 0.5g six-hourly to a total dose of 15g.

On the day after admission his temperature was normal and his general condition had improved. His chest was clinically clear on the sixteenth day and he made an uneventful recovery.

BLOOD CULTURE & SPUTUM
PNEUMOCOCCUS TYPE 8

TERRAMYCIN

1 G 6 Hourly

0·5 G 6 Hourly

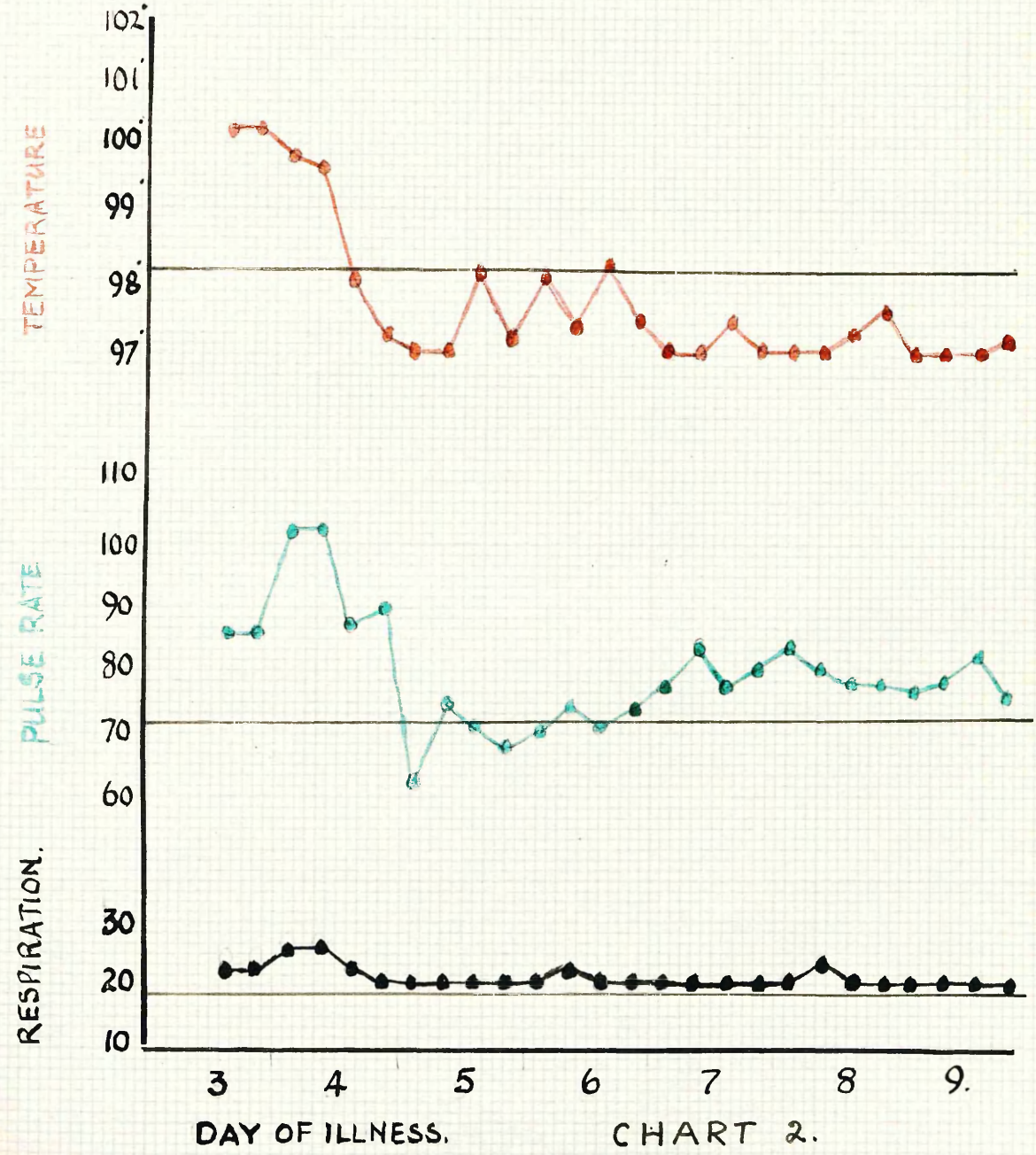


CHART 2.

He was discharged after 24 days in hospital but his chest was not clear radiologically until he reported back one month after discharge.

APPENDIX II.

The table on the following page gives details of the herpes febrilis in the pneumonia series.

Cases	Age Years	Day of Illness on Admission	Day of Onset of Herpes	Herpes at Height-day	Spread or Onset after start of Therapy	Day of Scab Formation	Day Healing Complete	Extent of Herpes						Treatment
								Upper Lip	Lower Lip	Angle of Mouth	Nose	Chin	Tongue	
1.	25	2	1	4	Yes	6	14	x	x	-	-	-	x	Terramycin
2.	46	3	4	5	Yes	7	14	x	x	-	x	-	-	"
3.	56	7	2	6	No	9	21	-	x	-	x	-	-	"
4.	38	2	3	4	Yes	6	11	x	x	-	-	-	-	"
5.	33	8	8	8	No	10	15	-	-	-	x	-	-	"
6.	57	5	4	5	No	7	11	-	-	x	-	-	-	"
7.	37	2	3	6	Yes	8	14	x	x	-	-	x	-	"
8.	48	5	3	5	No	9	15	x	-	-	-	-	-	"
9.	57	2	3	5	Yes	9	16	x	x	-	-	x	-	"
10.	35	2	4	5	Yes	9	12	x	x	-	-	x	-	"
11.	35	3	3	4	No	5	10	x	-	-	-	-	-	"
12.	52	5	2	3	No	5	7	x	-	-	-	-	-	"
13.	46	5	4	7	Yes	9	14	x	-	x	x	-	-	"
14.	35	2	2	4	Yes	7	12	x	-	x	-	-	-	"
15.	46	4	4	6	Yes	8	16	x	x	-	x	-	-	"
16.	41	4	3	4	No	6	9	-	-	x	-	-	-	"
17.	52	1	D-2	4	Yes	7	14	-	x	x	-	-	-	"
18.	67	4	2	3	No	6	10	x	x	-	x	-	-	S.D.
19.	53	1	4	5	Yes	7	10	-	x	-	-	-	-	S.D. + Pen.
20.	62	4	6	7	Yes	10	18	x	-	-	x	-	-	S.D.
21.	51	5	1	3	No	8	13	x	-	-	-	-	-	S.D.
22.	68	8	11	12	Yes	15	21	x	x	-	x	x	-	S.D.
23.	52	5	7	8	Yes	11	15	x	x	-	-	-	-	S.D. + Pen.
24.	37	1	3	3	Yes	5	11	x	x	-	-	-	-	S.D.
25.	22	4	4	4	No	6	8	-	x	-	-	-	-	S.D.
26.	31	3	4	5	Yes	7	14	x	x	-	x	x	-	S.D.
27.	62	11	7	12	Yes	14	21	x	x	-	-	-	-	S.D.
28.	52	8	6	8	No	11	16	x	-	-	x	-	-	S.D. + Pen.
29.	28	2	2	3	Yes	5	12	x	-	-	-	-	-	S.D. + Pen.
30.	21	3	4	5	Yes	10	17	x	-	x	-	-	-	S.D.
31.	59	4	5	6	Yes	8	13	x	x	-	-	-	-	S.D.
32.	58	5	7	7	Yes	8	12	-	-	x	-	-	-	S.D.
33.	30	2	4	5	Yes	6	12	-	x	-	-	-	-	S.D.

x = involved
- = not involved

APPENDIX III.

OPHTHALMOPLEGIA WITH CHLORAMPHENICOL

One patient in the tuberculosis series, when questioned about the side effects of chloramphenicol mentioned that towards the end of the course he had experienced difficulty in reading. The words became blurred and although he was able to resume reading after resting the eyes, the print soon became blurred again.

The syndrome of muscle fatigue with transient ophthalmoplegia as a side-effect of chloramphenicol was reported by Gray (1950). It was decided to repeat on this patient some of Gray's investigations.

METHOD

The patient was given a second course of chloramphenicol, 1g six-hourly for a total dose of 16g in four days. The following observations were made before, during and after the course.

1. Near point. With one eye covered, a card with two pin pricks, 2mm apart, was placed in front of the other eye. A pencil point held some distance away from the eye was gradually brought nearer until its image appeared double. The distance between the pencil and the eye was measured. The mean of three

readings was taken as the near point.

2. Skeletal muscle fatigue. A 14lb. weight was placed in the palm of the hand at arm's length and the period during which the patient could maintain this position before dropping his arm was timed with a stop watch. A mean of three readings was recorded.

At the same time as these tests were being made, the patient was asked to read from a newspaper and any subjective changes in vision were discussed.

RESULTS

These are shown in the table. The increasing distance

MUSCLE FATIGUE DURING COURSE OF CHLORAMPHENICOL.

PERIOD	NEAR POINT (Inches)		TIME OF HOLDING 14 lb. WEIGHT (Secs.)		SUBJECTIVE SENSATIONS
	Right Eye	Left Eye	Right Arm	Left Arm	
Before Chlor.	8	8	24	15	Vision Normal
After 5 g.	14	14	12	12	Vision Normal
After 8 g.	15	21	9	6	Blurring of small print on concentration
After 11 g.	23	31	8	6	Blurring of near and distant vision
2 Days after discontinuing Chlor.	10	8.5	12	14	Vision normal 15 hours after discontinuing drug

of the near point from the eye indicated that there was weakness of accommodation of the eye during the course of chloramphenicol. Similarly the diminishing time which the patient could hold a 14lb. weight showed that there was weakness of the arm muscles. Although the experimental error in the second test is probably quite large there does appear to be evidence that the fatigue affected the skeletal muscles as well as the ciliary muscle of the eye.

Gray found that this toxic reaction of chloramphenicol coincided with chloramphenicol blood levels of 50μg/ml and over and he considered that the antibiotic interfered with muscle metabolism. The effect on vision is merely annoying and on skeletal muscles is unimportant in a patient who is confined to bed. Nevertheless, as Gray pointed out, should the condition extend to the myocardium then its effects could be serious, especially in old or dangerously ill patients.

APPENDIX IV.

THE FAECAL FAT RESULTS

Details of the faecal fat results are given below. The daily readings are expressed as three-day averages. The mean of each day and the two succeeding days was calculated, assuming that food and drug taken on one day were still being excreted on the two following days.

Case	Day	Volume of Faeces ml.	Excretion of Fatty Acid g.	Excretion of Fat g/100ml. faeces
I.	1	90	3.29	3.65
	2	120	3.83	3.3
	3	160	4.04	2.83
	4	187	3.62	2.00
	5	253	3.26	1.7
	6	213	2.41	1.27
	7	213	2.94	1.57
	8	147	2.94	1.97
	9	193	3.69	1.97
	10	203	3.67	1.85
	11	250	3.92	1.55
	12	240	3.7	1.5
	13	240	3.7	1.5
	14	232	3.65	1.42
II.	1	120	2.59	2.37
	2	110	1.52	1.43
	3	107	1.45	1.4
	4	90	1.49	1.6
	5	135	1.91	1.45
	6	225	2.85	1.75
	7	323	3.28	1.1
	8	320	3.01	0.97
	9	367	2.69	0.77
	10	260	1.84	0.75
	11	327	2.55	0.72
	12	275	1.89	0.72
	13	350	2.3	0.70
	14	290	2.2	0.69

Case	Day	Volume of Faeces ml.	Excretion of Fatty Acid g.	Excretion of Fat g/100ml. faeces
III.	1	227	3.89	1.4
	2	230	3.61	1.57
	3	277	3.68	1.47
	4	217	2.94	1.37
	5	290	3.19	1.27
	6	327	2.75	0.90
	7	497	3.11	0.67
	8	453	3.15	0.77
	9	393	3.55	1.43
	10	193	2.91	1.40
	11	163	2.51	1.68
	12	213	2.31	1.12
	13	240	2.29	0.92
	14	280	2.88	1.0
IV.	1	197	2.56	1.37
	2	170	1.99	1.27
	3	125	1.70	1.4
	4	175	1.97	1.25
	5	285	2.08	0.75
	6	270	2.20	0.83
	7	297	1.88	0.8
	8	237	2.31	0.97
	9	297	2.38	0.83
	10	230	1.78	0.87
	11	233	1.89	0.9
	12	107	1.46	1.85
	13	90	1.49	2.27
	14	40	1.38	3.45

Case	Day	Volume of Faeces ml.	Excretion of Fatty Acid g.	Excretion of Fat g/100ml. faeces
V.	1	187	4.60	2.43
	2	220	3.91	1.80
	3	137	3.43	2.42
	4	340	4.48	2.12
	5	547	5.03	1.85
	6	703	5.31	0.8
	7	693	5.05	0.77
	8	587	4.33	0.77
	9	530	3.87	0.77
	10	530	3.79	0.73
	11	517	4.11	0.8
	12	575	4.42	0.75
	13	540	4.37	0.8
	14	520	4.35	0.78
VI.	1	80	2.59	3.33
	2	80	2.34	3.00
	3	120	2.87	2.67
	4	197	3.05	2.00
	5	227	2.69	1.27
	6	260	2.06	0.83
	7	193	1.63	0.93
	8	263	2.34	0.97
	9	210	2.27	1.18
	10	317	2.83	0.98
	11	303	2.48	0.88
	12	430	2.71	0.65
	13	440	2.45	0.6
	14	410	2.42	0.57

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