Sulphanilamide in the Treatment of Pulmonary Tuberculosis with Special Reference to its Action on the Blood Sedimentation Rate.

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On 22nd March 1882 Robert Koch isolated the Tubercle bacillus. More than two thousand years previously Hippocrates (460 B.C.) had described the "Status Phthisicus". The deformed spines of Egyptian mummies witness to the ravages of the Tubercle bacillus a thousand years even before the time of Hippocrates. No one has discovered when the disease started. But Koch's triumph opened a new chapter in the history of Medicine: the cause of Tuberculosis was known and subsequently new strides were made in every direction - in prevention and in treatment of the disease.

For the detection of Tuberculosis and for the propagation of knowledge concerning the disease there was founded in 1887 the first Tiberculosis Dispensary. This was the Victoria Dispensary in Edinburgh. After the dispensary came other institutions for dealing with Tuberculosis, sanatoria, hospitals, farm colonies, village settlements and open-air schools.

One of the earliest sanatoria was opened in Edinburgh in 1894. It was called "The Royal Victoria Hospital for Consumption and Diseases of the Chest." The observations on Sulphanilamide treatment of pulmonary tuberculosis in this Thesis were made during the writer's appointment in 1939 as Resident House Physician at The Royal Victoria Hospital. In the course of six months observations were made on 18 specially chosen cases of pulmonary tuberculosis.

The term consumption is no longer used synonymously with pulmonary tuberculosis - early diagnosis

of the disease is now held to be of paramount importance. In this respect the advent of radiology might be considered in tuberculosis second only in merit to the discovery of Koch's bacillus.

There is reason to believe that in the majority of cases of pulmonary tuberculosis radiological signs of disease precede symptoms. Until this fact is fully appreciated, however, and until facilities for radiological examination are extended enormously, patients will continue to expect their practitioner to make an early diagnosis in a disease which usually has no signs and often has no symptoms until well established. It is a source of grave anxiety to all workers in this branch of medicine that, of the cases notified as suffering from pulmonary tuberculosis, some two-thirds already have the disease in a moderately or far advanced form at the time of diagnosis.

In spite of the great advances in treatment made in the last twenty years, young persons still die from pulmonary tuberculosis. In the prime of life they are incapacitated for varying periods of one or two years and have to spend this time in institutions. Often the patient is the breadwinner upon whom others are dependent.

It is both interesting and instructive to compare the statistics of the Royal Victoria Hospital in the earliest days of its existence with those of today. Thus :-

	August 1894 to December 1896.	January 1937 to June 1939.
Cases Admitted:	180	431.
Average age:		
Both sexes	25.5	26.2
Males	27.6	27.8
Females	23.6	24.8

The similarity of these two sets of figures, which I calculated from available records, is indeed striking. The maximum age-incidence of pulmonary tuberculosis has not altered. It is still in the twenties.

In 1935 there were 27,415 deaths from pulmonary tuberculosis in England, Scotland and Wales: of these approximately one third (31%) were in the age group 15-35. Yet, despite this huge total, the mortality rate for the diseae has much decreased.

Deaths from Pulmonary Tuberculosis per 100,000 population.

Year : 1899 241.

" 1935 74.

How far the decrease is due to man's labours is a doubtful matter; natural influences may have played a large part. It is obvious, however, that the disease is still a menace to human life.

For the period January 1937 - June 1939 the average stay of each patient in the Royal Victoria Hospital was 183 days. Included in this figure were patients who left hospital prematurely against medical advice; some who were transferred, shortly after admission, to other hospitals; a few who died before they could be transferred. The usual stay in this sanatorium is therefore in excess of six months. Any new remedy or

therapeutic measure which will curtail the period of disablement, or lower the mortality rate, still further from pulmonary tuberculosis is something not to be despised.

When Ehrlich discovered salvarsan in 1909 chemotherapy became an established science. Nevertheless there was not for many years after this a discovery of comparable importance in this branch of medicine. Other, less toxic, preparations of arsenicals were produced. Diseases besides syphilis were found to respond to the organic arsenicals. Vaccines and sera enjoyed a boom. Sanocrysin and allied gold preparations were tried extensively in tuberculosis and in arthritis. But in 1935 chemotherapy again came into prominence.

Domagk (1935) introduced the compound Prontosil as a remedy for streptococcal infections. Its activity was confirmed and it was followed by many similar drugs - proseptasine, soluseptasine, rubiazol, sulphanilamide etc. Other organisms besides the streptococcus were also found to be susceptible to the drug. Although the mode of action was uncertain it seemed that the drug underwent a chemical change, possibly oxidation, in the body. But the activity of the sulphanilamide group of drugs was proven beyond all doubt and it was realized that important progress had been made.

The life-saving potentialities of the sulphanilamide compounds could be seen from the following two statements:

(1) The Medical Research Council Report for 1936 stated

that until recently more than twelve hundred women in the full vigour of life had been dying every year from puerperal fever.

(2) At Queen Charlotte's Hospital, London, the death-rate from puerperal sepsis was reduced from 24 per cent. in 1935 to 4.7 per cent. in 1936 when prontosil was first used. Such figures fully justified the hopes of Domagk, who had obtained results in experimental streptococcal infections in mice which seemed almost "too good to be true". He, it was, who introduced a noteworthy successor to prontosil - the drug called uleron - which was believed to be more effective against the staphylococcus and gonococcus than its predecessor.

It was the writer's privilege to use this drug on a case for the first time in Edinburgh (it was then called diseptal) early in the autumn of 1937. The case in question (unpublished) was that of staphylococcal septicaemia supervening in a young girl of 19 who was suffering from ulcerative colitis. Although her hectic temperature was controlled and reduced, temporarily, to normal by the drug, the termination was unfortunately fatal owing to the onset of bronchopneumonia.

The most potent sulphanilamide-derivative which has hitherto been tested extensively is the drug known as "M & B 693". It is particularly active against the pneumonococcus.

But while the therapeutic applications of sulphanilamide and its derivatives are legion, these drugs are

not a panacea. Knowledge is steadily growing concerning their toxic effects - effects which are sometimes serious, occasionally fatal. And there is a danger - by no means negligible - that treatment in the future will begin with administration of sulphanilamide and not with the making of a correct diagnosis. Such abuse of the drug might well occur in a busy general practice, for, though I cannot vouch for the absolute accuracy of the tale, I have heard of a practitioner in an English provincial town who disposed of 60 panel patients within an hour ! Had he prescribed sulphanilamide for them all (it did not then exist) he might have disposed of 120 in the same period of time !

The success of sulphanilamide is claimed in so many diseases - cerebro-spinal fever, otitis media, pneumonia, small-pox, malaria, trachoma and tetanus to quote but a few - that it is surprising to find a dearth of information concerning its action in tuberculosis.

In pulmonary tuberculosis there is very frequently a mixed infection - streptococci are found in the pulmonary lesion as well as tubercle bacilli. Their role is uncertain. Stanley Griffith (1924) thinks that the associated bacteria may be saprophytes which grow in pus and play no part in the pathological process, or that they may be pathogenic organisms which invade the tissues and contribute to the destruction caused by the tubercle bacilli. If the latter be true, then benefit might be expected from sulphanilamide by reason of its anti-streptococcal action.

It is therefore interesting that, prior to the time the present investigation was carried out, I have been unable to find any published work on the action of sulphanilamide in human pulmonary tuberculosis,

Birkhang (1939) has shown experimentally that sulphanilamide does exert, beyond all reasonable doubt, an inhibitory effect on the bovine tubercle bacillus in guinea-pigs. Rich and Follis (1938) and at least three other sets of workers had previously demonstrated a similar inhibitory effect against the human strain of bacillus.

Negative results were obtained by Smithburn, (1938) by Levin (1939), and by Kolmer, Raiziss and Rule (1938). But one observes that all these workers administered the drug for strictly limited periods of time - varying from 8 to 30 days. Would not they have obtained positive results if the administration had been more prolonged ?

Similarly, if results in humans have so far been negative and considered unworthy of publication, might not a more prolonged course of sulphanilamide have produced surprising and gratifying results ? Could this drug not help - even one iota - in the conquest of human tuberculosis ?

It was with a view to answering these questions that the investigations were carried out and that this Thesis came to be written.

To minimize the risk of toxic effects from prolonged dosage I chose, for the experiment, the French preparation rubiazol, which has been widely used on the continent and is probably least toxic of all the

derivatives of sulphanilamide. It is so closely allied to sulphanilamide in structure and action that one may reasonably assume that good results obtained with one drug will be identical with those which could be achieved with the other.

Messrs Roussel, who kindly supplied the rubiazol, did not hope for any favourable therapeutic action in this investigation. Search through their British and Continental records however revealed that no papers had ever been published on the use of rubiazol in tuberculosis.

This, then, was the question. What place, if any, should sulphanilamide hold in the treatment of pulmonary tuberculosis ?

THE PATHOLOGY OF TUBERCULOSIS.

Etiology.

Tuberculosis is a chronic inflammation caused by the tubercle bacillus. Variations of the disease are the result of interplay of the forces of destruction and repair.

The disease is widespread. It affects countries in every part of the world to some extent. Its incidence is highest in cities and crowded areas where there is poverty and undernourishment. It is one of the prices of civilization. In times of stress, in war and famine, in those suffering from overwork and worry it is especially likely to show itself.

The Tubercle Bacillus.

The bacillus is a thin, curved rod, sometimes beaded, staining with difficulty and growing in artificial culture with still greater difficulty.

Of the two important forms of tubercle bacilli in human pathology - the human and bovine - the latter plays a very doubtful part in causation of pulmonary tuberculosis. The two varieties of bacilli cannot be distinguished with certainty under the microscope, but can be readily differentiated by culture and animal inoculation.

For practical purposes it may be said that every adult case of pulmonary tuberculosis is human in type, though a number of cases due to the bovine bacillus are recorded periodically (Munro 1930). It is probable that the bovine bacillus in moderate numbers may serve to establish an immunity against the human type. There is however no experimental evidence to show that the

human type can become converted into the bovine, nor is it probable that the reverse process takes place (Griffith 1924).

The tubercle bacillus possesses a fatty envelope, constituting sometimes as much as 50 per cent. of its weight and making it acid-fast, so that when stained with hot carbol-fuchsin it does not lose the red colour if sulphuric acid is added: most other bacteria are thereby discolourised. In pure culture a number of bacilli may lose the fuchsin stain and take on the blue counterstain.

Chemical analysis show that the tubercle bacillus consists of a number of fractions: (Boyd 1937).

1. A protein fraction which will produce skin reactions in tuberculous patients.

2. A phospholipin which is an antigen, forms immune bodies and is responsible for the acid-fastness.

3. A saturated fatty-acid which stimulates connective tissue cells to produce monocytes and tubercles.

4. A polysacchardie which will kill a tuberculous animal.

The chemical composition is important as will be seen later in discussion of the mode of action of sulphanilamide on the bacillus in tuberculosis.

Detection of the Tubercle Bacillus in the Sputum.

Three methods of demonstrating the bacillus in the sputum are used.

(i) A film is made on a slide, suitably stained

and examined under the microscope. This is the usual method adopted, but at least 100,000 bacilli per c.cm. of sputum must be present to afford a reasonable chance of being found. An extensive case of pulmonary tuberculosis may however expectorate 2½ billion bacilli each day.

(ii) Infinitely more sensitive is guinea-pig inoculation, since this animal is susceptible to minute doses of virulent tubercle bacilli. There is a delay of 5 or 6 weeks before the result can be ascertained and this is the disadvantage.

(iii) Culture of the bacillus is quicker. Results may sometimes be obtained in three weeks and the accuracy of the results is claimed by some to be equal to that of animal inoculation (Holmes 1935). The original medium for culture - Dorset-egg medium - is today largely superseded by the media of Petroff, Loewenstein, Hohn and Petragnini.

Unfortunately many saprophytic non-pathogenic acid-fast bacilli occur in nature, e.g. in hay, butter, milk and in damp places such as the mouths of water-taps or corks of specimen bottles (Schwabacher 1937), and recovery by culture of an acid-fast bacillus from a specimen of suspected sputum cannot be accepted as establishing a diagnosis of tuberculous infection. Animal inoculation is required for confirmation.

It is possible to increase the chances of finding tubercle bacilli in the sputum by disintegrating the mucus, fat, cellulose, wax, hair and all ordinary

bacteria, with certain strong oxidizing agents. Owing to its resistant fatty envelope the tubercle bacillus is not affected and remains undissolved. Subsequently the mixture is centrifuged and the sediment examined for bacilli. By such method of concentration the probability of finding organisms in the stained film is increased from 15 to 20 per cent. (Dyke and Harvey 1937).

Detection of the Tubercle Bacillus in Absence of Sputum.

It may still be possible to find tubercle bacilli even in the absence of any sputum. Three courses are open to the searcher. He may wash out the stomach or collect a specimen of stool and examine the gastric contents or faeces for bacilli which have been swallowed in sputum. Or he may cause the patient to cough, thereby depositing flakes of tubercle-laden mucus, on to the face of a laryngeal mirror held horizontally above the larynx of the patient. This method was utilized several times in the investigations which are later described.

There is reason to believe that universal application of the methods of sputum culture and examination of gastric contents would cause much revision of current opinions as to the relative incidence of open and closed pulmonary tuberculosis (Kayne and Hounslow 1939).

The Mode of Infection.

There are four portals of entry by which the tubercle bacillus may enter the body. These are:-

(1) By inoculation into the skin or mucous membrane.

(2) By inhalation through the respiratory passages.

(3) By ingestion through the digestive tract.

(4) By placental infection, the bacilli being derived from the parents before the birth of the individual.

Inoculation is unusual but may occur from cuts usually inflicted by fragments of infected sputum jars. It is most improbable that pulmonary tuberculosis results from inoculation. Placental infection is of doubtful existence and similarly an extremely unlikely route of infection.

Romer (1918) said that none of the given channels of entry of tubercle bacilli is alone sufficient adequately to solve all the problems presented by tuberculous infection.

The relative importance of ingestion and inhalation of bacilli in causation of pulmonary tuberculosis has been the subject of much controversy in the past. It is generally agreed now that, if the bacilli are derived from human sources, they are usually inhaled, exceptionally ingested; if from bovine sources they are ingested.

The moist droplets eliminated by consumptives while speaking, and especially while coughing and sneezing, may be inhaled by persons who happen to be in their proximity. This is probably the most common mode of infection in pulmonary tuberculosis. Inhalation of dust containing desiccated sputum is undoubtedly possible, though less common, and conveying of infected material to the mouth may be a frequent cause.

The Primary Lesion.

The inhaled bacilli set up on the lung a small patch of broncho-pneumonia. The primary lesion thus caused may vary in situation.

In a series of 1800 post-mortem examinations on children under 13 years of age in Glasgow, Blacklock (1928) found a primary tuberculous lesion in the thorax in 173 cases (61.1 per cent. of all the cases of tuberculosis.) It was located most frequently in the right upper lobe: then, in order of frequency, in the right lower lobe, left upper lobe, left lower lobe and the right middle lobe.

In the upper and middle lobes the lesion was most commonly situated in the anterior part of the lung, whereas in the lower lobes it was usually posterior.

Cellular Response to Infection.

Polymorphonuclear leucocytes are the first to arrive at the point where tubercle bacilli invade the body. The leucocytes are actively phagocytic and engulf the bacilli; they prevent, to some extent, the drift of the bacilli through the body. The response of polymorphonuclear cells is very much more marked in a reinfection, i.e. in the allergic inflammation of someone already tuberculous. Their appearance in the primary lesion is however transitory, and within twenty four hours they are replaced by large mononuclear cells, also known as macrophages or monocytes.

It is to the fatty envelope of the bacillus that this cellular response is made, for the same effect, appearance of monocytes is obtained by injection of lipoid extracted from the bodies of the bacilli.

The mononuclears are highly phagocytic members of the reticulo-endothelial system. Bacilli and also polymorphonuclear cells containing bacilli are ingested by the mononuclears. The destruction of the ingested bacilli and progressive emulsification of their lipoid results in the transformation of the mononuclear cells into epitheloid cells (Long 1933).

The epitheloid cell, large, pale, with indistinct margins, bulky vesicular nucleus and abundant cytoplasm, is the most characteristic single feature of the tuberculous reaction.

Giant cells are probably formed by fusion of a number of epitheloid cells. They may attain a great size, and contain large numbers of nuclei usually arranged either around the periphery or at one or both poles. These cells are not formed until necrosis has occurred. They are found in small necrotic or caseous areas or at the edge of larger areas. Their function is to digest and remove dead tissue (Medlar 1926). They may be absent in the acuter forms of tuberculosis where resistance is low.

By the end of a week after infection lymphocytes appear and form a ring around the periphery of the lesion. Their function is uncertain.

The Tubercle.

The small mass of newly-formed or newly arrived cells constitutes a miliary tubercle - a very small translucent nodule visible to the naked eye.

It is avascular so that when vessels of a tuberculous lung are injected with a coloured medium the

tubercles stand out unstained. This avascularity presents an obstacle to treatment of tuberculosis by chemotherapy since circulating drugs can not easily permeate the tubercles.

The miliary tubercle may increase in size and several tubercles may fuse to form a larger mass.

By the end of the second week after infection caseation begins. This is a form of coagulation necrosis caused by the bacterial toxins, and the intensity of the necrosis varies with the size of the dose. Massive infection is likely to be accompanied by extensive caseation, e.g. as in acute tuberculous pneumonia. The cells in the centre of the tubercle lose their outline: their nuclei disappear and all structure is lost.

Caseation is not always present. It is absent in the hyperplastic form of tuberculosis where the virulence of the bacillus is low or resistance of the patient is high.

Radiological Appearance of the Primary Lesion.

If the primary tuberculous lesion is in the thorax it is often possible to demonstrate the resulting pathological changes by means of x-ray examination.

The extent of apparent lung involvement may be surprisingly large. The abnormal opacity in the film is produced mainly by inflammatory reaction around the small primary focus.

A triangular shadow, usually at the apex, and with the narrow end at the hilum, is characteristic of the so

called Epituberculosis (plate I.)

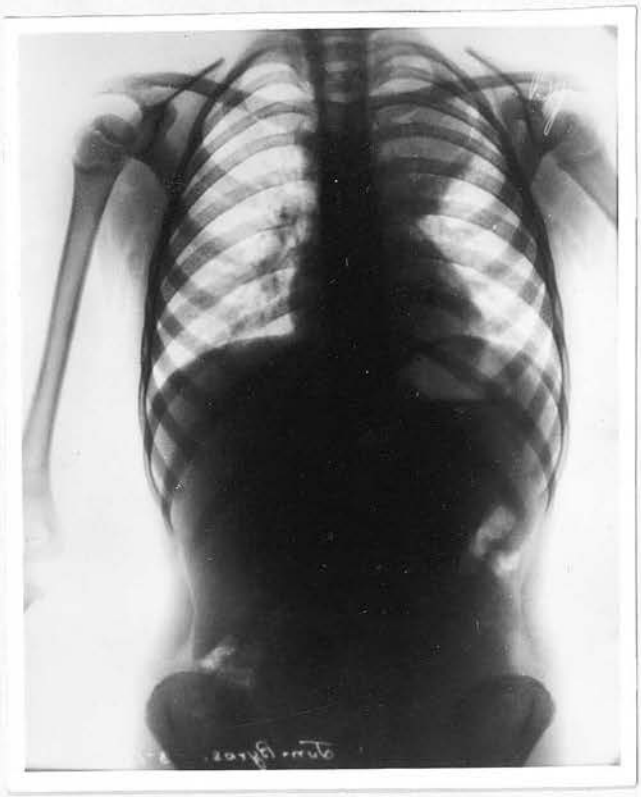


Plate I. Opacity at left apex due to epituberculosis in a girl aged 3.

Some maintain that this opacity is caused by collapse of the segment of affected lung following blockage of the communicating bronchus by a caseating gland (Epstein 1922). Most authorities think it indicates a severe inflammatory reaction around the primary focus (Goldsberg and Gasul 1930). The opacity may remain evident only a few weeks or as long as eighteen months.

The hilar-flare or ganglio-pulmonary lesion (plate II) is another manifestation of the primary

complex.

Plate II. Abnormal shadow of so-called hilar-flare extending outwards into the right lung from the hilum in a boy aged 3.

The primary focus is situated in the region of the hilum and an inflammatory reaction spreads outwards towards the periphery.

Post-Mortem Appearance of Primary Lesion.

Using the regional lymph node involvement as an indicator of the primary lesion, Ghon (1912) was able to demonstrate a primary lung lesion in over 90 per cent. of children. The lesion, often called the Ghon lesion, is a small caseous or calcified focus not more than 1 cm. in diameter, usually single, and situated in any part of the lung, but generally just under the pleura, and limited by a fibrous capsule. There is a larger caseous focus in the lymphatic glands draining this area. The size of the Ghon lesion contrasts strongly with

the apparently much larger lesion seen on radiological examination.

Reinfection with Tuberculosis.

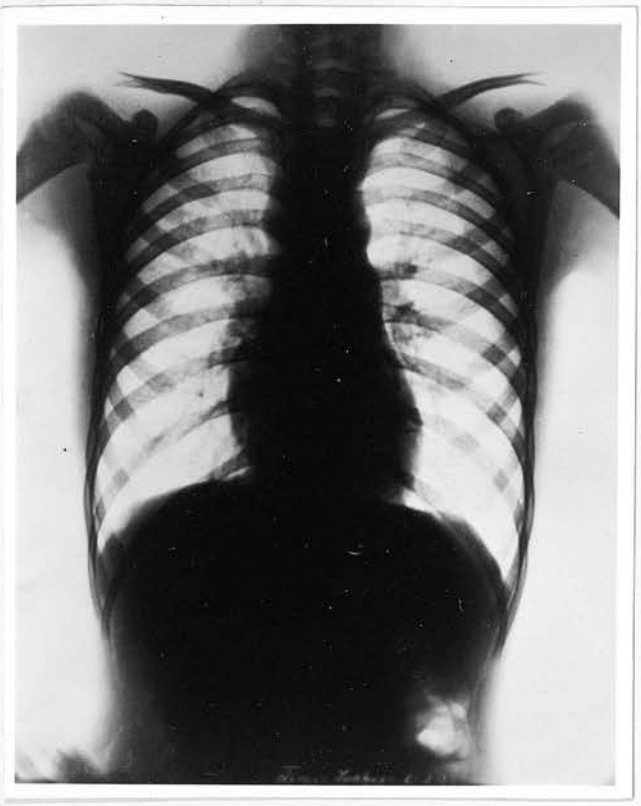
The channel of infection may again be inhalation, ingestion or inoculation, but there is yet another possibility. This is that the infection is endogenous, and results from renewed activity in the primary or Ghon lesion. It is usually held however to be exogenous, i.e. to result from reinfection from outside.

Reaction of the body to reinfection with tubercle bacilli is much more rapid and severe than in the case of primary inoculation. Owing to allergy the relative damage to the tissues is much greater (Wingfield 1934).

The Secondary Lesion.

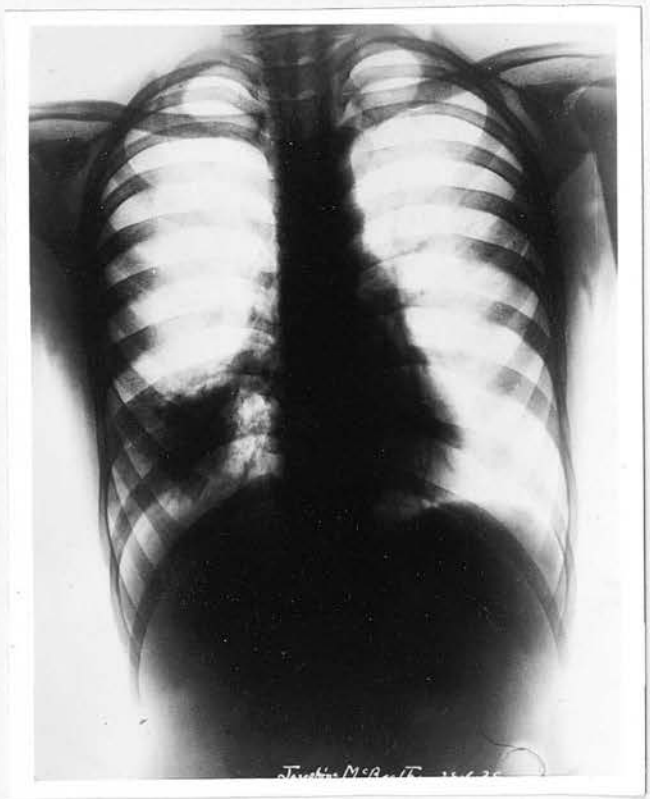
Radiology confirms the old teaching of Kingston Fowler that the earliest secondary lesions of pulmonary tubercle are not usually apical but are situated about one and a half inches below the summit of the lung. Burton Wood (1930) clearly describes the radiological picture. Usually an area of bronchopneumonia situated below one or other clavicle is revealed (plate III.), and a small area of coarse mottling in the centre of which a circular clear area may often be seen, indicating breakdown of the living tissue with resulting cavitation. Less commonly heavier shadows in the lower lobe reveal basal tuberculosis (plate IV), Occasionally a film shows supraclavicular shadows due to apical tuberculosis, a relatively benign form tending to heal spontaneously. Still more rare is the "snow-storm"appearance due to miliary tuberculosis in which all

Plate III:



Small tuberculous lesion in boy aged 10 simulating Assmann's focus in second right interspace. Manifestation of re-infection and early secondary disease.

Plate IV:



Coarse shadows in right lower lobe of basal tuberculosis in a girl aged 13 (Case 15.)

areas exhibit a fine stippling. Somewhat similar pictures are those of disseminated tubercle which gives rise to coarser granular opacities (plate `X.)

Spread of the Infection:

Dissemination of the invading tubercle bacilli in the lungs proceeds by four pathways..

(1) Haematogenous Spread: While the circulating blood is the vehicle of dissemination in miliary tuberculosis it apparently plays little part in the spread through the lung of chronic pulmonary tuberculosis. This is unfortunate, possibly, because chemotherapy might thereby be more effective in the disease.

(2) Lymphatic Spread: Though this plays some part it is of minor importance; in most instances of chronic pulmonary tuberculosis there is little active involvement of the hilar lymphatic glands apart from the residua of the primary complex.

(3) Spread by Contiguity: Direct extension of the tuberculous lesions occursin many cases, resulting in large caseous or fibrous-caseous masses especially in the upper lobes.

(4) Bronchogenic Extension: Dissemination along the bronchi is the most important means by which widespread lesions in pulmonary tuberculosis develop from the initial changes. In theory, therefore, anti-tuberculous substances administered by inhalation, should be more effective in checking spread of the disease than those depending on the circulation.

The Course of the Disease.

The course of the disease depends upon many factors but particularly on the size of the infecting dose and the resistance of the patient.

(1) Exceptionally the tuberculous lesion may resolve, disappear completely and leave no trace. This is referred to as natural resolution (Ellman 1939).

(2) Often the caseous area is walled off by fibroblasts, forming a fibrous capsule. Lime salts may be deposited and the calcified tubercle is said to be healed although living bacilli may still lurk in the quiescent lesion.

(3) There may be a low-grade inflammation with formation of tuberculous granulation tissue, many tubercles but no caseation.

(4) Not uncommonly there is spread of the infection giving rise to formation of new tubercles which fuse together until large caseous areas are formed.

(5) There may be an acute inflammatory reaction when the infection is virulent or massive as is seen in acute caseous pneumonia.

(6) If a massive dose of bacilli, as from a ruptured caseous gland, enters the blood-stream the disease may be widely disseminated in the form of miliary tuberculosis.

Fibrocaseous Tuberculosis. This is the form of tuberculosis which can be treated with encouraging results, especially in the early stages, by artificial pneumothorax, sanatorium regime etc. Often proliferation of fibroblasts and fibrosis are very marked, especially in those cases where resistance is good. Thickening of the

bronchi, blood-vessels and pleura result from the fibrosis. On the other hand, following union of many tubercles, caseation may be prominent. Much of the elastic tissue in the lung may remain intact and hold the caseous material together, but when secondary pyogenic infection occurs, the elastic tissue is destroyed and softening soon develops. This in turn is followed by the appearance of cavities (Boyd 1937).

Chronic Fibroid Tuberculosis. Many cases treated for chronic bronchitis, asthma, pulmonary emphysema, etc., are in reality suffering from fibroid tuberculosis. It is encountered mainly in persons between fifty and sixty years of age but is by no means uncommon below the age of thirty.

Fibrosis is the dominating pathological feature and the affected lung is usually decreased in size. In local fibrosis only the affected part of the lung may be contracted, while the rest fills up its place by compensatory emphysema. In the later stages cavities - pulmonary and bronchiectatic - are common, surrounded by dense, rigid walls.

The walls of the alveoli are thickened and finally obliterated or filled in. The interlobar connective tissue, especially round the large vessels and bronchi, proliferates enormously and, replacing the parenchymatous tissue of the lung, produces a state of induration through which the dilated bronchi pass.

Systemic disturbance is relatively slight in chronic fibroid tuberculosis. Many patients are able to lead an ambulant existence and strict rest and sanatorium

régime are unnecessary. This is not the form of tuberculosis which kills so many young people in the prime of life.

Tuberculous Caseous Pneumonia. In this acute form of the disease there is rapid caseation and destruction with no evidence of resistance on the part of the tissues. Lesions ulcerate through the walls of the bronchi in many places, and infection is spread widely throughout the lung by inhalation. Enormous numbers of tubercle bacilli are found in the sputum. The disease is rapidly fatal and resistant to treatment.

Miliary Tuberculosis. When the contents of a caseous focus are discharged into the blood-stream miliary tuberculosis ensues. It may be either acute or chronic, and though usually fatal recovery sometimes occurs in the chronic form (Zavod 1937). If the affected blood vessel be a branch of the pulmonary artery only one lung may show tubercles. If a vein, however, tubercles will be found in all the organs as well as in the lungs, and the patient often dies from tuberculous meningitis.

Cavitation. In a body already infected with tuberculosis, the characteristic reaction to an additional heavy dose of bacilli is breaking down of caseous tissue and formation of a cavity. The softened tissue is discharged into a bronchus and coughed up in the sputum.

The bronchial wall is involved in the softening and undergoes dilatation; the cavity thus results partly from caseation and softening and partly from bronchiectasis.

In acute phthisis the wall of the cavity is ragged, but in fibrocaseous tuberculosis it is smooth. It may be traversed by bronchi and blood-vessels, and erosion of the latter may lead to serious or fatal haemorrhage.

The first cavities are always the largest and form at the apex: later, as the disease progresses, other cavities may be formed in the lower lobes.

Immunity and Resistance.

The human body may be protected against tuberculosis by three mechanisms:

1. Natural Immunity.
2. Acquired Immunity.
3. Tolerance.

Natural Immunity. The degree of natural resistance to tuberculosis varies both in different races of mankind and in different individuals. It also varies from time to time in the same individual. It may be increased in the individual by good feeding, rest or other means; decreased by cold, fatigue or insufficient food, especially fats.

Susceptibility increases if people live under unnatural or unusual conditions. Also natural resistance varies with age, and sexual activity appears to increase the susceptibility of the individual to tuberculosis. It has already been mentioned that young women have not contributed to the fall of death-rate from pulmonary tuberculosis which has been so prominent in the last half century in the British Isles. It may be that at the onset of and during sexual activity some change occurs in the body which impairs its natural resistance.

Natural resistance is strong enough to overcome an ordinary dosage of infection with tubercle bacilli. Thus the overwhelming majority of individuals survive the initial infection without any clinical disease or even any signs of ill-health.

Acquired Immunity.

The change that takes place in the body some days after primary infection with tubercle bacilli may be compared to the change which takes place after infection by typhoid bacilli when the Widal reaction develops.

The change occurs about two weeks after the first inoculation with tubercle bacilli. The body tissues become hypersensitive to tuberculin or tubercle bacilli, and this condition of hypersensitiveness is spoken of as allergy.

Clinically the acquired allergy may be manifest in certain general signs of ill-health previously absent. Burrell (1937) stressed that if one wished to speak of a primary stage in tuberculosis this should be the incubation or pre-allergic stage. This stage may be regarded as the length of time taken by the body to establish resistance. It ends with onset of allergy.

The state of allergy which follows the primary infection may be harmful if too great, but in a moderate degree it produces an acquired resistance to tuberculosis.

Acquired resistance is less important than natural resistance. When once the natural resistance breaks down the acquired resistance alone is rarely sufficient to check the progress of the disease.

Nevertheless encouraging results have been obtained in many countries by producing an acquired immunity in babies shortly after birth. For this purpose B.C.G. (Bacilli Calmette Guérin), a living but non-virulent culture of bovine tubercle bacilli, is used. The bacilli, rendered avirulent by culture and subculture for many years are administered either orally or parenterally. There ensues an acquired immunity which affords some degree of protection against both human and bovine strains of bacilli (Calmette 1929).

Infection produces allergy but the connection between allergy and immunity is uncertain. Rich (1933) showed that active immunity can exist or be produced without allergy and that allergy can be produced without conferring immunity.

Tolerance. Must be distinguished from natural or acquired immunity. Like them it varies with different people and may wax and wane in the same individual.

It is best seen in the chronic fibroid type of case of tuberculosis where extensive disease may exist with very little impairment of general health. Patients who are exposed to small regular doses of infection over a long period of time often develop a considerable degree of tolerance. Widespread fibrotic changes may take place in the lungs before any definite impairment of health is noticed. Tolerance prevents the infection from producing toxic symptoms. It may be compared to the tolerance for alcohol in those who take frequent small doses.

Certain workers (Rich and Follis 1938, Ballon and Guernon 1938) have found an altered course of disease

in guinea-pigs infected with tuberculosis if sulphanilamide is administered. These animals have little or no natural immunity towards tuberculosis. What is the explanation of the fact ? Is there an action on the tubercle bacillus itself or is there an altered reaction on the part of the body? A degree of acquired immunity or increased tolerance? These questions are answered at a later stage.

Sulphanilamide and its Action.

Historical Survey.

The first description of the preparation of para-amino benzene sulphonamide is to be found in an article by Gelmo (1908). The investigations in this case were of a purely scientific nature, without any technical object.

A year later, Dressel and Kothe (1909) prepared the first azo-dyes with sulphonamide and substituted sulphonamide groups. They were used for textile purposes and were distinguished by greater fastness for washing and milling than those of the corresponding sulphonamide-free products.

The possible use of azo-dyes, that is compounds containing the linkage - N:N -, as bactericidal agents was first demonstrated by Eisenberg (1913), who showed that chrysoidine, m-diaminobenzene, would kill streptococci. Unfortunately the bactericidal effect found in vitro could not be repeated in infected animals.

Scarlet red (o-tolueneazo-o-tolueneazo-β-naphthol),

another azo-dye has been shown to have the power of promoting the growth of epithelial cells; trypan blue (sodium ditolyldisazo-bis-8-amino-1-naphthol-3: 6 disulphonate) has given successful results in canine piroplasmosis; and later pyridium (phenyl-azo-a-a-diaminopyridine hydrochloride) was put on the market with claims for an antiseptic action against the bacillus coli and the gonococcus.

The first German patent for prontosil was dated Christmas Day 1932. This prontosil was prepared by Mietzsch and Klarer (1932) in the Elberfeld Laboratories.

Example I of the patent gave details of the manufacture of a red dye-stuff (today known as prontosil rubrum) by diazotising para- amino -benzene sulphonamide (now-a-days known as prontosil album) and combining the diazo compound with meta-phenylenediamine.

Domagk (1935), the director of the Elbenfeld Experimental Pathological Laboratory, made the discovery that the azo-compounds containing the sulphonamide group ($-So_2NH_2$) had a remedial action in streptococcal sepsis of mice and rabbits. The results obtained with these and similar compounds seemed, however, too good to be true, so that before publishing them several years were devoted to intensive clinical and experimental work.

In subsequent clinical tests, streptococcal infections, such as erysipelas, puerperal fever and septic sore-throat, occupied a prominent position. They confirmed the action of prontosil against haemolytic streptococci.

Prontosil did not prove so specifically effective in staphylycoccal infections in mice as in streptococcal

infections. On the other hand it proved to be an effective chemotherapeutic in staphylococcal infections in rabbits. It was claimed that good results were obtained by its use on the continent in staphylococcal infections in man (Hoerlein 1937).

Other conditions in which it was found, at an early date, to be efficacious were infections of the genito-urinary tract due to B.coli and the gonococcus, and also meningococcal, pneumococcal and gas-gangrene infections.

Numerous German workers repeated and confirmed Domagk's investigations on streptococcal infections, and French workers, Levaditi and Vaisman (1935a) in particular, were not slow in recognising the fundamental importance of the results.

Substances were prepared by Girard (1936) the French chemist xx xxxx which formed the basis of Levaditi's experiments. The substances - the original sulphamido-diamino-azo-benzol and a carbonic acid derivative of this dye, carboxy-sulphamido-chrysoidine or rubiazol - were formed by following the methods described in the patents of Mietzsch and Klarer.

It was shown by other French workers (Tréfouel et al. 1935), and has since been confirmed by others, that the azo-linkage was unnecessary and that a colourless antistreptococcal product - p.aminobenzene-sulphonamide (sulphanilamide) - though a much simpler chemical was equally effective.

The same workers - Tréfouel et al.- investigated a large number of derivatives of this compound but were unable to improve on the chemotherapeutic action

of p.aminobenzene sulphonamide. However the pioneers of prontosil, Domagk. Klarer and Mietzsch made the next step forward. With the object of finding substances which, while possessing the lowest possible toxicity, would influence the largest number of bacterial diseases apart from streptococcal infections, they spent a couple of years investigating three compounds named, for experimental purposes, diseptal A, B, and C.

According to Domagk (1937a) all these preparations were in comparison with sulphanilamide more or less equally effective in streptococcal infections in mice; at the same time he found a considerable improvement over sulphanilamide in gas-gangrene infections and a striking increase in efficacy in staphylococcal infections in mice.

These compounds also proved superior in gonococcal infections, the first results published in this connection being those of Grütz (1937). It came to be recognised that alteration in the chemical structure of the drug might endow it with bactericidal powers against organisms thitherto insusceptible to chemotherapy. And in this respect diseptal or uleron, (as it is now called), was important, because instead of introducing a substituent into the amino group of sulphanilamide - like prontosil rubrun. - the substituent was introduced into the amide group.

Today, as a result, a host of new compounds have been created along the lines of diseptal, and these are being tested for their efficacy against diverse organisms as well as for their relative toxicity.

It is not known whether the sulphur atom is indis-

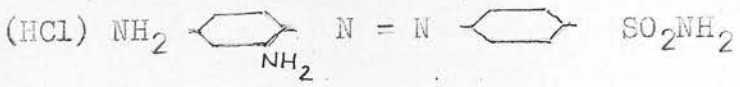
pensable for the chemotherapeutic property, but, so far, no compound showing activity comparable to that of sulphanilamide has been described which does not contain sulphur in some form. Therapeutically active substances exist, however, such as the diphenyl sulphones, which it is difficult to conceive as being converted into sulphanilamide or yielding identical derivatives in vivo.

Chemical Composition and Nomenclature of the Sulphonamide Drugs.

Sulphanilamide is marketed under a number of proprietary names some of which appear quite meaningless and which cause confusion, particularly owing to the advent of new and more complex derivatives of sulphanilamide.

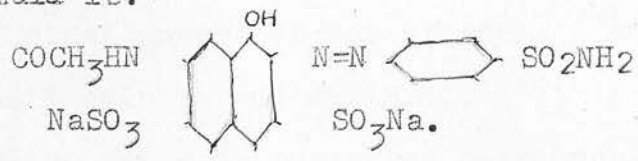
Prontosil, (first called streptozon, subsequently known as prontosil rubrum, prontosil flavum or prontosil), used in many early investigations, has recently fallen out of favour and is not much used today. It is given by mouth in the form of red tablets containing 0.5 gm. each of the dye. It is sparingly soluble, dissolving in 1600 parts of slightly acid water and in 20,000 parts of slightly alkaline water. It is ~~xxxxxx xxxx~~ excreted very slowly, a large dose still colouring the urine many days after it is administered. It gives a stronger colour in acid than in alkaline solution. When it is reduced it gives sulphanilamide and tri-amine benzene. This latter compound is unstable and is almost certainly destroyed in the body.

Prontosil is 4'- sulphamido - 2:4 diaminoazobenzene hydrochloride. Its structural formula is :-



Prontosil Soluble. In view of the unsuitability of the hydrochloride for injection prontosil soluble was produced. This even more complex chemical is the disodium salt of 4'-sulphamido-phenyl-2-azo-7-acetylamino-naphthalene-3:6 disulphonic acid.

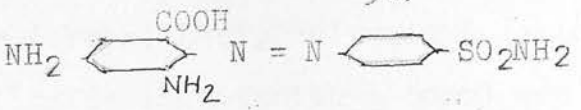
The structural formula is:-



It is soluble up to 4 per cent in water. Administered by intramuscular injection, it is reduced in the body to give sulphanilamide and 2-amino-7-acetylamino-1-hydroxy-naphthalene-3:6 disulphonic acid; it is rapidly excreted, practically all being found in the urine in the first few hours after a dose. It gives a much deeper colour in alkaline then in acid solution.

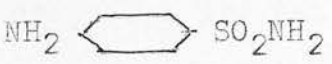
Estimation: Either variety of prontosil may be estimated by comparing the colour of the urine with that of a solution of the corresponding prontosil of known strength and of the same pH. Prontosil soluble can even be estimated in the presence of prontosil(rubrum) provided the solution is strongly alkaline; there is however no method of estimating prontosil when prontosil soluble is also present.

Rubiazol: This is the French equivalent of prontosil and it had, originally, the same composition as the German product; now it is a compound with an added COOH group. It is 6.carboxy 2:4 diamino. 4-sulphamido-azobenzene, and has the structural formula:-



It is administered orally as red tablets, each 0.2 gm., and is claimed to be highly active in low dosage and yet to have very low toxicity. For this reason it was chosen for the present experiments.

Sulphanilamide. This simple chemical is probably responsible mainly, if not entirely, for the bacteriostatic or bacteriocidal power of the preceding drugs, prontosil, prontosil soluble and rubiazol. It is p-aminobenzene sulphonamide (also called p-aminophenyl sulphonamide) and has the graphic formula :-



Sulphanilamide is a white crystalline powder, melting between 165 and 166.5°C., with no perceptible odour, and possessing a bitter taste. It is only slightly soluble in cold water but is soluble in hot water.

Solutions for parenteral administration are made by dissolving 1 gm. at 80°C in 80 c.cm. of distilled water containing 0.5 gm. of sodium chloride.

Sulphanilamide is now supplied by nearly all the manufacturers in the form of tablets each containing 0.5 gm.

Nomenclature. In the prontosil series, (Bayer Products, Ltd.), it is called prontosil album; three English manufacturers (Allen and Hanbury's Ltd., Burroughs, Wellcome & Co., and the British Drug Houses, Ltd.) have abbreviated the name to Sulphonamide-P.; it is also called colsulanyde (Crookes Laboratories, Ltd.,) P.A.B.S. (C.J. Hewlett & Son, Ltd.), prontylin (Winthrop Chemical Co. Inc.), streptocide (Evans Sons,

Leschor & Webb, Ltd), sulfamidyl (Abbott Laboratories), sulfanilamide (E.R.Squibb & Sons) and sulphanilamide (Boots Pure Drug Co., Ltd.).

Estimation: Sulphanilamide can be estimated in the blood by the following method:-

One c.cm. of blood is laked with a c.cm. of water: 1 c.cm. of 20 per cent. trichloracatic acid is added and the blood filtered under pressure. The filtrate is cooled in ice and one drop of 0.5 per cent. sodium nitrite added. Equal volumes of standard solutions of sulphanilamide in acid are treated similarly. After a few minutes one drop of 1 per cent. alkaline thymol and 0.2 c.cm. of 40 per cent caustic soda are added to all tubes; the blood filtrate is compared in the colorimeter against the appropriate standard. This method is found to give a fairly accurate determination of sulphanilamide added to normal blood down to a concentration of 1 mgm. per 100 c.cm.

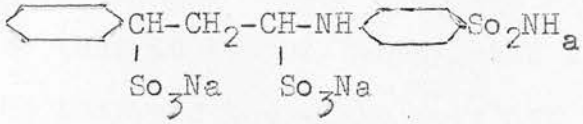
By reason of its amino group attached to the benzene ring, sulphanilamide gives a positive "diazo" reaction. This is utilized in estimation of sulphanilamide in the urine. Thus:- prontosil, if present, must first be removed by boiling the strongly acidified urine with charcoal, cooling to $0^{\circ}C.$, and adding excess of sodium nitrite; after a few minutes alkaline β-naphthol and caustic soda are added. The red solution thus obtained is compared in the colorimeter with that obtained in the same way from a solution of sulphanilamide of known strength.

Proseptasine is the benzyl derivative of sulphanilamide. That is:- p-benzylaminobenzenesulphanamide:-

It is supplied in tablets, each weighing 5 grains, and is intended for oral administration. It has been used on a very large scale owing to its low toxicity, which is in part due to the poor absorption of the compound : in animal experiments some 80 per cent. of the drug given is found unchanged in the faeces (Buttle 1939, B.M.J. 2. 270). For this reason Buttle emphasizes that it is not a suitable drug for cases of severe or resistant infections.

Soluseptasima is a white crystalline powder, readily soluble in water giving an approximately neutral solution. It is intended for parenteral use either in place of proseptasine, e.g., if vomiting precludes oral administration, or as an adjuvant to the oral therapy. Soluseptasine may be given intravenously, intramuscularly, subcutaneously, or, in cases of meningitis, intrathecally.

Chemically it is disodium-o-(7-phenyl-propyl-amino) benzene-sulphonamode-d-7-disulphonate and has the following structure:-

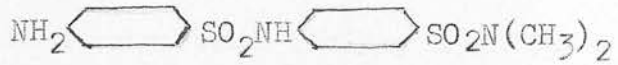


The preceding drugs - prontosil, prontosil soluble, rubiazol, proseptasine and soluseptasine - are compounds in which the amino (NH_2) group of sulphanilamide is the connecting link by which is attached the

characteristic radicle of each compound. It is probable that the activity of all these drugs is due mainly to the severance of this same link in the body resulting in the release of sulphanilamide (Fuller 1937).

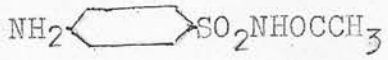
More recent compounds are of a different variety. Though still sulphanilamide derivatives, substituents are introduced into the amide group (SO_2NH_2) and, unlike the first group, they do not appear to be broken down to sulphanilamide in the body. Probably they are themselves the active agents. Three of these may be described :-

Uleron (also known as diseptal, diseptal A, D.B.90 or uliron), produced by Bayer Products Ltd., is said to be more active than sulphanilamide against staphylococcal and gan-gangrene infections (Domagk 1932): it is used now mainly for the treatment of gonorrhoea. Preferred to sulphanilamide by some authorities owing to its lower toxicity, it has to be used in a series of short courses since it may give rise to cases of peripheral neuritis. It has the structure:

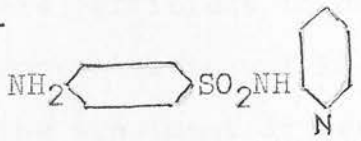


Albucid is also mostly used for gonorrhoea; it is stated that it is not acetylated like sulphanilamide in the body and therefore does not become partly inactivated. It seems to be of extremely low toxicity. Good results have been obtained with it in gonococcal cases when given with the usual adjuvant treatment, but in streptococcal infections in mice it has very little activity (Buttle 1939). It has the following

structure :-



"M & B 693" (Dagenham) represents a considerable advance in chemotherapy compared with all the previous compounds. It is 2-sulphanilylaminopyridine, with the structure :-



It is a white powder with slightly bitter taste and which is soluble in water to the extent of 1 part in 1000. It is active against all types of pneumococci whereas sulphanilamide is effective only against type III: it is also superior against the staphylococcus (Bliss and Long 1939) and in clinical gonorrhoea (Lloyd, Erskine and Johnston 1939), while it is no less active than sulphanilamide in meningococcal meningitis (Bryant and Fairman 1939) and in experimental streptococcal infections (Whitby 1938a).

It appears that "M & B 693" is effective whenever sulphanilamide is effective and is also active in certain conditions where sulphanilamide fails. It is much more expensive but is probably the drug of choice for any severe case of pyrexia where the bacteriological diagnosis is doubtful (Whitby 1938b).

It should be mentioned that there is another group of drugs which, like "M & B 693", is also superior to sulphanilamide, - 4:4'-diaminodiphenyl-sulphone and its derivatives (Buttle, Stephenson et al 1937), but these are not related to sulphanilamide and they are not at present of much clinical interest owing to their toxicity.

Dosage:

In order to obtain the best therapeutic effect it appears to be necessary to maintain a constant concentration of the drug in the blood. Four-hourly to six-hourly doses are sufficient to do this.

A blood concentration of 10 mgm. per 100 c.cm. is required for the treatment of severe infections, and this is obtained by a dosage scale of one gram per day to 20 pounds of body-weight (Bliss and Long 1937a) - that is, about seven grams for an average ten stone man. Children require fifty per cent. more than this and infants three times as much (Banks 1938).

For less serious cases half the dosage or less may be enough. Opinion on the advisable duration of treatment has not yet crystallised, but there is a tendency for limiting a course to ten days and only resuming it, if necessary, after an interval. What these drugs can do they usually will do within that time or less, and fatal agranulacytosis is a possible consequence of prolonged administration. In the experiments, later described, I used a compound of very low toxicity, rubiazol, in small doses - 1.2 to 1.8 g. daily - over periods varying from two to five weeks but with a precautionary weekly estimation of the leucocyte count and examination of the blood film.

Repeated administration of sulphanilamide to mice over a period of many weeks produced no pathological changes in liver or kidneys, though a variable amount of haemosiderin was found in the spleen, perhaps suggestion of increased erythrocyte destruction (Hageman 1937).

An animal should be used to ascertain the relative toxicity of a new remedy, but the final and only true test of effectiveness of that remedy must be carried out on the human subject. This is justifiable if the remedy is unlikely to do harm and has some prospect of doing good. I therefore felt it was permissible to administer the rubiazol to patients over the extended period of several weeks.

Absorption, Circulation and Excretion:

The absorption and excretion of the sulphonamide drugs has been studied fully only in the case of sulphanilamide itself but some data are available for other compounds.

Sulphanilamide is absorbed very rapidly when taken by mouth; it is absorbed entirely from the small intestine, not from the stomach, and the process of absorption is complete in four hours. It enters the circulation at the same rate if given subcutaneously. The concentration in the blood is maximal in about three hours, thereafter falling gradually to zero in the course of the following twenty-four hours (Marshall, Emerson and Cutting, 1937a).

The drug is very readily diffusible and finds its way rapidly into all the secretions of the body. Marshall demonstrated its presence in pleural and peritoneal effusions, saliva, pancreatic juice and cerebro-spinal fluid. In the last, in the dog, in a normal man and in a patient convalescent from cerebro-spinal fever, all gave similar results; the curve of concentration paralleled that in the blood at about three-

quarters of the blood level.

The drug has also been found in the sweat and, when given to pregnant animals, in the amniotic fluid and in the foetal blood (Lee 1938).

Marshall estimated the drug in various organs and found the concentration almost identical everywhere except in bone and fat where it was diminished.

The drug seems to be selectively absorbed on to the corpuscles of the blood, for the concentration here is 50 per cent. greater than that in the plasma (Hansen 1939). About 20 per cent. of the drug in the blood is in the acetylated inactive form, and in some cases this proportion may be as high as 40 per cent., but these differences do not seem to be correlated with the therapeutic efficiency of the drug in different subjects.

Sulphanilamide is excreted partly as the free base and partly in the inactive acetyl form (Marshall et al 1937b).

The excretion is delayed if renal damage is present.

So far as can be ascertained the drug does not undergo any other change in the body, for 90 per cent. of the total sulphanilamide given to mice can be found in the urine either as sulphanilamide or as acetyl sulphanilamide (Marshall 1939a).

In the urine the acetyl form accounts for over 50 per cent. of the total sulphanilamide, and the rate of excretion follows the urine flow and not the concentration in the plasma. The explanation of this seems to be that 70 to 80 per cent. of the drug is reabsorbed

in the kidney tubules, after filtration through the glomeruli.

Fuller (1937) found that up to 75 per cent. of excreted prontosil was in the reduced (sulphanilamide) form. He also found sulphanilamide did not appear in the urine until 4-6 hours after the first dose of prontosil, and that although three-quarters of the twenty-four hourly excretion of injected sulphanilamide was excreted in the first 8 hours, only one-eighth of that derived from prontosil was excreted during this period. He suggested that the steady supply of sulphanilamide derived from prontosil might be more effective than the sudden flood from sulphanilamide.

In the course of studying the urinary excretion in mice Fuller determined that in the normal animal prontosil is excreted, as sulphanilamide, in a lesser quantity than in infected animals. This discovery has remained unexplained, though Bliss and Long (1937b) claimed to demonstrate a reducing action on prontosil excreted by streptococci themselves.

"M & B 693" is absorbed and excreted more slowly than sulphanilamide in animals (Marshall et al 1938a). It reaches the cerebro-spinal fluid less rapidly than sulphanilamide, and it is excreted in the urine partly as the free base and partly in the inactive acetylated form.

The sodium salt of "M & B 693" is very soluble and is more rapidly absorbed than the free base; it is very alkaline in solution, - about pH 11. It has been used successfully parenterally when oral treatment was

impossible owing to vomiting (Marshall and Long 1939b).

Further work on the absorption and excretion of members of the sulphonamide series, and on the chemical transformations which they undergo in the body, is still required in order to enable these drugs to be used to the best advantage as regards choice of drug, dosage and spacing in time.

Mode of Action of the Sulphonamide Drugs.

Attempts to explain the mode of action of the sulphanilamide drugs have not led to concordant results, but the problem is clearly of wide importance in view of the variety of infections which are influenced.

Prontosil, entirely devoid of action on bacteria in vitro, is none the less therapeutically active in infected subjects. Sulphanilamide, on the other hand, is active both in vitro and in vivo. Streptococci are found to be inhibited or even killed by considerable dilutions of this drug in ordinary media, human blood (with leucocytes present or removed), or serum but only provided the number of organisms used in the inoculum is small enough (Colebrook et al 1936, Buttle 1937, Hoare 1938, Britton 1938).

The influence exerted by the size of the inoculum is manifest also with various other antiseptics - e.g. mercuric chloride or acriflavine (Garrod 1935). Though the antibacterial effect has been held to explain the therapeutic action of the sulphanilamide group, Levaditi and Vaisman point out that there exist far more powerfully antiseptic substances which

cannot cure a general streptococcal infection. For example acriflavine or proflavine are both toxic for the mammalian body and at the same time are enormously more potent antiseptics than sulphanilamide, while their rate of excretion is not significantly different from that of the latter; nevertheless they fail to cure a general infection. Colebrook (1936) remarks: "It is somewhat surprising that the low bactericidal power of the blood of mice treated with ~~xxx~~ sulphonamide should be associated with such a notable therapeutic effect". It must be concluded that the weak anti-bacterial property demonstrable in vitro is not likely to be more than a subsidiary factor contributing to the chemotherapeutic action of the sulphanilamide group.

The problem is whether, when an infection is cured by these drugs, it is the organisms which are acted upon or the host. Sulphanilamide itself does not set up an anti-bacterial condition of any permanence within the body. When, subsequent to the repeated administration of sulphanilamide and following an interval of some hours after the last dose of the drug, an inoculation is made with organisms, the progress of the infection is less influenced than when similar dosage of the drug is given at and after inoculation. For therapeutic action therefore it is necessary that the organisms and the drug meet in the body of the host .

To add to the confusion, the view that prontosil owes its therapeutic activity to being reduced in the body to sulphanilamide is strongly opposed in some

quarters. Foremost among those on the continent who contest this view is Domagk (1936 and 1937a): he believes that prontosil has an action per se, apart from that of sulphanilamide which it liberates. He argues that weight for weight prontosil is more effective than sulphanilamide, that the amount of sulphanilamide which it liberates is less than that of sulphanilamide which has to be given to achieve the same result, and that other therapeutically active compounds, e.g. uleron, are not reduced to sulphanilamide in the body.

Meave Kenny, at a meeting of the scientific sections of the British Medical Association at Aberdeen in July 1939, discussed the use of sulphonamides in puerperal infections. She held that prontosil rubrum was the most effective preparation in streptococcal infections. Quoting statistics from the Queen Charlotte's Hospital Isolation Block, she said the mortality figure was lowest in 1936 at the time when prontosil rubrum was being used in combination with prontosil soluble. The average dose of prontosil rubrum was then 18 gm. as against very much larger doses of sulphanilamide and other colourless preparations which were now used to produce the same effect.

Another speaker at the meeting, T. Anderson, stated that 0.4 gm. rubiazol was, according to his findings, equivalent to 1 gm. of sulphanilamide in treatment of erysipelas; accordingly the action of rubiazol could not be due entirely to breakdown into

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sulphanilamide within the body. He concluded that there must be some special therapeutic activity in the "red compounds" (azo-sulphonamides) which had been in use in the early days of sulphonamide therapy.

Hoare (1938) found that the blood of patients taking prontosil or sulphanilamide was bactericidal to streptococci and that the blood may assume this property within an hour or after some delay. The difference in time he attributed to variation in the rate of absorption of the drug.

Substitution experiments showed that no change in the leucocytes was responsible for the bactericidal property. The active agent was in the serum. Sulphanilamide was active in the serum alone, i.e. with red cells and leucocytes removed) but this effect required double concentrations of the drug. Hoare held that sulphanilamide had a direct damaging action on streptococci, either actually killing them or at least preventing their growth.

The work of Colebrook and his colleagues (1936), and Finklestone-Sayliss and others (1937), established that the bacteriostatic action of sulphanilamide upon haemolytic streptococci was preceded by a phase of growth stimulation. Compared with the control, organisms in blood containing sulphanilamide multiplied excessively during the first four hours of incubation. Thereafter aterilisation began and was so far advanced by the eighth hour that it was nearly complete.

The sudden fall in population following the rapid rise might be explained in one of three ways:-

1. Sulphanilamide may have a much more efficient bactericidal action upon cultures that have passed through the logarithmic phase of growth than upon young cultures. Finklestone-Sayliss (et al.) found, in fact, that the growth stimulation was more conspicuous in young cultures than in cultures that had passed through the logarithmic phase.

2. Sulphanilamide may be slowly changed into some other compound which is the actual bactericidal agent. This did not appear to be the case according to the same workers.

3. Sulphanilamide may have a slowly engendered stimulatory action upon the normal mechanism of destruction of organisms in the blood. This mechanism seems necessarily dependent upon primary phagocytosis. The third postulate seems improbable as both Colebrook and Hoare have shown that sulphanilamide is able to kill haemolytic streptococci in blood whether leucocytes are present or not.

Sulphanilamide is only sparingly soluble in aqueous solution but its solubility is much increased in certain fat solvents such as acetone. Ficklestone-Sayliss thought that as sulphanilamide was soluble in fat there was little doubt that it was far more soluble in the fatty envelope surrounding haemolytic streptococci than in aqueous solution. He claimed to demonstrate this fact experimentally. He held that the bacteriostatic effect was due to the drug being initially concentrated in the fatty envelope of the organisms. It was difficult to correlate the presence in young cultures of a higher concentration of fat - a relatively

good solvent of sulphanilamide - with the fact that sulphanilamide stimulated the growth of young streptococci. However he suggested two explanations without attempting to decide which was correct. They were:- (1) That with the diminution of the percentage of fat as age increases the concentration of sulphanilamide in the fat of each cell becomes greater, and this increased concentration is responsible for the bacteriostatic action upon older cultures; (2) That sulphanilamide acts first as a stimulant and secondarily as a depressant. Such pharmacological action is not unknown and that of nicotine may be instanced as a parallel.

Levaditi and Vaisman (1935b) put forward their view that prontosil, with which they were experimenting, prevented capsule formation by streptococci, so rendering them susceptible to phagocytosis; also they believed that prontosil neutralised streptococcal toxins - leucocidin and haemolysin. But, once again, phagocytosis is unnecessary for destruction of streptococci by sulphanilamide.

The same may be said in commenting on the work of Gley and Girard (1937). They claimed that exposure in vitro either to prontosil or sulphanilamide diminished the virulence of streptococci. But even though avirulent why should the organisms be killed in deleucocyted serum?

Long and Bliss (1937d) favoured the view that the metabolism of the organisms was interfered with and that their growth was prevented by sulphanilamide.

Bacteriostasis, they said, if complete must ultimately result in victory for the bodily defence mechanism. So also thought Gay and Clark (1937) who were unable to find any stimulation of the defence mechanism in the sense of an altered behaviour of leucocytes.

Though Finklestone-Sayliss had observed change neither in appearance nor in motility of leucocytes, he found that in rabbits production of polymorph leucocytes by the bone marrow was stimulated and the phagocytic activity of the reticulo-endothelial cells of the spleen was increased. The latter observation may throw some light on the work of Buttle and Parish(1938) who found in experimental tuberculosis that the most pronounced effects occurred in the spleen of the animals treated with sulphanilamide.

In the case of intraperitoneal inoculation of mice with pneumococci, McIntosh and Whitby (1939) showed that successful treatment with "M & B 693" did not prevent an initial invasion of the blood stream. They held that sulphanilamide drugs did not stimulate leucocytosis, nor did they influence the quality, quantity, or rateof formation of specific antibodies to pneumococci. But they found that in animals treated with "M & B 693" the capsules of pneumococci in the peritoneal cavity showed degenerate changes. This, on an analogy of B.anthracis injected into immunized animals (Preisz 1909), is what would be expected when conditions are unsuited for continued proliferation and the development of pathogenic properties.

Accordingly it would appear that, while it is under the influence of the drug, the body behaves

towards particular highly virulent organisms much as the normal body does to those of a non-pathological type which are gradually destroyed.

Levaditi and Vaisman (1938) have reached a similar conclusion from their observation that certain drugs of the sulphanilamide group render mice resistant to various endotoxins, e.g. killed cultures of organisms such as gonococci, meningococci, bacillus aertrycke etc. Thus the chief action of the drug would be to alter the reactivity of the host. Such an explanation also fits in with the clinical observation in pneumonia that the first and most striking effect of the treatment is reduction of the pyrexia. But it remains impossible to rule out the hypothesis that the drug may have some gradual direct action on the metabolism of the organisms in the infected animal.

Lastly, one may recall the interesting work of Gay and Clark (1937) who, using a streptococcus which was completely resistant to the action of sulphanilamide in vitro, produced experimental empyaemata in animals. Cure resulted in a high proportion of these animals on oral treatment with sulphanilamide. Since the sulphanilamide per se had no action one might conclude that the sulphanilamide acted rather on the body than on the organism.

Therapeutic Action of Sulphanilamide.

Just as the mode of action is uncertain so, it must be admitted, is the extent of the anti-bacterial effect. The original experiments, in which strepto-

cocciwere employed, have been extended to discover what action sulphanilamide and its derivatives have on other bacteria, on protozoal infections and on disease due to virus infections. Knowledge is accumulating rapidly both in regard to the possibilities and the limitations of chemotherapy with the sulphonamide drugs. Successes in treatment are frequent, startling and widespread. Some are quite unexpected. One reads - "Since the drug did not appear to be a respecter of bacterial personalities we decided to try its action in this case"..... and there follows a description of yet another disease which has apparently responded favourably to the drug.

Streptococcal Infections:

It is easy to understand why the discoveryof a genuine remedy for streptococcal diseases immediately aroused scientific interest throughout the world. After the publication by Domagk concerning the favourable influence of prontosil in mice in 1935, numerous clinical observations were made by others confirming the findings of Domagk. Naturally attention was at first focussed on the streptococcus and diseases such as erysipelas, puerperal fever and septic sore throat received special attention.

Not all streptococcal infections are influenced by sulphanilamide drugs; only those due to the streptococcus pyogenes are susceptible; those due to the streptococcus viridans and the streptococcus faecalis are uninfluenced. But even in the streptococcus pyogenes group there are resistant types.

Recent work by Lancefield (1933) showed that haemolytic streptococci could be divided by serological methods into a number of groups of which nine are now known. These are distinguished by the latters A to K. Lancefield and Hare (1935) later showed that, of these groups, group A was almost invariably the one that was responsible for causing severe infections in the human species.

Bliss and Long (1937a) ascertained that streptococci of Lancefield's serological group D were resistant to sulphanilamide. Subsequent in vitro studies of bacteriostatic action showed that, whereas groups A and C were fully susceptible, the effect on group B, E and G was variable, and on D there was none. It is therefore fortunate that most serious streptococcal infections are due to members of Group A.

Puerperal Sepsis:

Colebrook and Kenny (1936) were the first to demonstrate that the drug (prontosil) appeared to have a most favourable influence amongst puerperal patients on the clinical course of infections due to group A haemolytic streptococci.

The average death rate for the previous five years for all haemolytic streptococcal infection at Queen Charlotte's Maternity Hospital Isolation Block was 22.8 per cent., but in 1936 the death-rate amongst the 64 cases at this hospital treated by prontosil and recorded by Colebrook and Kenny was only 4.7 per cent. Although there is some evidence to show that the haemolytic streptococcal infections at that time may

have been less virulent than formerly, this fact is insufficient to account for so large a reduction in the death-rate. Moreover there was a sudden reduction in the severity of peritonitis associated with the puerperal sepsis in those cases treated with prontosil, and none of the patients developed a palpable pelvic or abdomino-pelvic inflammatory mass or abscess, after the beginning of the treatment, although this was formerly one of the commonest complications of puerperal infections by haemolytic streptococci.

Prophylaxis : Johnstone (1938) gave either sulphanilamide or proseptasine to five hundred women after labour, but it was doubtful from his observations whether it had any useful effect in preventing the onset of puerperal sepsis.

Colebrook (1937), discussing the question of prophylactic administration in obstetrics, concluded that as sulphanilamide treatment was not free from danger it was undesirable to give the drug as a prophylactic to every woman in labour. He thought it was justifiable, however, to use it whenever there was sound reason to anticipate puerperal sepsis, for example in any case delivered with much instrumental interference or in suggestive circumstances.

Tonsillitis and Ludwig's Angina:

Acute follicular tonsillitis responds readily to sulphanilamide provided, as is usually the case, haemo - lytic streptococci are in part at any rate responsible. A fall in temperature by crisis is to be anticipated

within twenty-four hours. Remarkable improvement is also seen in patients desperately ill with Ludwig's angina (Palmer 1937, Lyth 1937). The more alarming the condition of the patient the more dramatic the effects of therapy appear to be.

Streptococcal Septicaemia:

Fatalities from post-mortem and operation wounds, so tragically familiar to hospital workers, are the result usually of streptococcal septicaemia. It is to be hoped that such calamities will dwindle to insignificance under the power of sulphanilamide. Though positive blood cultures can often be made, the prognosis now is fairly good and the fever abates in two or three weeks. Robinson (1937) reported recovery in one such case with positive blood culture, and McIntosh, Wilcox and Wright (1937) recorded various cases presumably of true septicaemia in children cured by the drug.

Streptococcal meningitis and Infections of the Ear:

The mortality from streptococcal meningitis no matter how acquired has hitherto been appallingly high. Its development as an extension of otitis media and mastoiditis was well-nigh hopeless. It is therefore of especial interest to find convincing reports of recovery following the use of sulphanilamide.

One such case is recorded by Lucas (1937). His patient was a boy with suppurative otitis media who developed meningitis. The cerebro-spinal fluid contained haemolytic streptococci and much pus. 10

ccm. of the drug was injected intramuscularly daily and two tablets given by mouth thrice daily. The temperature was normal within thirty-six hours of starting treatment and recovery was complete. In America, Neal and Appelbaum (1938) obtained recovery in 13 of 17 cases of streptococcal meningitis with sulphanilamide, using subcutaneous oral and intrathecal routes.

Erysipelas:

There is now abundant published testimony to the value of sulphanilamide in the treatment of erysipelas. Snodgrass and Anderson (1937) in a well controlled series of 312 cases concluded that sulphanilamide is the best form of treatment for a disease which, nevertheless, reacts well to many modern forms of treatment such as streptococcal serum or ultra-violet light. For the experiment they used prontosil rubrum.

Becker (1937) compared the results of 50 cases of erysipelas treated with prontosil with a similar number treated by other methods. He found that the spread of disease was always arrested and its duration much reduced, more so by oral administration of prontosil than by intramuscular or intravenous. Local application of prontosil was useless, as was fully expected.

Striking results were also obtained by Peters and Havard (1937) in a series of 47 patients - ranging in age from four months to eighty-seven years - suffering from erysipelas of severity varying from mild to very severe. The spread of the disease was arrested

within 24 hours in every case. In 31 cases the temperature was normal also within 24 hours, while in a further 12 it was normal within 48 hours. Two developed relapses, ten days after the primary attack, which responded at once to further doses of the drug.

Scarlet Fever:

The same workers in this paper reported the results of treating scarlet fever with proseptasine (p.Benzylamino-benzene-sulphonamide). The dose given was from 0.75 to 6 gms. per day according to age, and it was administered by mouth in tablet form, divided into four-hourly doses. The full dose was given for two days, then half the quantity for another two to four days according to the course of the illness. As controls, 150 alternate cases were treated expectantly or with antitoxic serum when considered necessary (56 cases). They found the incidence of complications in the two series was :-

Series of cases treated with proseptasine.	Control series
53 (35 per cent.)	84 (56 per cent.)

They discovered however that the mean duration of the primary fever from onset to termination was twelve hours longer in the test series. They believed the antitoxic serum administered to a third of the control series was responsible for reducing the pyrexia in that group.

They concluded the drug had some effect on the invasive side of the streptococcal infection, that results should be better if the drug were given early

in the disease, and that the streptococcus was probably less accessible to the drug once spaces such as nasal sinuses were infected. They thought possibly a combination of drug and serum would be more effective than either of these alone.

Measles:

The danger of measles lies in the liability to develop complications, and there is no doubt that the streptococcus is often involved in such cases. As with scarlet fever, so also one would expect benefit in measles from administering sulphanilamide on account of this fact.

In the Annual Report for 1937, the Medical Superintendent of the Cardiff City Isolation Hospital stated that the low death-rate from measles in that area was attributable to the facts that all cases of broncho-pneumonia were nursed in the open air day and night, and that, in addition, all the patients suffering from measles were given ¼ to 2 tablets of prontosil daily as a prophylactic against secondary infections such as otitis media and broncho-pneumonia. The latter condition did not develop in any case after admission.

Meningococcal Infections:

In a series of one hundred and thirteen cases of acute meningococcal meningitis reported by Stanley Banks (1938) thirty-eight were given large doses of serum intravenously and intra-thecal serum twice daily for five days. No infants were included in this group. Fifty-nine cases including ten infants were

were treated with serum and sulphanilamide, and sixteen cases received only sulphanilamide. The death-rate in the first group was about 16 per cent., in the second 11.8 per cent., and in the third group only one case proved fatal. In those cases treated with sulphanilamide, alone and combined with serum, it was noted that recovery was rapid. The best results were obtained when high initial doses of sulphanilamide were given, sufficient to bring the sulphanilamide level in the cerebro-spinal fluid up to 5 mgm. per 100 c.cm. in twenty-four hours and to maintain this level for four days.

Equally convincing are results of treatment of cerebro-spinal fever with "M & B 693" (-sulphanilylaminopyridine).

Somers (1939) reviewed one hundred and forty-three cases of that disease occurring in the Sudan where the mortality rate is usually high (68-80 per cent.) These cases were given "M & B 693" in watery suspension or watery and oil suspension by intrathecal, intramuscular and intraperitoneal injection. The total amounts of drug used were small - 1.2 gm. of water suspension and 3 gm. when this was combined with oily suspension. In most cases the cerebro-spinal fluid became clear before the temperature fell to normal. Intraperitoneal injections caused a more rapid general improvement than intramuscular. The death rate in the series was only 10 per cent.

Gonococcal Infections:

The value of sulphanilamide in gonorrhoea is

difficult to assess. Criteria of successful treatment are not readily amenable to exact statement. Almost all workers report good results, but there is frequent mention of a minority of patients (10 to 20 per cent.) who entirely fail to respond to the drug.

A series of forty-seven cases reported by Dees and Colston (1937) showed an average duration of five days only when treated with sulphanilamide alone. Crean (1937) has treated one hundred cases with sulphanilamide, together with irrigations, and concluded that the drug reduces the usual period of disability from the disease by two-thirds.

Similarly O'Hanlon (1938) found that the average period of invalidity among troops at Aldershot had been reduced from 62 to 21 days.

It is agreed that complications, both local and metastatic, respond well, and rapid disappearance of gonococci from exudates in distant situations as well as the urogenital tract is a usual finding.

Successful results obtained in two infants suffering from gonococcal ophthalmia by treatment with "M & B 693" tablets and boric acid lavage was reported by Michie and Webster (1938).

Bowie (1938) described the results of using various sulphanilamide drugs in treatment of gonorrhoea. Sulphanilamide gave cures in 70-80 per cent. of cases, uleron in 70-90 per cent. and "M & B 693" in 85-95 per cent. "M & B 693" appeared to be the drug of choice since it could be given at once, whereas optimal results with sulphanilamide and uleron were obtained if treatment was postponed for about ten days from the

onset of disease. After treatment with "M & B 693" there was a very low incidence of complications (1.5 per cent.) as compared with the high figure (25-30 per cent.) which was the rule before chemotherapy. A total of 20 gms. of "M & B 693" was usually sufficient to produce a cure.

Reports of 120 cases of gonorrhoea treated with uleron by Wilkie (1939) and of 102 cases treated with "M & B 693" by Batchelor C.L. Lees R., Murrell M. and Braine G.I.H. confirm the accuracy of Bowie's conclusions.

Levaditi and his colleagues (1937) have investigated the effects produced by seventy-five compounds in mice infected with the gonococcus. Of these the most potent was a new compound, 4-nitro-4 amino-diphenyl sulphoxide which was from fifty to one hundred times as effective as sulphanilamide. Though useless in pneumonia and streptococcal infections it proved efficient against the meningococcus.

Other Venereal Diseases:

Chancroid responds well to treatment with sulphanilamide (Batchelor and Lees 1928) and so also does lymphogranuloma inguinale (Gjurié 1938), but no one has claimed the slightest value from use of the drug in syphilis (Campbell 1937).

Pneumococcal Infections:

It appeared ~~xxxxx~~ from experimental work, that pneumococcus type III. was more amenable to treatment with sulphanilamide than other types. Heinzelman (1937) treated 9 cases of type III. pneumonia with

only 2 deaths whereas in 10 cases not so treated there were only 2 recoveries. Results of treatment of pneumonia with "M & B 693" are so imcomparably better, however, that sulphanilamide itself is not now used for this condition except on rare occasions.

Gaisford and Evans in a series of 627 cases of lobar pneumonia occurring between March 1938 and June 1939 had a mortality rate of only 5.4 per cent. as a result of treatment with "M & B 693." The incidence of empyaema was 4.5 per cent., and though the total percentage of cases showing a pleural exudate was equal to previous control cases, in ten cases the exudate was of clear fluid. This was considered as evidence of aborted empyaema.

Particularly striking were the results obtained in elderly patients. Results in cases of broncho-pneumonia were less good - probably owing to the mixed type of infection.

Pneumococcal meningitis has been treated successfully in 8 out of 18 cases with prontosil or sulphanilamide according to the report on a case by Lockie (1939). Consequently it is only to be expected that even better results may be obtained with "M & B 693."

Staphylococcal Infections:

It is the general experience of investigators that bacteria which produce an exotoxin are not influenced to any great extent by sulphanilamide or its derivatives. Such bacteria are b.diphtheriae, b.tetani, v.septique, b.histolyticus and the staphylococcus. In the case of the last however, successful therapy has been reported not uncommonly.

The first therapeutic success with prontosil ever published (Foerster, 1933) as long ago as 1933, concerned a case of staphylococcal septicaemia.

Colebrook and Purdie (1937) had two successes out of three cases of puerperal staphylococcal septicaemia treated with large doses of sulphanilamide.

Domagk (1937) found a better response in experimental staphylococcal infection to uleron than to sulphanilamide. This observation has, however, so far remained unconfirmed, and the drug is now used mostly for treatment of gonorrhoea.

In controlled experiments with the compounds sulphanilamide, uleron, "M & B 693," rodilone (p.p-diacetyl-diamino-diphenyl sulphone) and the monocetyl derivative, the last three were the most effective against staphylococci (P. Browning, unpublished).

Bacillus Coli Infections:

The use of sulphanilamide in bacillus coli infections of the urinary tract was first advocated by Huber (1936) who obtained striking results in pyelitis of children. Kenny, Johnston and von Haebler (1937) treated forty-six cases in adults with good results, mainly in cases of pregnancy and the puerperium. Using prontosil album they obtained cures in from 2 to 5 days - results comparing extremely well with those cases treated by mandelic acid or hexamine (Rosenheim 1935), in which 10 to 21 days of treatment was found to be necessary. Kenny and her colleagues did not find that all strains of bacillus coli were equally susceptible to the bactericidal action of

sulphanilamide; some were almost completely resistant. Combining their clinical observations with in vitro tests on the bactericidal power of sulphanilamide in urine, they found that this power was proportional to the sulphanilamide content of the urine. It has, in addition, been shown by Helmholz and Osterberg (1937) that sulphanilamide is much more bactericidal in alkaline than in acid urine.

Admittedly the types of infection treated by Kenny and her colleagues respond more readily to treatment of any kind than the more chronic forms of the disease. Nevertheless other reports (Cook and Butchtel 1937 and Türk 1937) claimed success with chronic bacilluria. Dundas (1937-8) recorded successful results using sulphanilamide in pyelonephritis and appendicitis, and two cases of periappendicular abscess in children (F. Roberts - unpublished) responded rapidly to administration of "M & B 693" with complete disappearance, in each case, of the palpable lump. There is therefore good evidence that sulphanilamide is effective in bacillus coli infections.

Bacillus Typhosus:

A case of typhoid pyelitis and bacilluria, which had failed to respond to hexamine and ammonium mandelate treatment yet showed a negative culture for B. typhosus after five days treatment with sulphanilamide, was recorded by Barer (1937).

It seems that sulphanilamide has not sufficient action on bacillus typhosus to hold out hopes of much benefit during the acute phase of the disease. (Schmidt 1938). Yet, it appears that it may be of

use in treatment of typhoid carriers.

Bacillus Welchii:

Long and Bliss (1937c) succeeded in protecting mice from Bacillus Welchii infections with sulphanilamide provided the inoculum did not contain too much exotoxin, and Domagk (1937) obtained the same results with uleron.

Impressive results in human beings were reported by Bohlman (1937). Three cases of extensive injury, due to car or lift accidents, developed gas gangrene in spite of prophylactic antitoxin; all recovered under treatment with oral sulphanilamide, two with dramatic rapidity.

Brucellae Abortus and Meliteusis :

Favourable reports have been made on the action of sulphanilamide both on Br. Abortus and Br.Meliteusis. Francis (1938) described two cases of undulant fever and referred to five other papers on the subject; he told of in vitro experiments from which it appeared that brucella abortus was more susceptible than the streptococcus pyogenes to bacteriostasis by sulphanilamide.

Bacillus Pestis:

Schultze (1939) obtained favourable results in mice and rats infected with bacillus pestis, especially with "M & B 693." Successful treatment of bubonic plague in Africa was reported by Carman (1937-38): he used prontosil rubrum.

Malaria:

Prontosil was said to have given successful results in malaria (Hill and Goodwin 1937), but a special

committee appointed to investigate this question in the United States reported entirely negative results (Faget, Palmer and Sherwood (1938). It was considered that earlier reports of cure must therefore be discredited.

Virus Diseases:

In general, virus diseases have proved resistant (McKinley 1939) In neurotropic diseases, e.g., poliomyelitis, sulphanilamide has no therepeutic action.

The action on the virus of lymphogranuloma inguinale has already been referred to in connection with venereal diseases.

Elyan (1938) recommended the use of sulphanilamide in treatment of the common cold. He had treated over one hundred patients and stated that the results were "swift, positive, and, in those cases treated in the prodromal stage, most dramatic". He had experienced no failures.

A case of small-pox in which apparently both pustulation and the invariable accompanying secondary rise of temperature did not occur was reported by King and Rosario (1938).

Investigating five drugs of sulphanilamide derivation, Oakley (1938) found only one, 4=4'diaminodiphenylsulphone glucoside, was of any value in mice infected with the influenza virus.

Actinomycosis:

A case of actinomycosis developing in a youth with an open abdomimal sinus following an operation for gangrenous appendix was reported by Walker (1938).

Six days of treatment with sulphanilamide by mouth caused rapid lessening of the purulent discharge and disappearance of sulphur granules. After ten days interval, the treatment was repeated for a further five days resulting in healing of the sinus.

Bacillus Tuberculosis:

The general impression conveyed by all the work done is that tuberculosis can be retarded to some extent, but not controlled, by chemotherapy. It also appears that infection with the human type of tubercle bacillus is more amenable to treatment in the guinea-pig than is bovine infection.

Rich and Follis (1938) observed that sulphanilamide "exerted a striking inhibitory effect upon the development of the tuberculosis" in guinea-pigs infected with a human strain of bacillus. The sulphanilamide was administered subcutaneously in doses totalling daily from 200 to 500 mgm. The latter appeared to be the optimum therapeutic dosage. In spite of the inhibitory effect however the drug failed to prevent completely the growth of tubercle bacilli. They observed that macroscopic lesions in the spleen were much slower in appearing in the treated animals than in the controls.

In an attempt to confirm the findings of Rich and Follis, Buttle and Parish (1938) obtained less striking results. The discrepancy, they thought, might be due to a difference of strain of bacilli.

They inoculated guinea-pigs with human tubercle bacilli in doses of 100 and 1000 million organisms: others were

inoculated with bovine bacilli in doses of 20 and 200 million organisms. Eighty animals in all were inoculated, and half in each group were kept as controls while the other half were given sulphanilamide, 500 mgm. daily; this was administered in a suspension by mouth in four equal doses. The dosage of sulphanilamide was halved after the sixth day on account of toxic manifestations - loss of weight and temporary paralysis - in some of the guinea-pigs. Alll surviving animals were killed on the forty-second day.

It was found that sulphanilamide had not completely arrested the development of generalized tuberculosis, but that it had apparently produced some degree of inhibition of the disease. The lesions of the treated animals that died or were killed after the fourth week of the experiment appeared less than in the controls. Although macroscopic foci were present in the spleens of all the guinea-pigs, they were fewer, smaller and showed less tendency to coalesce in the treated animals; and while in many spleens of control animals no normal splenic tissue could be found microscopically, in most of the treated animals each tubercle was surrounded by a broad zone of more or less normal spleen. But in no instance was there the slightest sign of healing. Many tuberculous foci were present in the lungs of both treated and controls, but they were somewhat fewer and more discrete in the former group and there was less associated basal consolidation. Also the inguinal and tracheo-bronchial lymphatic glands were much smaller and not so caseous in the treated guinea-pigs.

The livers showed macroscopic lesions and variation in extent of the infection in the treated and control groups was slight.

The drug had very little influence on the course of infection in guinea-pigs, and none in rabbits, when the bovine strain of bacillus was used.

Greey, Campbell and Culley (1938) obtained some beneficial effects against human tubercle bacilli provided administration of the drug took place from the very beginning of infection: when treatment was delayed until 17 - 24 days after inoculation sulphanilamide failed to alter the macroscopic appearance of the tuberculous lesions.

Ballon and Guernon (1938) fully confirmed the work and findings of Rich and Follis.

On the other hand Smithburn (1938) noted no beneficial effects from intra-abdominal administration of 200 mgm. sulphanilamide daily for thirty days in guinea-pigs which he had inoculated intracerebally with human tubercle bacilli.

Negative results were also obtained by Kolmer Raiziss and Rule (1938). They administered 200 to 500 mgm. of sulphanilamide per kilo. intramuscularly twice daily for eight days after inoculation of guinea-pigs with human tubercle bacilli. There was no curative effect from this interrupted therapeutic procedure, and a further study of six derivatives of sulphonamide also yielded negative results.

Levin (1939) treated a small group of guinea-pigs with 15 to 150 mgm. of sulphanilamide intramuscularly

each day for eight days before and seven days after the subcutaneous inoculation with tubercle bacilli (type not stated). Necropsies performed eight weeks later failed to reveal any prophylactic or curative action.

Greey, Boddington and Little (1939) repeated the earlier (1938) study of the senior author, and found that the daily oral administration of 300 mgm. of sulphanilamide, divided into four equal doses in twenty-four hours, inhibited the tuberculous process in guinea-pigs infected with human tubercle bacilli.

Birkhaug (1939) was able to show an undoubted inhibitory action of prontosil soluble against bovine tubercle bacilli. Each guinea-pig was inoculated with an exceedingly small dose of bacilli and the experiment was controlled with extreme care. Effect of treatment was assessed in several ways. Whether judged by changes in body weight, by behaviour of the blood-picture, or by the extent of the disease found post-mortem and the numbers of bacilli in the lesions, it seemed clear that the chemotherpay had a restraining influence on the development of tuberculosis and that for the time being it mitigated its effects. Even this partial success was noteworthy being, as it was, in an animal incapable of actual recovery from infection with virulent tubercle bacilli.

Inasmuch as sulphanilamide only exerted an incomplete bacteriostatic effect on the tubercle bacillus further investigation needed to be carried out with new compounds - derivatives of sulphanilamide.

Birkhaug mentioned that he was already investigating the action of "M & B 693" in experimental tuberculosis.

In this connection a report has already been published by Feldman and Hinshaw (1939). By giving comparatively enormous multiple doses of "M & B 693" (2-sulphanilyl-amidopyridine) to guinea-pigs, they were apparently able to retard and modify the course of subsequently inoculated tuberculosis.

Twenty guinea-pigs were inoculated subcutaneously with 0.0001 mgm. of a strain of tubercle bacilli isolated three months earlier from a patient with pulmonary tuberculosis. For three days before and ten days after inoculation 250 mgm. of the drug was given twice daily by mouth to the selected animals. After the tenth day, until death or the end of the experiment eight weeks after inoculation, the dose of drug was halved.

Lesions were found at necropsy in all the members of the control group. The spleen of each was strikingly tuberculous and the lungs of those that survived for five weeks or more after inoculation were slightly or moderately affected. In the group treated with "M & B 693" the following lesions were found:- One animal had definite lesions in liver, lungs and spleen; four had lesions in the lungs but doubtful ones in the spleen; one had only a doubtful splenic lesion; six animals had no macroscopic lesion in liver, lungs or spleen.

The action of "M & B 693" was recorded recently in the case of a woman, aged 45, who had had pulmonary tuberculosis for ten years with occasional exacerba-

tions, whose lungs were now extensively involved and who showed continued pyrexia (Wilson 1939). She had profuse sputum, night-sweats and was wasting rapidly. "M & B 693" was given more or less in desperation to avoid the apparently inevitable fatal outcome. The effect was immediate. Her temperature began to fall at once and, by the end of the week, was normal, The drug was stopped for a week owing to side-effects and her temperature had by then risen again to 99°-100°F. The drug was restarted with the same immediate effect; it was continued for a fortnight, and by the beginning of the second week the temperature had fallen to 97°F where it remained. Sputum had decreased to about half its previous volume, but there seemed to be no alteration of the physical signs in the lungs.

Some weeks after the present investigations were concluded, two American workers, Nayer and Steinbach (1939), published their results of treatment with sulphanilamide of eight patients with advanced pulmonary tuberculosis. All cases had bilateral disease and five in addition showed cavitation. Other forms of therapy had proved useless.

The dosage of sulphanilamide was variable, between 2-3 gm. being administered daily for periods ranging from ten to seventy-one days. Sodium bicarbonate was given at the same time to counter any tendency to acidosis.

Mild cyanosis was observed in every case, most intense during the first few days and persisting throughout to some degree. It disappeared completely within

twenty-five to forty-eight hours after the drug was stopped. Headache, nausea, anorexia, some loss of weight, and one instance of haemolytic anaemia were recorded.

As far as could be evaluated by clinical observations, radiological examination of the chest or laboratory tests for activity, there was no effect, either beneficial or harmful, upon the disease.

Toxic Effects of Sulphanilamide:

New drugs nearly always go through a phase in which their toxic effects receive too little attention in the medical press: later they go through another phase in which they receive too much. The sulphanilamide drugs have for a considerable time been in the second phase, and the medical journals are still flooded with reports of isolated cases illustrating the toxic effects.

Certain toxic effects, usually but not always the result of prolonged administration, may arise during or soon after sulphanilamide treatment. By far the commonest symptom is the so-called cyanosis or blueness of the skin (discussed later).

Nausea, with epigastric pain and sometimes vomiting, are symptoms produced by sulphanilamide. These often appear during the first day or two of administration and subsequently disappear, so that they can be neglected in most cases where there is an indication to continue the drug. There is less likelihood of vomiting if sodium bicarbomate is administered -

due, no doubt, to combatting the tendency to acidosis which exists.

Southwark (1937) found clinical evidence of acidosis in two out of fifty patients treated with sulphanilamide. This led him to study the Co_2-combining power of the plasma of fifteen further cases. In every instance a consistent though variable fall in this power occurred. The mechanism whereby it was produced is thought to be interference with the reabsorption of bicarbomate in the kidney tubules (Marshall, Cutting and Emerson 1938).

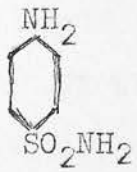
Skin rashes: Occur in about 6 per cent. of cases (Hageman and Blake 1938). The rashes may be purpuric, scarlatiniform, morbilliform or maculo-papular, and the distribution may be general or patchy. So closely do the eruptions simulate the rashes of the common exanthemata that they may lead to difficulties in differential diagnosis during epidemics. Occasionally the rashes are accompanied by itching. The rare condition of exfoliative dermatitis has been described following sulphanilamide.

Drug fever : May occur seven to twelve days after the drug has been started; the temperature may rise to 102^{o}, and it is sometimes accompanied by a rash on the exposed parts of the body. The fever disappears as soon as the drug is withdrawn. It has been suggested that this fever may be caused by liberation of the lysed products of the bacteria. The symptom may easily be confused with a recrudescence of the original infection, although usually the latter will occur after the drug has been withheld. (Colebrook

and Purdie 1937)

Nervous symptoms may arise. Dizziness, depression and headache are common, especially in ambulant patients. Depression seems to be worse with "M & B 693" than with sulphanilamide. Palpitation, paraesthesia, tinnitus and peripheral neuritis are also seen; the last mentioned symptom is very rare with sulphanilamide, but has often occurred with uleron.

By far the most serious condition produced by these drugs is agranulocytosis. Young (1937) pointed out that amidopyrine, phenacetin, certain gold salts, and arsphenamine could produce agranulocytosis, and had in common the benzene ring with an attached amine group (NH_2), which increases the case of oxidation.



Sulphanilamide qualifies for inclusion. In view of observations made later in this thesis on the peculiar combined action of gold and sulphanilamide, it is interesting to note here that claim is made for combined therapy with prontosil rubrum and amidopyrine by Müller (1939): he has had great success thus treating both streptococcal and staphylococcal infections. That all three drugs should be potential causes of agranulocytosis is indeed interesting.

Burton and Howkins (1938) performed serial leucocyte counts on fifty patients undergoing treatment with sulphanilamide (21 gm. over a period of fourteen days). They found a transient polymorph leucopenia in 46 per

cent. and monocytosis in 44 per cent. The blood changes usually occurred between the seventh and twentieth days of treatment. There is no doubt that slight degrees of leucopenia are common, but up to August 1939 only fifteen cases of agranulocytosis due to sulphanilamide had been described - nine of them fatal (Jennings and Southwell-Sander 1937, Johnston 1938). It may well be that it is commoner than is at present considered, as it is impossible to diagnose the condition unless a blood count is done; the symptoms associated with it are intense headache, fever and a deterioration of general condition.

Agranulocytosis seems to be particularly common in cases that have not responded well to the drug. It seems to occur with "M & B 693" as often as with sulphanilamide. It has been more rare, but recorded, with prontosil rubrum and proseptasine. So far no cases have been associated with administration of rubiazol.

Haemolytic anaemia, like agranulocytosis, is also a rare condition, but it occurs usually in the first few days of treatment. There is a sudden fall in the number of red cells and a varying amount of jaundice together with haematuria.

Harvey and Janeway (1937) having treated a series of patients without mishap were, in the course of three weeks, faced with three examples of haemolytic anaemia following sulphanilamide which had been given in large doses. Recovery occurred after transfusion with citrated blood.

One should mention the tragedy which occurred in

America with a proprietary "elixir of sulphanilamide" in the autumn of 1937. The elixir consisted of a solution of sulphanilamide in a menstruum containing diethylene glycol. It was the latter substance which was held to be responsible for the 73 deaths which resulted - usually, it seemed, with anuria.

Cyanosis:

The cyanosis which occurs in the course of sulphanilamide treatment is not associated with respiratory distress, and investigations have shown that it is not necessarily accompanied by a change in the condition of the blood pigment. It seems likely that it is due to the condensation products of the drug itself (Marshall and Walzl 1937c), and it is generally considered that it is not a symptom which should deter the physician from further administration of the drug.

The other causes of cyanosis are methaemoglobinaemia and sulphaemoglobinaemia: they arise quite often during treatment and are responsible for cyanosis which may develop rapidly and to a considerable degree.

Paton and Eaton (1937) concluded that it is methaemoglobin which is the true toxic product of sulphanilamide, but that sulphaemoglobinaemia arises with frequency if sulphates are being taken as well. Methaemoglobin causes no trouble as it is rapidly reconverted into haemoglobin on cessation of treatment and even more rapidly on parenteral administration of methylene blue. In this respect it differs greatly from sulphaemoglobin on which methylene blue exerts no

influence. Sulphaemoglobin has been detected six weeks after administration of sulphanilamide.

Sulphaemoglobinaemia is due to the union of intestinal H_2S with the haemoglobin, a reaction which is catalysed by sulphanilamide: it is to be avoided by withholding purgatives, except very mild ones like liquid paraffin, and by giving a low-residue diet excluding eggs (Archer and Discombe 1937).

Colebrook and Kenny (1936b) in a series of 38 cases of puerperal infection treated with prontosil, recorded non-fatal sulphaemoglobinaemia in three patients, in one of whom it developed after as little as 4 gm. had been taken; all the patients in this series had magnesium sulphate. Later (Colebrook et al 1936c), they recorded another series of 26 cases of puerperal sepsis treated with prontosil but from whom magnesium sulphate was withheld; none of these patients developed sulphaemoglobinaemia. Though very rare, fatal cases have been recorded. One was described by Frost (1937). His patient, a girl of 12 suffering from suppurative arthritis of the knee, succumbed after only 10 c.c.m. Prontosil soluble and 6 g. Proseptasine had been given. It seemed therefore to be more a question of idiosyncrasy to the drug than of overdosage in this case.

Diagnosis of sulphaemoglobinaemia is made by spectroscopic examination of the blood. This method is seven times more sensitive than is perception of visible cyanosis. Archer and Discombe were able to detect sulphaemoglobin in concentration greater than that corresponding to 4 per cent. haemoglobin (Haldane), while cyanosis became notable only when about

30 per cent. hamoglobin had been converted.

The characteristic band of sulphaemoglobin is in the red part of the spectrum - lying between 6150 and 6280 Angström units. To distinguish sulphaemoglobin from methaemoglobin, ammonia (0.4 per cent.) is added to the specimen of dilute shed blood; ammonia destroys the α-band of methaemoglobin but does not affect that of sulphaemoglobin.

Other confirmatory tests for the presence of sulphaemoglobin can be made: such are in the persistence of the α-band after addition of reducing agents, eg. ammonium sulphide, sodium hydrosulphite or sodium cyanide; (2) shift of the α-band towards the violet on treatment with carbon monoxide.

With experience it is possible to detect quite small quantities of sulphaemoglobin, even without drawing off blood, by using a torch and direct vision spectroscope (Harrison 1930). The blood in the lobe of the ear is examined. Such a method is particularly acceptable to patients, who may exhibit cyanosis even before sulphanilamide is commenced - as in pneumonia or tuberculosis.

Discombe thought it was highly probable that all drugs containing the group $C_6H_5N=$. were capable of causing methaemoglobin and of facilitating the production of sulphaemoglobin. Such drugs are derived from aniline or nitrobenzine, e.g. phenacetin, acetanilide, methyl acetanilide, sulphanilamide or nitrobenzene. He thought that if any new drug containing this group were administered in large doses such a complication

should be anticipated, and he considered that in treatment with sulphanilamide it was important to examine spectroscopically the blood of all patients who developed cyanosis.

TREATMENT OF PULMONARY TUBERCULOSIS.

There is more than a little truth in the saying that nature cures the disease while the remedy amuses the patient. But to keep a patient happy and amused when ill will contribute to his recovery. A drug may be used not only for its pharmacological action but also for its psychological influence, and the secret of the present popularity of heterodox practitioners is that they appreciate and fully utilize methods which are impressive to the patient.

In few diseases have there been a greater number of vaunted remedies than in pulmonary tuberculosis. So long as these remedies act as psychological tonics they all prove to be of value, but their value is short-lived. As soon as the novelty has worn away the benefit is no longer apparent, the old symptoms return and the patient reverts to his former condition. The phthisical patient is often swayed by others - easily influenced by suggestion - and therefore ready prey for the plausible quack who may scarcely know one end of a stethoscope from the other. But pulmonary tuberculosis is a chronic disease and is not cured overnight by suggestion alone, nor is it cured by the starvation-diet of certain so-called naturopaths.

Even amongst the orthodox opinion varies. The therapeutics of any one generation are always absurd to the second succeeding generation, but the basic treatment for tuberculosis, aiming to build up the natural resistance of the patient by means of rest, fresh air and a nourishing diet,has withstood the test of time.

Most alleged remedies for the disease, after enjoying a brief popularity, have been discarded as useless. It remains to be seen whether sulphanilamide merits an extensive trial or whether it should be added to the already long list of discarded "remedies" for tuberculosis.

Treatment is the most important part of the medical art from the point of view of the patient. Treatment of pulmonary tuberculosis is tedious and requires great patience. Despite the introduction of collapse therapy there is still no short-cut to cure. Rest, and prolonged rest at that, remains the sheet-anchor of all treatment.

Before assessing the role that should be played by sulphanilamide in treating tuberculosis one must consider the lines of therapy already employed - consider how effective they are, the results that they can produce, the occasions when they can or cannot be used, their disadvantages as well as advantages, and whether or not sulphanilamide may be used coincidently with them. When these points have been clarified one can better adjudge what scope there is for the use of sulphanilamide.

The ordinary lines of treatment adopted for pulmonary tuberculosis may be classified under three headings:-

(a) Treatment to improve the general health of the patient.

(b) Treatment to check the tuberculous lesions.

(c) Treatment of specific symptoms.

Treatment to Improve the General Health of the Patient.

Anything which undermines the general health of a patient and reduces his vitality may prepare a favourable soil for the growth of tubercle bacilli within the body. Anything which stimulates the vital defensive forces that are inherent to some degree in every individual, or which improves the nutrition of the body, should hinder proliferation of the bacilli.

With improvement in the general condition the local lesion may cicatrize, or the dissemination of bacilli may be prevented.

The aim of the treatment is therefore to increase the resisting powers of the patient and so render his body an unsuitable soil for growth of the invading bacilli. Rest , fresh air, sanatoria and good food are the chief examples of such treatment.

Rest:

To formulate a method of treatment applicable to all cases of pulmonary tuberculosis is impossible. Treatment must be elastic, adapted to suit each case, fitted to the polymorphous nature of the disease and to the various accidents and complications arising in its course.

Rest in bed is required in pulmonary tuberculosis to ensure that respiratory movements shall be sufficiently quiet and shallow as to allow the formation of fibrous tissue to take place in the lungs. Rest provides the opportunity for nature to arrest the disease.

Wingfield (1929) describes seven stages of rest. On the one extreme, absolute physical and mental rest as for cases with typhoid fever; on the other, permission to wash out of bed and visit the bathroom though otherwise remaining in bed. Intermediate stages are permission to feed oneself and talk; to read, write and have visitors; to wash oneself and sit upright for meals; to sit in a chair beside the bed; to walk to the lavatory.

The duration of rest is dependent on the rate of progress and it is judged by various criteria. These are the temperature, pulse-rate, weight, blood-sedimentation rate, x-ray appearance, symptoms, physical signs, blood examination (polymorph-lymphocyte-monocyte ratio and haemoglobin estimation), and the vital capacity of the lungs.

Briefly, in case of exudative tuberculosis, the temperature should be settled, resting pulse-rate below 90, blood-sedimentation below 20, nutrition reasonably satisfactory, symptoms improved and x-ray appearance considered to show satisfactory progress before the patient is allowed out of bed .

More latitude is permissible in cases of chronic fibroid tuberculosis since pyrexia etc. have less significance and may indeed be quite compatible with a reasonable state of health.

Exacerbation of existing symptoms or appearance of new ones, increase in moist râles, return of pyrexia, increased pulse or blood-sedimentation rates, significant loss of weight or radiological evidence

of spreading disease, all call for more prolonged or even complete rest in exudative cases.

Fresh Air.

When one speaks of fresh air it does not mean air rich in oxygen. There is the same proportion of oxygen in city as in country air, and there is less at high altitudes, such as Switzerland, which are so popular for tuberculous patients. The benefit of fresh air is probably due to the cold which has a stimulating action upon the body.

As long ago as 1840 George Bodington urged treatment of tuberculosis with fresh air and a generous diet. Yet there are many still living who recall the curtains, weighted down with sandbags, which used to be employed to exclude fresh air and sunlight from the rooms in which lay patients dying from consumption.

Nowadays fresh air and tuberculosis are so closely linked together in the popular mind that fresh air is believed to be a specific for tuberculosis. This is of course a fallacy since, with few exceptions, all sick persons do better if they are nursed in the fresh air. But there is no question about the good results attributable to fresh air in tuberculosis. The temperature subsides, night-sweats vanish, sleep becomes sounder and more refreshing,and there is a very striking improvement in the general appearance of the patient. That is evident to all onlookers and acts as a tonic to the patient himself.

Besides the obvious benefit of fresh air to the tuberculous patient, there is another consideration,

less obvious but no less important. It is that he is less likely to contract catarrhal conditions in the open air than in crowded, stuffy and overheated rooms.

Sulphanilamide does not enhance the natural resisting power of the body. Sulphanilamide is employed for its anti-bacterial properties. It should therefore be classified in the second group of anti-tuberculous treatment, among therapeutic measures intended to check tuberculous lesions. It is in no sense a substitute for measures such as rest and fresh air which are calculated to improve the general health and resistance to disease. No measure calculated to check tuberculous lesions is by itself sufficiently potent to replace or entirely dispense with rest and general tonic treatment.

Sulphanilamide may be given to tuberculous patients but only at the same time as they are deriving benefit from rest and fresh air.

Sanatorium Treatment.

The aim of the sanatorium may be summarized as follows:- It aims to teach the patient how to live under his altered circumstances and how to train the body to as high a condition of physical fitness as possible.

The patient is treated for a time in exceptional surroundings with the ultimate object that he may be able and willing to perform ordinary work in his usual environment, unless this is obviously unhealthy, when his occupation should be changed.

While in hospital he is removed from those whom,

by carelessness or ignorance, he might infect. He learns the principles of how he should live and on his return home he can teach others likewise.

A summerhouse in the garden at the patient's home is a poor substitute. The co-called "sanatorium treatment at home" usually fails because it is not possible to produce at home all the factors which are present in a sanatorium.

A sanatorium is the method of choice for all early cases of pulmonary tuberculosis. Acute fulminating cases, chronic fibroid disease and advanced phthisis are not suited for treatment in a sanatorium, but with these exceptions probably all cases of pulmonary tuberculosis would benefit from institutional treatment.

As an aid to hastening recovery, sulphanilamide might be a valuable adjuvant to sanatorium treatment. It is relatively cheap and its benefits or toxic effects could be closely observed in hospital. Indeed it is really unsuited for patients outside an institution, in places where facilities for blood-examination and control are lacking.

Heliotherapy.

Medical literature abounds in favourable reports about heliotherapy in extrathoracic tuberculous lesions. Inasmuch as the mortality of patients with such lesions is negligible, and the disease tends to spontaneous recovery, the statistical results will almost invariably be excellent.

Most of those who have applied heliotherapy in

pulmonary tuberculosis agree that its only field of usefulness is in patients with sclerotic or fibroid lesions; that patients with fever, tachycardia, and other symptoms of toxaemia are liable to be harmed by the treatment. Cooper (1928) wrote that "taking the consensus of opinion of medical officers who are using heliotherapy on such classes (hospital) of patients, it appears that heliotherapy intelligently used in fibrosing cases of pulmonary tuberculosis showing a tendency to improve, will hasten improvement."

In other words heliotherapy is recommended in pulmonary tuberculosis only for those cases that tend to spontaneous recovery. It is likely that the benefit, if any, is derived from the stimulus of fresh air on the skin or from psychological causes, and not from the sun rays.

For those patients with pulmonary tuberculosis or other diseases who are receiving sulphanilamide, exposure to sunlight should be restricted. Thomson (1939) points out that sunlight is a prominent factor contributory to production of skin rashes in those sensitized to the drug.

Climate and Sea-Voyages.

A change of environment has for centuries been considered beneficial. Celsus (25 B.C.) wrote:- "The patient must change his climate, taking care to remove to a grosser one than that he leaves, and therefore from Italy to Alexandria is a very agreeable change."

A century ago the tropics were advised, then Maderia was fashionable and later Davos became the Mecca of the consumptive. Belief in the mountain air for consumptives was held by the ancient Greeks and Indians.

The modern tendency is to regard climate as a matter of secondary importance. There is less desire to send the patient abroad.

Gauvain (1930) thought the English climate was good for the tuberculous by virtue of its variability. But no air in the world can make up for the absence of medical guidance and discipline which a well-conducted sanatorium provides. Still, popular belief in the value of climate is so strong that it is generally wise, for psychological reasons, to allow the patient to go where he wishes, provided he can get proper treatment there and the place he selects is not actually unsuitable for him. No patient, however, suffering severely from the toxaemia of tuberculosis ought to be sent abroad. The fatigue of the long journey may do infinite harm.

High altitudes are suitable for early afebrile or advanced quiescent cases: unsuitable for active, febrile cases, for cases with emphysema or advanced fibrosis, for cases with cardiac or renal complications, and for patients who have recently had an haemoptysis. The sea-coast is suitable for cases with laryngitis, bronchitis and emphysema.

In treatment of active tuberculosis a sea-voyage is almost always a mistake. It should be reserved for

those in complete convalescence and preferably for those who can stand a sea-trip well. Theoretically the good food, the rest and the opportunity for fresh air and sunshine are all satisfactory. In practice the cabin may be extremely hot and ill-ventilated, not at all suited to the tuberculous patient. Moreover the monotony causes a consumptive to be introspective, and this may produce depression of spirits.

Diet.

A variety of dietetic systems have been recommended in the past for the treatment of tuberculosis but none has proved to be of specific value. Some may even have been harmful.

In outlining the modern principles of diet in tuberculosis Dunlop (1939) remarked that no diet was definitely contraindicated provided the digestion was good, and held that a good cook was more useful than a detailed diet sheet.

In principle the patient requires sufficient food to cause a gain in weight. This gain should be steady and weekly, though the ultimate weight to be aimed at is a matter of opinion. Some think it should be about a stone above the previous best weight. Wingfield (1939) held that the normal weight of the individual in health need not be exceeded and that all attempts at stuffing or over-fattening should be avoided.

The ordinary diet will require slight alteration if the patient is to receive sulphanliamide, "M &

B 693" or allied drugs, with the exception of rubiazol, because sulphur-containing foods or medicines are prone to cause sulphaemoglobinaemia. Eggs and onions must be excluded and magnesium sulphate and like saline purgatives avoided.

Sulphaemoglobinaemia has never been recorded with rubiazol even under provocation with massive doses of magnesium sulphate.

Exercise:

Exercise is complementary to rest and like the latter must be very strictly supervised. Over-exertion can quickly undo the benefit of many months of rest in bed.

At many sanatoria walking is the only form of exercise permitted, and it is sound to allow no other form of exercise for at least two years after the disease has become arrested. Patients ought never to run nor walk quicker than three miles an hour.

For patients who have to earn their living by manual labour a system of graduated labour may be employed when they have finished the initial period of rest. Paterson (1911) developed a system along these lines. He believed that the reactions in tuberculous patients, which followed a moderate amount of exercise, were beneficial; that the patient was in effect being treated by his own tuberculin. Whether this was the true explanation or not, the results of the treatment were said to be very good.

Cooper and Dow (1928) described certain exercise tests which they found to be of value in prescribing

exercise and as an aid to forming an ultimate prognosis. They considered the temperature was the most important guide to the patient's capacity for exercise, but other signs such as loss of weight, increase of symptoms, greater sedimentation rate or decreasing vital capacity called for readjustment of treatment and usually increased rest.

In regard to recreation, the best course seems to be to forbid no game or pastime, unless it is harmful to the patient's health. He has quite enough to bear without any unnecessary restrictions. Patients should be allowed to choose their own recreations and all harmless amusements should be encouraged. They should not be allowed to play any game which unduly excites them, and it must be remembered that relapse is more often the result of outdoor games than any other caues. All energetic games, e.g., hockey, tennis, football, cricket, must be forbidden.

TREATMENT TO CHECK TUBERCULOUS LESIONS.

Collapse Therapy.

There is no question but that operative measures in treatment of phthisis represent a tremendous advance in this sphere. The treatment is still comparatively young but the principle is not so. Tuberculosis requires rest. A tuberculous joint must be immobilized. So, if possible, must a tuberculous lung.

Every day the lungs of a patient have to open and close nearly 30,000 times. This number will be greater after exertion but minimal if the patient is at rest. Immobilization of the diseased lung is greatly facilitated by collapse-therapy, which acts as a local splint. The methods of established value are:-

1. Artificial pneumothorax.
2. Intrapleural division of adhesions.
3. Phrenicectomy (crushing or evulsion of the phrenic nerve).
4. Extrapleural Thoracoplasty (local or extensive resection of the ribs.)
5. Extrapleural pneumothorax.

Early and progressive cases of the exudative or caseous type represent an urgent problem, and are treated by the simpler methods such as artificial pneumothorax. The more drastic measures involving rib resection are reserved for established fibrotic disease, especially when cavity formation predominates. They may, without detriment to the patient, be performed only after considerable delay. Sometimes the methods may be employed in combination with advantage.

Bilateral disease presents an obvious barrier to the treatment and so also, with the exception of ulceration of the larynx, do complications. It may be seen therefore that sulphanilamide could be usefully combined with certain forms of collapse therapy. In bilateral cases with one lung collapsed, sulphanilamide might be given to check disease in the opposite lung as well as to assist in arresting the activity in the collapsed lung. It is probable theoretically that the drug would be of assistance in cases more suitable for artificial pneumothorax or phrenicectomy than for thoracoplasty since the latter measure is utilized mostly in fibrotic lesions.

Complications such as extrathoracic tuberculous foci would not contra-indicate the use of the drug but rather call for its employment, since a drug circulating in the blood might influence an early metastatic focus which had resulted from blood-borne infection having its origin in the lungs.

Artificial Pneumothorax.

More than a century ago this measure was suggested on theoretical grounds. Now it is employed all over the civilised world.

The principle is to relieve tension, produce lymph stasis and rest the diseased lung, thus preventing spread of the disease and allowing nature to effect a cure. If in addition a cavity is present, it may be closed when the tension of the lung is relieved by collapse.

Artificial pneumothorax implies the injection or aspiration into the pleural space of sterile air or other harmless gas, the quantity injected being regulated by reference to a manometer which registers the intra-pleural pressure. Normally, after the induction, this pressure is a negative one, e.g. - 10 to 5 cm. water. At subsequent refills the intra-pleural pressure is increased gradually until the desired degree of collapse in the diseased lung is attained. Thereafter, by regular refills, usually every 1-2 weeks, the pressure is kept at the same level for an extended period - commonly two or three years. Provided the disease appears to be arrested the collapsed lung is then allowed slowly to re-expand.

Failure to effect an induction or a satisfactory collapse is most commonly due to the presence of pleural adhesions or an adherent pleura.

Indications.

Artificial pneumothorax is carried out in all but the very earliest cases of acute or subacute exudative tuberculosis of a unilateral nature; also it is used in less acute cases in which activity persists in spite of rest in bed, or where the disease in the lung remains stationary, and especially if constitutional improvement is not satisfactory. Repeated haemoptysis or cavity formation are likewise indications for timely pneumothorax control.

Almost always artificial pneumothorax is attempted before resort is made to other more drastic operative procedures. It may be performed in selected

bilateral cases with activity mainly in one lung. Sometimes it is employed in bilateral cases, a pneumothorax being induced on both sides, but in such cases it is rather a policy of desperation. Obviously, while both lungs are actively diseased, both cannot be really effectively collapsed at the same time.

Contra-indications:

Extensive bilateral disease, pulmonary emphysema and dangerous cardiac complications are the chief contra-indications to artificial pneumothorax, but a satisfactory induction can seldom be obtained in old-standing fibroid cases owing to the presence of dense pleural adhesions. Chronic, thick-walled cavities may be so rigid that they are not obliterated completely even when the rest of the lung is satisfactorily collapsed.

Treatment carried out for a period such as two or more years demands much patience and co-operation between doctor and patient alike. It is time-consuming and may interfere with working-hours, and on these grounds there are those who prefer phrenic nerve operations.

Were sulphanilamide effective it might well aid in shortening the period for which the lung would need to be collapsed. Although indeed a potent therapeutic weapon it is unfortunate that artificial pneumothorax is so often impracticable.

In this connection I reviewed the records of the last five hundred patients admitted to the Royal Victoria Hospital, a sanatorium only for early cases of pulmonary tuberculosis. Out of this number it was

possible to secure an induction in only 92, and of these 7 had shortly to be abandoned as being unsatisfactory. It is probably true to say that even 85 cases out of five hundred (17 per cent.) is a higher percentage than usual among sanatorium inmates.

Since some authorities quote a figure in the region of 10 per cent. of cases as being suitable for artificial pneumothorax it leaves much to be desired.

Complications:

It is doubtful whether sulphanilamide could be of any service in preventing complications from arising during artificial pneumthorax therapy. Certainly it would not abort those sudden occurrences, air embolism and pleural shock, either of which may be fatal, which may happen during induction. Nor, obviously, could it prevent puncture of the lung, pneumo-peritoneum, mediastinal displacement, pleural hernia or surgical emphysema, all of which sometimes occur.

It is possible that the drug might lessen alarming febrile reactions though it would probably not prevent the commonest of all complications, pleural effusion, which occurs in approximately 50 per cent. of cases of artificial pneumothorax.

In the majority of cases these effusions disappear spontaneously and therefore call only for expectant treatment, but in a small proportion the effusion becomes purulent and a pyopneumothorax results. This is a serious occurrence and usually an indication to abandon pneumothorax. Possibly use of sulphanilamide would avoid the necessity, though such is unlikely.

Results of Treatment by Artificial Pneumothorax.

Saugman and Gravesen classified the results of treatment of pulmonary tuberculosis under three headings:-

Group (i) cases with a free artificial-pneumothorax (A.P.)

" (ii) cases with adhesions but otherwise a satisfactory A.P.

" (iii) cases with adhesions which prevented the A.P. from being satisfactory.

Their results over a period of from 5 to 13 years showed:-

Group (i) - 70 per cent. well and at work.

" (ii) - 33 per cent. well.

" (iii) - 11 per cent. alive and well.

The experience of the London County Council of artificial pneumothorax therapy is interesting. Bentley (1935) compared the results of 677 cases with artificial pneumothorax, under the L.C.C. anti-tuberculosis scheme, treated between 1921 and 1930 with a control group of 3329 conservatively treated subjects discharged from L.C.C. tuberculosis institutions in 1927 and followed up for 5 years.

The survival of all cases investigated was approximately 20 per cent. higher in the group with A-P (artificial pneumothorax) than among those conservatively treated. But of the A-P cases no fewer than 60 per cent. had an incomplete collapse of the lung. This had a notable effect on the mortality. The figures were:-

Alive at the end of 3 years -

Group with complete collapse 66 per cent.

" " incomplete collapse 50 per cent.

Of the survivors the medical condition was much better in the group with A-P than in the control. Thus the disease was quiescent at the end of 5 years in:

Group with A-P - 64 per cent.

Control group - 38 " "

Intrapleural Division of Adhesions:

All the above figures point to the importance of obtaining a complete, or at least selective, collapse. If, in the last series, 20 per cent. is taken as accurately representing the benefit of an artifical pneumothorax before 1930, it is most probable that the results at present would show a higher figure. This is because the practice of dividing adhesions is now widely used. Only 5 per cent. of Bentley's series had undergone adhesion-section.

It has been estimated by Alexander (1937) that 85 per cent. of the cavities which remain patent kill their hosts within three years. A pneumothorax which does not close a cavity is therefore of very little value. Adhesion section often converts an incomplete lung collapse into a complete one and therefore obliterates persistent cavities.

There is no reason why sulphanilamide, for what it is worth, should not be combined with artificial pneumothorax or other forms of collapse therapy in treatment of pulmonary tuberculosis.

An objection might be raised that, using the two methods of treatment in combination, it would be impossible to assess the true value of either. If, however, the lung had been collapsed for a considerable period, it would be reasonable to assume that

sudden amelioration in the condition of the patient, coinciding with administration of sulphanilamide, were due either to the chemotherapeutic or psychological effect of the drug.

Phrenic Nerve Paralysis:

Section or evulsion, crushing or injection of alcohol into the phrenic nerve will cause paralysis of one half of the diaphragm, and consequently, those movements of the lungs which are controlled by the diaphragm will cease.

Opinion varies greatly on the value of this procedure in phthisis.

Morin (1931) regarded paralysis of the phrenic nerve as preferable to artificial pneumothorax, because there were fewer complications, it did not necessitate frequent visits to the physician for refills and it often gave the lung sufficient rest to effect a cure. Moreover a pneumothorax could always be induced later if necessary. He treated 321 patients with artificial pneumothorax and 174 with phrenic nerve paralysis with the following results, but many more of the pneumothorax cases than of the phrenic paralysis became sputum negative for tubercle bacilli.

	Artificial Pneumothorax.	Phrenic Paralysis.
Better.	50 per cent.	58 per cent.
Stationary.	27 " "	32 " "
Worse.	19 " "	10 " "

Sauerbruck (1930) advocatedphrenic evulsion before thoracoplasty but thought that in itself it was practically valueless.

Edwards and Stevens (1938) considered the popularity of phrenic evulsion at any given time was inversely proportional to the success of major surgery. They give a detailed analysis of 1000 phrenicectomy operations. They suggested that the paralysed dome of diaphragm far from impairing the efficiency of the cough actually enhanced it by offering less resistance to contraction of the abdominal muscles. As to the lung, they found that dense pleural adhesions tended to limit the collapse to the less affected area; also the greater the extent of disease the less was the likelihood of achieving universal relaxation.

Durran and Sierra (1938) recording their results in 143 cases, found phrenic nerve operations on the right more successful than on the left. This might be due to presence of the liver on that side. As regards complications, Harper (1938). reviewing 173 cases of phrenicectomy found clinically significant gastric-intestinal symptoms in 25 to 50 per cent. of cases after operation. There was a different syndrome for the two sides. On the left it was characterized by decreased appetite, feeling of fulness, and often nausea and vomiting, while the stomach was perpendicular, and pylorus acutely angled on radiological examination; on the right, pain in the right upper quadrant and symptoms of gall-bladder disease predominated, while the stomach assumed a transverse position with fundus narrow and devoid of gas. Harper thought that temporary interruption of the

phrenic was therefore preferable to permanent.

Phrenicectomy may be combined with or preliminary to either artificial pneumothorax or thoracoplasty, and also it may be used to relieve thoracic symptoms arising from adhesions, but the value of the operation is most uncertain.

Thoracoplasty.

Morriston Davies (1933) considered this operation a serious one, which was usually advised to prolong a patient's life when other methods had failed. Some were cured, others received no benefit and others were made worse by the operation even in carefully selected cases. He wrote, "For those who win the gain is enormous, whilst those who lose have gambled a year or two of an invalid's life against health and freedom."

He gave the following indications for thoracoplasty:-

(1) Every case of chronic unilateral tuberculosis in patients up to the age of forty-five which cannot be arrested by simpler means. The term unilateral does not exclude some fibrosis in the contralateral lung, but does exclude active processes.

(2) Every unilateral case with single or multiple cavities with rigid walls.

(3) Cases with haemoptysis which cannot be controlled. When the haemoptysis is a danger to the patient's life some latitude is permissible in respect of disease in the other lung. Such disease must not however be progressive and cavities are a contra-indication.

(4) In exceptional cases, thoracoplasty is done when

the disease is exudative in character.

To this list one might add certain cases of tuberculous empyaema with thickened pleura when the pleural cavity will not close.

Thoracoplasty entails excision of lengths of bone from the posterior parts of the ribs as far back as, and sometimes including, the transverse processes of the vertebrae. The number of ribs and amount of each removed varies according to the extent and character of the disease: it comprises from four to ten ribs and always should include part of the first and second.

Surgical opinion is more and more becoming in favour of a partial as opposed to a full thoracoplasty. Mason (1937) remarks that the principal requirement of a fibrotic lesion is facility for its scar tissue to retract, but an exudative lesion requires above all things rest, at any rate until fibrosis develops.

At present, thoracoplasty is the best method of treatment known for certain stages of the disease, but the physician should aim to prevent the patient from reaching that stage in which such serious surgical procedures become necessary. In these stages, as has been pointed out, sulphanilamide is unlikely to be of value.

Extra-pleural Pneumothorax.

This, comparatively recent addition to operative treatment of pulmonary tuberculosis, is rapidly becoming popular. It is used when artificial

pneumothorax fails and when the age or condition of the patient contra-indicates thoracoplasty.

The operation consists in stripping the parietal pleura from the deep surface of the chest wall and mediastinum to allow collapse of the underlying lung. The result is to leave a large raw space into which air can be introduced under pressure to maintain collapse.

First employed by Tuffier in 1891, when he used neutral fat instead of air for maintaining collapse, it underwent a variety of development and modification until Nissen (1937) finally popularized the operation in its present form.

Schmidt (1936) has given personal reports on 200 cases of extra-pleural pneumothorax. At the end of one year 63 per cent. of his patients had to be given oil, air being unsatisfactory, to maintain the collapse.

At the Laennec Hospital in Paris, Maurer and de Savitsch (1938) reported good results in about two-thirds of a series of 78 cases with extra-pleural pneumothorax. They considered that the operation could in no way be considered safe or beneficial when the lesion was of a type which could not be treated by intra-pleural pneumothorax. They thought it very promising for children in whom thoracoplasty caused profound changes in the growing skeleton; also in pregnant women, as rapid collapse of developing lesions, in absence of much trauma, often achieved satisfactory clinical results without interrupting pregnancy.

The operation has been performed on both sides, and can be combined with an intra-pleural pneumothorax on the same or contralateral side. In the latter instance it may prove preferable to a bi-lateral intra-pleural pneumothorax.

Gold Treatment.

Preparations of gold have been used for many years in the treatment of pulmonary tuberculosis, and sanocrysin is the form that has been most commonly employed. Sanocrysin is the double thiosulphate of gold and sodium, which was prepared by Moëllgaard and was believed to destroy tubercle bacilli in vivo. This is almost certainly untrue. Although weak solutions of gold salts will inhibit the growth of tubercle bacilli in culture, very few still believe that gold has a bactericidal effect on bacilli within the body. If it has a beneficial effect, its mode of action is not clear. There is much doubt about its efficacy but none about its dangers.

One of the pioneers of gold-treatment, Secher of Copenhagen (1938) after using gold for 15 years concluded that the reactions provoked by sanocrysin therapy were due to liberation of toxins from tuberculous or rheumatic lesions. He thought they might be prevented by giving large doses of vitamins A, B and C before and during treatment.

The view of the majority is that the symptoms are due to metal poisoning, and they are usually described as gold intoxication.

I would venture to suggest that both views are

correct up to a point. I have witnessed a severe pyrexial reaction accompanied by the appearance of moderate albuminuria following the first injection of gold - Crisalbine 0'01 gm. The reaction was analagous to that produced by a large injection of tuberculin. The disturbance lasted 3-4 days. Surely such reaction was not due to poisoning by so small a dose of gold ?

On the other hand, admittedly, there are toxic manifestations undoubtedly due to gold-intoxication - and which cannot be imitated by injecting tuberculin. These appears rather later, after a gold-depot has formed in the body, and they may not coincide with an injection. They are more persistent and dangerous. They include certain skin conditions (exfoliative dermatitis etc.), effects on the bone-marrow (aplastic anaemia, agranulocytosis or thrombocytopenic purpura), on the liver (hepatitis and jaundice), on the nervous system (peripheral neuritis, epileptiform attacks etc.), and on the digestive tracts (stomatitis and diarrhoea). Probably marked albuminuria, particularly if persistent and if associated with the presence of casts or red blood cells in the urine, is also due to gold. The others, pyrexia, mild albuminuria, anorexia, possibly diarrhoea, increase in cough and sputum etc. are, I suggest, manifestations of tuberculous toxaemia.

The frequency of symptoms of toxicity is very variable. I analysed the records of 88 patients at the Royal Victoria Hospital, Edinburgh, who had been

given gold-treatment during the year 1937, 1938 and the first six months of 1939.

The preparations of gold that were used for these cases were sanocrysin and crisalbine - chiefly the latter. The dosage employed was usually as follows:- initial dose 0.01 gm.; then 0.02 gm. and weekly increases of the same quantity up to 0.1 gm; thereafter increases each week of 0.1 gm. up to a total of 0.7 gm. The following results were recorded:-

Results of Treatment with Gold	Males	Females	Total
Patients treated with gold:	41	47	88
Completed full course:	20	8	28
Discontinued owing to toxicity:	16	34	50
Developed albuminuria:	4	20	24

Some cases were discharged before completing their course and the gold was discontinued in others as being useless. The total percentage of toxic reactions was nearly 57, and as can be seen the predominating sign of toxicity in the women was albuminuria.

Apart from the high incidence of toxic effects, the opinion of gold-treatment at the Royal Victoria Hospital is summarized in this statement - "That gold appears to do good in just those cases which would do well without it." Its use has been discontinued at the hospital.

While gold has been abandoned for tuberculosis also in many other parts of the world, there remain those who still have faith in it. One of these is Menendez (1938) who gives the following results of

of gold in 150 hospital patients:-

Clinical and radiological cure - -	17%
Clinical cure and radiological improvement	34%
Unimproved - - - -	13%
Worse or died - - - -	34%

He believes gold should be applied in cases with bilateral pulmonary lesions when the exudative character is not predominant, and in cases with fine bronchogenic or haematogenous nodes of recent origin, provided no extrapulmonary lesion is present. An exception is made in cases of laryngeal tuberculosis and in those with small well-delineated cavities where the remaining parenchyma is not involved. He considered it of no value in confluent haematogenous lesions with extra-pulmonary involvement, in broncho-pneumonic infiltrations, in large pneumonic lesions with cavities and in cases of large thick-walled cavities.

With courses of 8-9 gm. he records complications in 45 per cent. of the cases.

It has been suggested that gold acts as a catalyst and that equally good results may therefore be obtained with small as with large doses. Some of those, therefore, who still believe in the value of gold, are now employing very much smaller doses than previously.

Regarding the uew of sulphanilamide and gold together, a matter which is discussed elsewhere in this thesis, it must be admitted that theoretically it is unsound as both are apt to cause agranulocytosis.

Tuberculin.

After nearly fifty years the believers in tuberculin, one time a supposed cure for tuberculosis, have not succeeded in convincing the world that tuberculin has any real value in treatment.

In favour of tuberculin are claims that some patients who have failed to improve under sanatorium or other treatment do improve with tuberculin; also that patients with incipent pulmonary tuberculosis treated with tuberculin fail to develop the disease, and that strong hypersensitiveness is corrected so that after treatment the patients fail to react even to large doses of tuberculin.

On the other hand the great majority of investigators have not observed any genuine benefit from tuberculin. Some patients certainly appear to improve with it, but others do not; and the tuberculin-therapy may well coincide with a period of remission in those who seem to improve, since pulmonary tuberculoiss is a disease that ebbs and flows. Moreover patients who are hypersensitive to tuberculin do not necessarily develop clinical pulmonary tuberculosis, and the incipient type of case is just the type that does well under any treatment.

Administration of tuberculin is equivalent to a natural auto-intoxication, similar to that which can be produced by exercise in the tuberculous. Consequently tuberculin is unnecessary when slight auto-intoxication is already taking place and is harmful when it is acute.

To summarize:- There is no definite proof of benefit from tuberculin in any form of the disease: considerable risk is attached to its use: although still used in France and Germany, it has been abandoned in the United States and most other parts of the world.

Shock Therapy.

The reaction or shock which follows an injection of a quantity of tuberculin is an allergic or specific reaction, because it is not obtained in those who are non-sensitive to tuberculin. The shock is however very like that produced by copper or other substances, and closely similar to anaphylaxis.

Patients with pulmonary tuberculosis have sometimes made sudden and unexpected improvement following shocks - e.g. rupture of a lung, pleural shock, over-exposure to sunlight. On this basis, attempts have been made to produce the same results by large injections of serum, sanocrysin etc.

Burrell (1937) thought it was a method to be used with the greatest caution. He considered the most striking cases of improvement occurred in young patients of fourteen to eighteen years of age with acute pulmonary tuberculosis.

Owing, no doubt, to its extreme danger it is a method but little used.

Calcium

Prest (1922) described a series of cases of tuberculosis treated with collosol calcium. He gave

0.5 c.cm. hypodermically at intervals of a week or longer. In a few cases there was some reaction, but no serious complications arose. In many patients he noted distinct improvement, such symptoms of activity as night sweats disappearing readily under the treatment.

Calcification plays an important role in the cure of tuberculous lesions and, though some may deny it, there is usually a calcium deficiency in the blood of tuberculous patients. In addition, workers in lime are notoriously free from tuberculosis.

Yet, administration of calcium to patients usually produces poor results. Indeed, I have been most impressed with the apparent futility of the measure. I have seen a patient receive 10 ccm. Calcium Gluconate daily by injection for three months without manifesting any benefit. In numerous case records at the Royal Victoria Hospital, dating back several years, it was most exceptional to find even the least evidence of improvement after a prolonged course of calcium.

Calcium is claimed by some to give great relief in intestinal tuberculosis and by others to be a useful haemostatic for arrest of haemoptysis. Most authorities are however very sceptical about, or deny, both claims.

Calcium and Sulphanliamide are not incompatible and might be given together.

Cod-liver-oil and Vitamins.

Cod-liver-oil is widely used in Tuberculosis. It can be obtained in tasteless form. Rich in vitamins A and D., it is very nutritious and especially useful in

chronic cases who are under-weight. It is quite unnecessary to use it as a routine; moreover it has been found at Midhurst Sanatorium that patients who are taking cod-liver-oil regularly do no better than those who are not, although in special cases its value is admitted.

For the dispensary patient, lacking in means, it may be of particular help in improving nutrition, especially in winter. There is no reason why sulphanilamide should not be given coincidently with cod-liver-oil, just as with calcium, but its exhibition would appear to be pointless with both tuberculin and shock-therapy because it does not cause but counteracts systemic upsets. It might therefore prevent occurrence of the desired effects.

TREATMENT of SPECIFIC SYMPTOMS.

The orthodox method of dealing with symptoms is somewhat as follows :-

Cough. In many cases the cough is due largely to habit and patients can easily be trained not to cough. If asked to count the number of coughs or paroxysms which they have each day, they will make a conscious effort to reduce this number. With each reduction they feel they are improving and will determine to improve still further, thereby deriving considerable benefit.

Paroxysms of cough, which are due to difficulty in bringing up sputum are especially liable to occur in the morning. They are usually relieved by a warm alkaline drink on waking.

A certain amount of coughing is often beneficial, especially in cases of pulmonary cavitation, in order to free the air-passages from secretions which are frequently toxic. Patients with cavitation may discover positions in bed in which the secretion from their cavities drains most easily into their bronchial tubes. By adopting such an attitude they are able at certain times during the day to empty their cavities by coughing.

In the case of continuous cough which is unproductive and which interrupts sleep, a sedative has to be prescribed. Codein is the drug of choic, since it has a depressant action on the cough centre while having but few of the undesirable effects of the other alkaloids of opium. It may be given as syrup codein phosphate in doses of 1 to 1½ drachms. If something stronger is required heroin will often give relief. It is given in the form of a linctus.

A cough is often caused by smoking, but in this case many patients prefer the cough to being deprived of tobacco.

Troublesome and very resistant is the emetic cough - paroxysms of cough terminating in vomiting. Patients with this symptom require to rest in bed immediately after meals and should be forbidden either to talk or to smoke at such times. Meals are best if small and frequent, and a sedative cough mixture should be given before each meal.

Sulphanilamide possesses no expectorant property nor has it any known sedative effect upon the cough centre. Only by diminishing the sputum will it indirectly improve a cough.

Being liable to cause vomiting it might be wise to refrain from giving the drug to patients with an emetic cough.

Haemoptysis: It has been said that the correct treatment for haemoptysis occurring in a patient's home is to reassure the patient and give morphia to all his relatives. The patient is much alarmed and his alarm is increased by the even greater anxiety of those around him. It is a popular but erroneous belief that coughing up blood forebodes a fatal issue.

Treatment, therefore, is directed first to keeping the patient quiet, reassuring him and silencing or removing others in the room.

Provided it is not accompanied by other signs of increased activity of disease, slight streaking of the sputum need not affect the general course of treatment in any way. Even with moderate bleeding, rest in bed is all that is required.

Profuse haemoptysis is an indication for complete rest and careful nursing; and to control undue cough, restlessness and apprehension an injection of morphia may be given.

Many claims are made for the use of haemostatic drugs - emetin, calcium, pituitrin, adrenalin, congo-red, amyl nitrite, coagulen, haemoplastin to mention but some - though most authorities consider them worthless in the treatment of haemoptysis.

Measures which are of acknowledged value are artificial pneumothorax and transfusion with blood or

saline. Induction of an artificial pneumothorax is, of course, not always possible, and in addition there must be no doubt as to which lung is the source of the bleeding. When, however, the collapse is satisfactory bleeding is often dramatically arrested.

Transfusion is indicated when the life of the patient is in danger owing to shock or anaemia following one severe or several repeated haemoptyses. Each case must be treated on its merits.

Sulphanilamide does not affect the coagulability of the blood and can be of no assistance in arresting the bleeding. Indeed there are several reasons why it would be wise to withhold the drug in a case of haemoptysis.

Firstly, should it provoke vomiting, it might interfere with clot-formation and retraction and cause new bleeding. Secondly it might interfere with blood regeneration following the haemorrhage since haemolytic anaemia, lemcopenia and agranulocytosis may follow its use. Thirdly in severely anaemic patients cyanosis is not evident and sulphaemoglobinaemia might exist in absence of cyanosis, endangering life by further reducing the already deficient oxygen-carrying power of the blood.

Fever. The best treatment for fever is rest. If rest in bed is insufficient the pyrexia may be due to spread of the active lesion or to some complication. Either induction of an artificial pneumothorax or strapping of the chest wall may be required to increase the degree of rest in the affected lung.

It is easy to reduce the temperature by antipyretic drugs, but to do so is useless except for the mental effect on the patient who worries about his temperature. cryogenin grs. V. or grs. X. after lunch will usually reduce the evening temperature, which, however, rises again as soon as the drug is stopped if the activity continues.

If the patient is uncomfortable on account of high fever he may derive considerable relief from tepid sponging in bed.

Sweating. Sweating at night usually disappears after the patient has had a few days in bed. It is uncommon to find night-sweats persisting long after admission to a sanatorium. They cease usually within a few days.

Excessive clothing, or bed-clothes, ill-ventilated rooms or heavy meals at night: these are contributory factors. But for the most part sweating is a sign of persistent activity of disease. Fresh air is by far the best remedy, though a glass of milk and a biscuit before going to sleep, and repeated if the patient wakes during the night, will often prevent sweating. The much vaunted pills containing belladonna and zinc oxide are probably worthless.

Gastro-Intestinal Symptoms.

Poor appetite and dyspeptic symptoms are common in tuberculosis. They may result from overfeeding and always necessitate a review of the patient's diet. On the other hand they may be due to the general toxaemia, to irritation from swallowed

sputum or possibly to a deficiency of hydrochloric acid in the gastric juice.

Rest and fresh air and avoidance of over-feeding are the most effective lines of treatment. A simple bitter mixture before meals may be useful or, if achlorhydria is present, one or two drachms of dilute hydrochloric acid taken in water at mealtimes may assist in relieving symptoms.

Sulphanilamide, by lessening tuberculous toxaemia, might well check persistent fever, banish night-sweats and improve the appetite. But since it sometimes causes nausea, vomiting and epigastric pain, it must be used with caution if at all during gastro-intestinal upsets for fear of aggravating the symptoms.

Diarrhoea.

Diarrhoea may be due to toxaemia without any ulceration of the intestine, or there may be actual ulceration in which case probably blood or pus cells will be found in the stools.

If the patient is kept warm and given an initial dose of castor oil the diarrhoea may cease. If it persists the diet should be attended to, and, in particular, milk should be restricted. A low-residue high vitamin diet is usually given.

Ultra-violet radiation of the abdomen, intraperitoneal injection of oxygen, and massive doses of cod-liver-oil and tomatoes have all been advocated in America as specific for tuberculous enteritis: so also have intravenous injections of calcium chloride.

Such measures may be useful palliatives, but few have any real faith in them.

Pain. Severe pain in the chest in the course of pulmonary tuberculosis is usually due to pleurisy. Occasionally it is due to a spontaneous pneumothorax. Also Dunlop and Dick (1939) state that fracture of a rib, resulting from stress of coughing, is not uncommon in emaciated patients and may be missed. However, as they point out, the treatment of this complication is the same as for pleurisy. Overlapping pieces of broad strapping are firmly applied to the affected side at the moment when the patient's chest is fully collapsed in expiration. This causes limited expansion on the affected side. If insufficient to relieve all pain, pyramidon grs. v-x or veramon grs. vi can be given in addition. Morphia is rarely necessary if the strapping has been correctly applied.

THEORETICAL GROUNDS FOR USE OF SULPHANILAMIDE.

Sulphanilamide is a drug of high value in treatment of many conditions. Experimentally it has appeared to influence the cause of tuberculosis in the guinea-pig, an animal notoriously susceptible to the effects of the disease. The influence was apparently dependent upon an adequate dosage being administered for a sufficiently prolonged period.

Humans are naturally resistant to tuberculosis, the guinea pig is not; most persons are infected by tuberculosis without showing any symptoms of disease but the guinea pig invariably succumbs no matter how small the infecting dose.

Sulphanilamide retards the process of caseation and de-destruction and mitigates tuberculous toxaemia in the guinea pig, without admittedly arresting the disease. Sulphanilamide had not hitherto been tried in human beings except possibly in a few individual and unpublished cases. Is present day treatment of pulmonary tuberculosis so entirely satisfactory that a form of supplementary treatment which might prove beneficial is not worthy of a trial ? Surely the still high mortality rate from tuberculosis alone justifies such a trial ?

From the foregoing discussion of treatment of tuberculosis certain facts stand out. After rest and sanatorium régime, the most valuable individual measure is the artificial pneumothorax. It can be used in unilateral exudative disease if not too acute, used to close up cavities or to arrest haemoptyses. It is of much more doubtful value in bilateral disease and useless if there is much activity on both sides. Often attempted induction proves unsuccessful. There are many cases unsuited to this form of therapy.

What treatment is there for extensive bilateral disease of an exudative nature ? Failing a combination of an artificial pneumothorax on one side with a phrenicectomy or extra-pleural pneumothorax on the other, there is only rest and possibly gold. Gold is of undoubtful value and apt to produce symptoms of intoxication - more particularly in widespread exudative disease.

I have noticed that one can foretell with very

considerable degree of accuracy which patients will exhibit signs of gold intolerance. If moist râles be at all abundant on examination of the chest the patient will not tolerate a full course of gold. Reference to the graphic charting of physical signs in patients at the Royal Victoria Hospital who had received gold during the last five years fully proved my belief. Patients with widespread bilateral disease of an exudative nature could not and can not benefit from gold. All will show signs of intolerance.

Here then in bilateral exudative tuberculosis is one form of disease in which sulphanilamide might be tried. It is a form not entirely unlike that seen in the guinea pig - a form in which caseation is extensive and the disease is actively spreading.

Fibroid tubercle can be treated in many ways: it tends, in any case, to spontaneous cure. Even tuberculin or ultra-violet light may be given to persons suffering with this form of tuberculosis. It is relatively benign and on pathological grounds - the avascularity of the abundant fibrous tissue - one would anticipate no benefit from chemotherapy in general or sulphanilamide in particular.

Cavities require to be closed, and if large obviously nothing but some form of collapse therapy can be successful in effecting the closure. Sulphanilamide could only act by preventing spread of disease round and extension of the cavity, and conceivably by sterilizing the contents of the cavity.

Miliary tuberculosis, resistant usually to all therapy, should theoretically respond to sulphanilamide, if the drug were bactericidal for the tubercle bacillus. I have only tried the drug twice in this form of disease - each time entirely without effect.

It seemed that the disease had, in each case, got too far advanced - too great a start over the drug - to expect any benefit. Even in the guinea-pig the progress of disease was not arrested but merely retarded.

Fibrocaseous tuberculosis is the form which usually responds well to rest, sanatorium régime and some form of collapse therapy. But there are resistant cases, those in which rest does not check the spread of disease and collapse therapy has failed or is counterindicated. Here again one might plead for the use of sulphanilamide. Even if no claim were made for an anti-tuberculous action, sulphanilamide could be exploited if there was reason to presume secondary infection were present. The evidence of such would be based chiefly on the degree of pyrexia and tachycardia, but also possibly on demonstration of many streptococci and organisms other than the tubercle bacillus in the sputum.

The greater the systemic upset the more likely is it that secondary infection is at work. The more the degree of toxaemia, the fewer are the possible forms of treatment that can be employed. Tuberculin, sunlight, gold and even possibly collapse therapy become dangerous or absolutely contraindicated. But sulphanilamide acts best in those cases of streptococcal

and other infections which are most acutely ill and show the greatest toxaemia. Surely sulphanilamide might be of use in the hopeless or most acutely active cases of tuberculosis ?

Dosage.

The dosage of sulphanilamide to be used will depend on the object in view. If it be to clear up secondary infection or relieve signs of acute tuberculous toxaemia a short course of the drug in its maximum dosage, i.e. 1 gm. daily for every 20 pounds bodyweight (Long and Bliss), would be the wisest method to adopt. Such a course could only be continued safely for a few days.

If the object were to attempt to check proliferation of tubercle bacilli in the absence of very severe toxic signs it would be wiser to employ a medium dosage over a prolonged period. Dangerous complications would thus be less likely to arise, and there would be a continued presence in the blood of sulphanilamide to exert an inhibitory action on the tubercle bacillus.

The latter was the course adopted in the work about to be described. Rubiazol was used in place of sulphanilamide because weight for weight it was two and a half times as effective as the latter (Anderson 1939), even in big doses it was almost entirely non-toxic, and the more slowly excreted azo-compounds (prontosil rubrum and rubiazol), as has been mentioned, probably exerted a more prolonged effect than sulphanilamide.

EXPERIMENTAL WORK.

The average case of pulmonary tuberculosis undergoing sanatorium treatment is so apt to become apyrexial, to gain weight, and to improve by all the usual criteria, that such a case would be unsuitable for proving a new remedy. Hence I selected my cases mainly from two groups, (a) acute or bronchopneumonic cases with marked pyrexia, unlikely to improve on any known form of treatment, and (b) "bad chronics", - i,e. cases with fairly extensive disease which after a reasonable period of observation were found to be making little progress or slowly retrogressing. Eighteen cases in all were treated, three being acute and thirteen "bad chronics", while a further two pleurisies with effusion were included for interest.

Treatment with rubiazol was carried out over periods varying individually from two to six weeks.

The manufacturers, Messrs Roussel, recommended 6 to 12 tablets daily, (each tablet containing 0.2 gm.), according to the acuteness of the illness. It seemed unwise to risk administering the maximum recommended dosage for any considerable time, and each patient was given an initial daily dosage of 6 tablets (2 tablets three times daily), but where this produced no benefit it was usually increased to 9 tablets daily. Certain of the selected cases had been treated previously, without success, by gold or collapse therapy, but in some cases rubiazol was actually combined with these forms of treatment. No alteration was made in diet and treatment in general was carried on exactly as it had been done before the rubiazol was given.

Special care was taken to avoid exciting the interest of patients in the rubiazol. It is, of course, well-known that tuberculous patients are highly susceptible to suggestion, and there is no drug so powerful as hope. Injections of sterile water, a change of scene, a new doctor or a new medicine may produce startling improvement. But oral therapy, as was employed, is much less impressive than parenteral; and further, by deliberate avoidance of suggesting that even the slightest improvement might follow taking the drug, I attempted to minimize any psychological influence.

It was my intention to follow up the course of illness for at least six months after the rubiazol, but in many instances this proved to be impossible. War broke out, patients were evacuated from hospital and their mode of living became suddenly altered. Many did not trouble to report back at the hospital and others celebrated their unexpected freedom from sanatorium regime by excesses of all kinds.

In analysing the results I have excluded appetite and cough as indications of improvement, it being clear that these subjective symptoms are too vague and too susceptible to the suggestion of benefit from a new and special treatment. Also, with the exception of the sedimentation rate, which is often in direct ratio to the degree of toxaemia, I have avoided producing blood changes as evidence of improvement.

Sulphanilamide affects the blood picture in varying ways which have already been mentioned; and since such alterations may occur as often in healthy

as in diseased persons, a diminished leucocyte count in tuberculosis is not necessarily any evidence of improvement if sulphanilamide is being administered.

Nevertheless, in the present experiment, leucocyte counts and differential white cell counts were performed each week on every patient, at the same time as the blood sedimentation rate and haemoglobin were determined. This was done for reasons of safety - to guard against agranulocytosis or severe degrees of leucopemia.

I have read no literature concerning the influence of sulphanilamide on the sedimentation rate, but in a small series of normal persons de Caires (personal communication) concluded that there was a slight increase in the rate following administration of "M & B 693." One might conclude therefore that a decrease in sedimentation rate, after a course of rubiazol, would probably be due to the influence of that drug on the pathological processes at work.

Some cases are described in rather greater detail than others. These are placed first. They are, if anything, the more instructive of those under review.

Temperature charts are included for the first three patients, these being the only three who had persistent and obstinate pyrexia at the time rubiazol was started. In other cases rises of temperature were merely transitory or tending to settle spontaneously.

Tables are included for most patients to show at a glance the effect of the rubiazol. Effects on the sputum, weight, pulse-rate and sedimentation rate are usually included in the tables. The figures for the

sputum indicate the total quantity of sputum expectorated during the week in question, and those for the pulse-rate represent the average evening pulse-rate - obtained by adding all the evening pulse records for the week and dividing by seven. Daily fluctuations thus disappear and it is easier to see the general course of the disease.

Some of the patients were considered too ill to leave their beds for the purpose of being weighed, and consequently no figures could be given for these patients.

In regard to the sedimentation rate, the routine was to record the height of sedimentation after a period of two hours. At first this was the only figure used, but latterly I found it more informative to record the figures obtained after one, two and three hours.

At the conclusion of the case descriptions, I have discussed the findings individually and as a whole, and decided whether or not sulphanilamide should be given to persons suffering from pulmonary tuberculosis.

Description of Cases:

Case 1. J.M.C. male, age 19, a student. The patient was a well-built youth, 5 feet 10 inches tall and weighing eleven stones a month before coming to hospital.

He was shortly to have left school and started training as a gymnastic instructor when he first began to look unwell. He had been taking a lot of exercise, playing hockey or rugby football every day, quite apart from studying for an examination, and to begin with it was thought that he had merely been over-exerting himself. But his mother had lost a sister, who died of tuberculosis some years previously, and fear that history would repeat itself made her anxious when the boy perceptibly cyanosed.

She made him rest more. He gave up rugby, stayed at home and went to bed early, but could not stay awake when he tried to read in bed.

He developed a hacking cough and began to sweat a lot especially at night. He failed in his examination.

A week later, on the 26th March 1939, he was again playing rugby and, running "flat out" from one end of the field to the other, he scored a try. The game was played in pouring rain. He went home at the finish, feeling none the worse, but by evening he began to shiver and ache all over his body. His doctor diagnosed bronchitis and ordered him to bed.

After a week his temperature was normal, but

next day he again became febrile and when, in addition to a swinging temperature, he was found to have an enlarged gland in the left groin a specialist was called in for consultation. The presence of pulmonary tuberculosis was suspected and it was confirmed by x-ray examination.

The radiologist, who found extensive bilateral disease, held that the patient would be dead within a month.

He was admitted to the Royal Victorial Hospital on the 27th April 1939. By then he only weighed ten stones having lost a full stone in four weeks. He had a cough but no sputum, nor did he have any pain or feel breathless. He had never previously had pleurisy or any other illness of note.

Examination showed pallor, cyanosis of the lips, cheeks and nail-beds, bright but sunken eyes, a toxic yellowish discoloration of his palate, a tired expression and very atonic muscles with myotatic irritability.

Over the upper half of the chest, both back and front, the percussion note was impaired, breath-sounds were bronchial, vocal resonance was much increased and there were abundant adventitia. The accompaniments were audible on both sides over almost the entire lung field : they were predominantly subcrepitant moist râles, but between the spine and the vertebral margin of the left scapula they were coarse and consonating.

Radiological examination (plate V.) showed

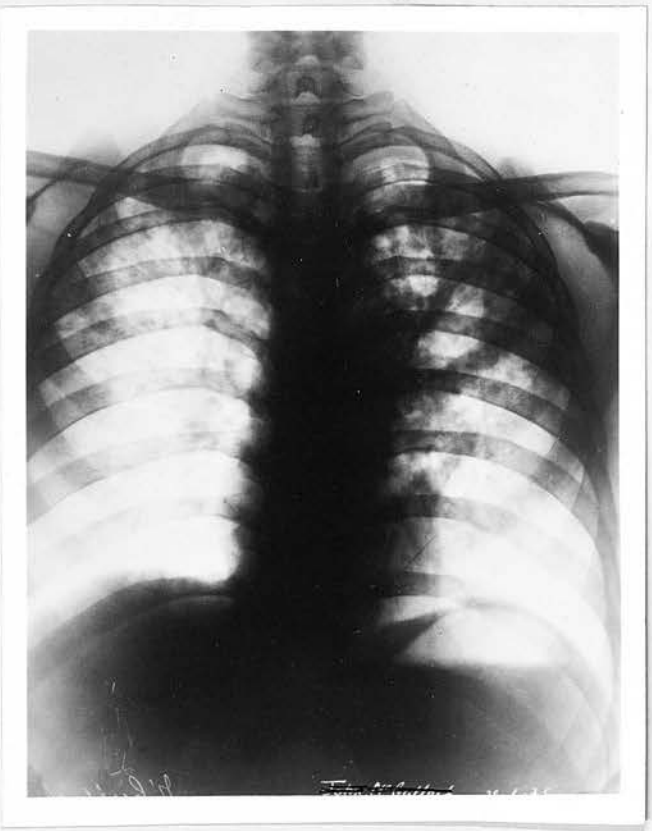


Plate V. J.M.C. aged 19, showing numerous soft ill-defined shadows indicative of bilateral exudative tuberculosis.

extensive bilateral disease of an exudative type with very little evidence of fibrosis.

Sputum contained numerous tubercle bacilli and the blood sedimentation rate was 84 after two hours.

He was confined strictly to bed, but after a month in the sanatorium, his temperature remained elevated, sedimentation rate had risen to 85, and sputum was much more copious and laden with bacilli.

After two months in the sanatorium pyrexia still showed no sign of abating and the sedimentation rate had risen further to 88 after two hours. The patient was perceptibly thinner and it was obvious that he was going steadily downhill. Night-sweats had become worse, his cough was very troublesome and spasms of coughing

were often followed by vomiting, and there was practically no alteration in the physical signs. Moist râles were still abundant though the sputum was not quite so profuse.

Since rest alone and symptomatic treatment were not checking the disease I thought he was a suitable subject for the experiment with rubiazol.

I gave him six tablets daily for the first fortnight and nine tablets daily for a further three weeks.

The results of the treatment are shown in Table 1.

Table /

TABLE 1.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sputum (ozs)	½	1⅞	22⅝	17¾	19.	18½	7½	12⅛	10⅝	12½	11¼	5½	7	13	14	15⅞	8¾	11
Evening Pulse Rate	92	91	90	89	98	108	104	105	99	101	95	96	93	96	93	97	95	97
B.S.R.	?/84	-	-	-	?/85	-	-	-	-	?/88	50/78	42/68	38/66	39/64	29/57	34/62	28/56	

Table showing effects of treatment with rubiazol on the total quantity of sputum (in ounces) expectorated during each week, on the average evening pulse-rate for the week, and on the blood sedimentation rate (B.S.R.) for 1 and 2 hours.

The weeks during which rubiazol was given are underlined in red.

129A.

Several interesting things happened. The total sputum dropped to approximately half the previous quantity after two weeks on rubiazol, but rose again a fortnight later. Even before rubiazol was started, during the seventh week in the sanatorium, the quantity of sputum had suddenly fallen to a low figure for a few days, and one must, therefore conclude that the second decrease during the twelfth and thirteenth weeks was probably a coincidence.

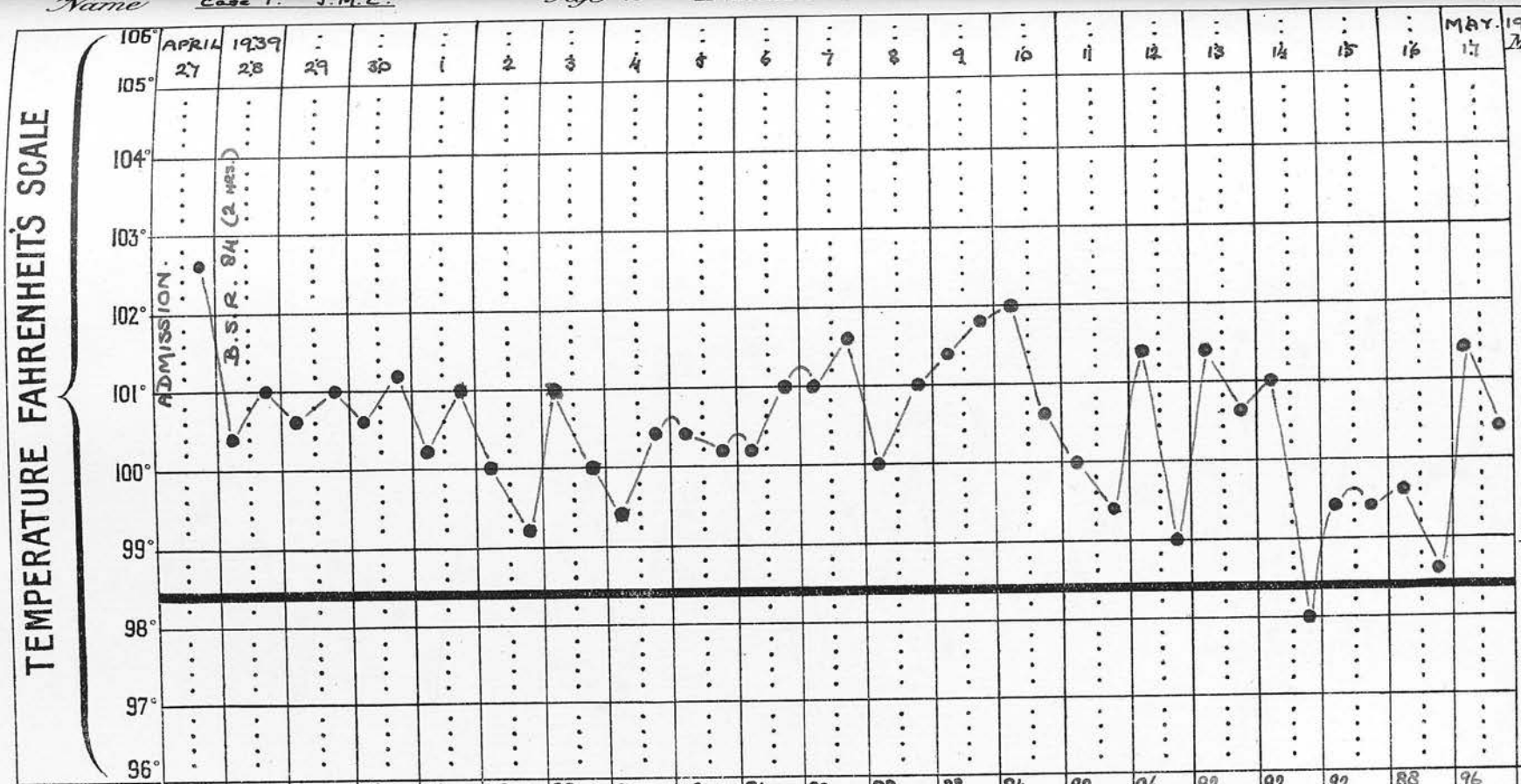
The same cannot be said of the sedimentation rate which, having risen slowly from 85 to 88 after two months dropped when rubiazol was started, in one week to 78, in two weeks to 68, and thereafter fell each week except one until it was 56.

The fall was continued after cessation of the rubiazol, so it was not explained on the grounds either of a transient interference with the normal mechanism governing sedimentation or a temporary neutralisation of tuberculous toxaemia.

The pulse-rate seemed to be slightly slower after the rubiazol was started, but the slowing was not progressive and was too slight to be conclusive.

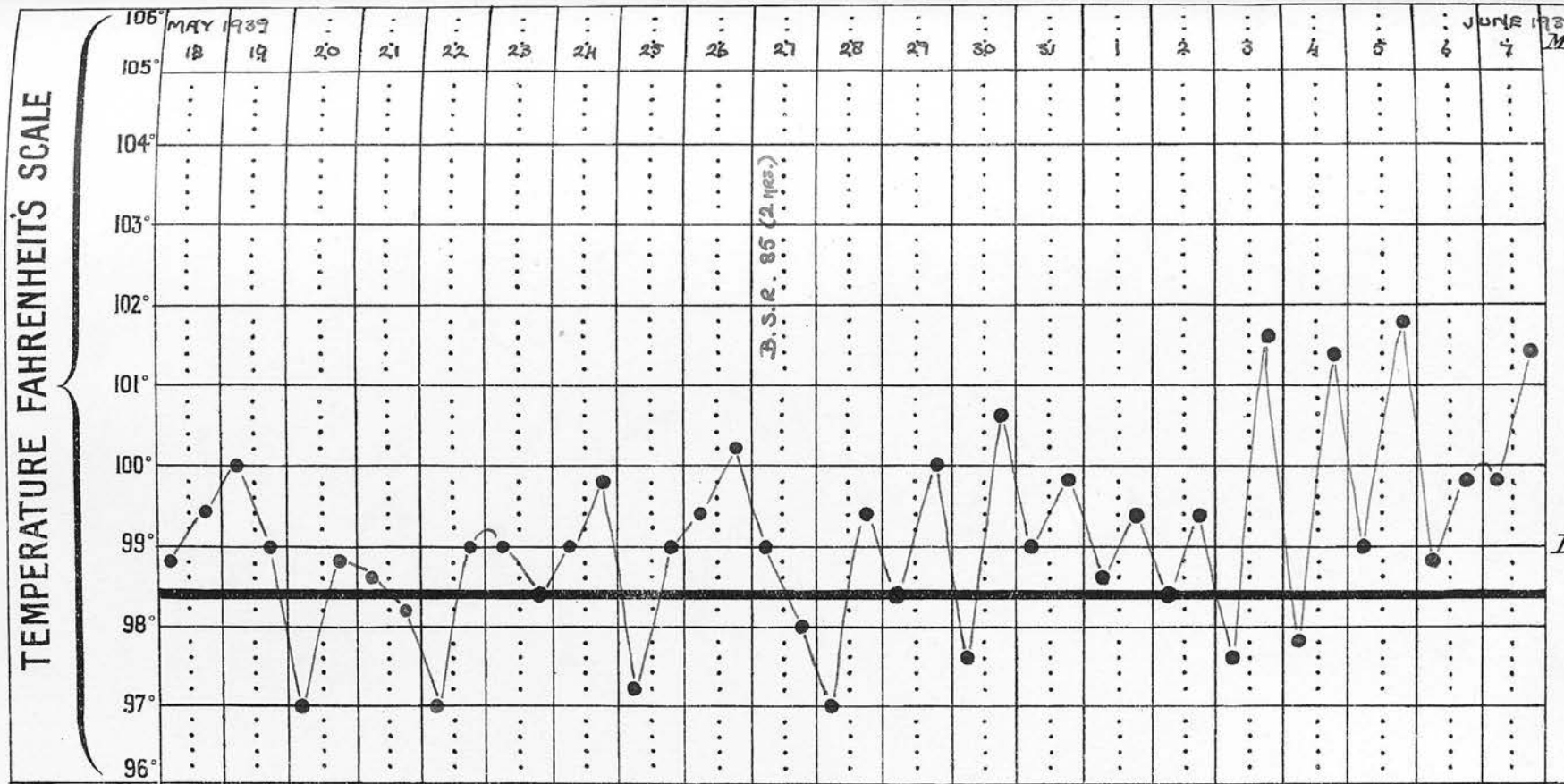
Similarly the temperature tended to subside so that it was often normal in the morning, though the evening pyrexia remained. (Plate VI.)

Name — Case I. J.M.C. — Age 18 — Disease Tuberculosis. — Admitted 21. 4. 39. — Result —



Pulse m		76	96	88	96	88	88	84	88	84	92	88	88	84	92	96	92	92	92	88	96	Pulse m
Pulse e	80	96	92	96	96	96	92	86	92	84	92	88	92	100	88	88	92	92	90	92	88	Pulse e
Resp. m		18	20	20	16	20	20	20	20	20	20	20	20	20	20	20	20	20	22	20	20	Resp. m
Resp. e	20	20	20	22	22	20	22	20	22	20	22	20	22	22	20	20	20	20	20	20	20	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	1/2	0/1	1/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction	Acid							Acid							Acid							„ Reaction
„ Albumen	–							–							–							„ Albumen
„ Blood	–							–							–							„ Blood
~~WEIGHT~~ ~~C.S.Fluid~~	10 ozs.																					~~WEIGHT~~ ~~C.S.Fluid~~
Sputa ozs.	–	–	1/8	1/8	1/8	T2.	T2.	1/8	T2.	T2.	1/8	1/4	1/2	3/4	1/2	1	2 1/8	4	4	6	4 1/2	Sputa ozs.
Day of Disease or Residence	1		3		5		7		9		11		13		15		17		19		21	Day of Disease or Residence

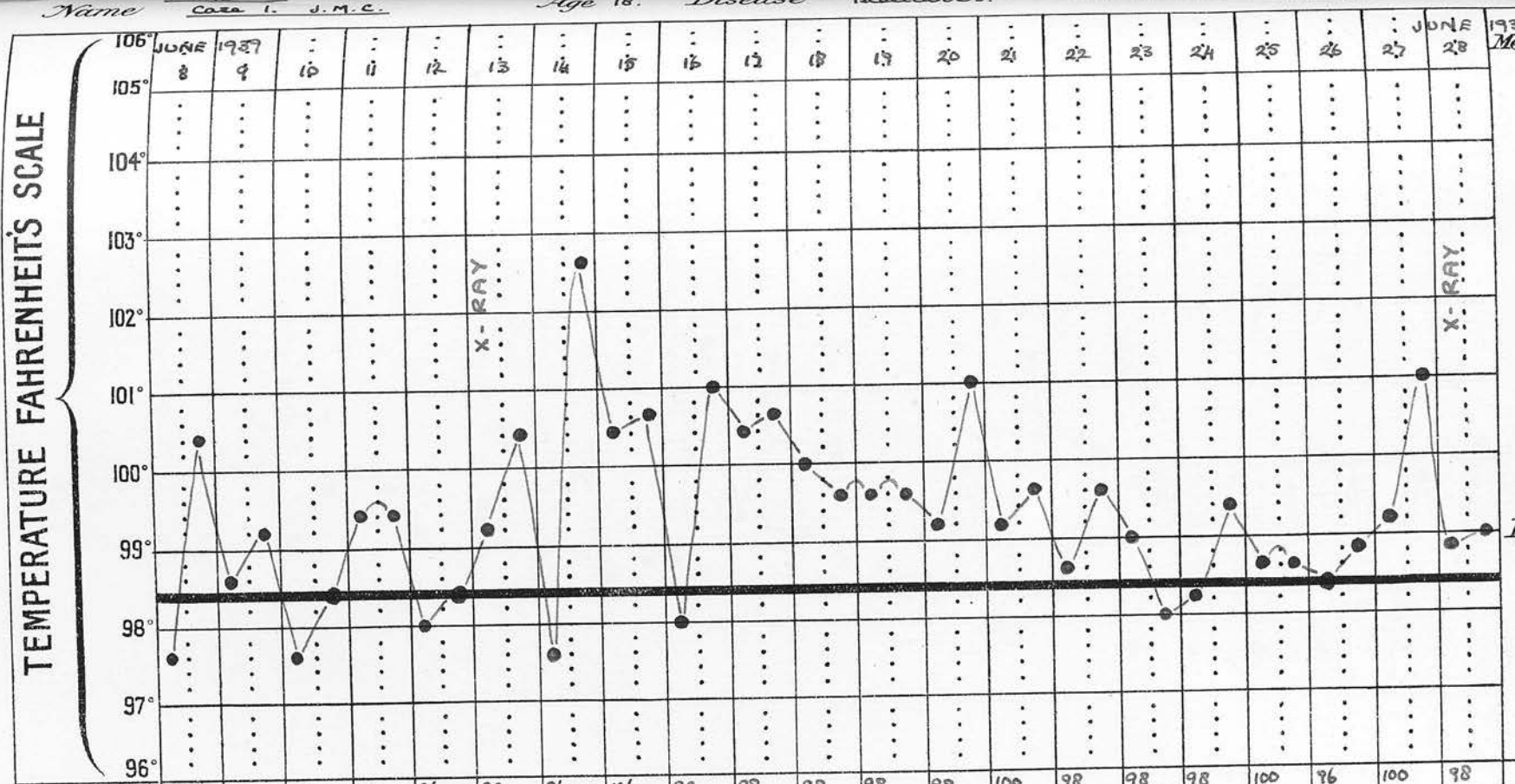
Name [illegible] Case 1. J.M.C. Age 18 Disease Bilateral Pulmonary Tuberculosis. Admitted 27.4.39. Result —



	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6	7	
Pulse m	92	88	80	88	72	80	80	82	84	84	72	80	80	102	84	102	104	96	104	104	88	Pulse m
Pulse e	94	88	86	86	92	84	96	96	104	88	94	92	112	98	116	104	104	120	104	108	102	Pulse e
Resp. m	20	20	24	22	16	20	20	20	20	20	16	20	20	22	20	22	22	20	24	22	20	Resp. m
Resp. e	20	20	20	20	20	20	22	20	24	20	26	22	24	20	24	22	22	22	22	20	22	Resp. e
Motions	0/1	1/1	0/1	0/0	0/1	0/1	0/0	0/1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction	Acid														Acid							„ Reaction
„ Albumen	—														—							„ Albumen
„ Blood	—														—							„ Blood
~~C.S. Fluid~~																						~~C.S. Fluid~~
Sputa ozs.	1¼	3	3½	3	3	2	2	2	2	3	1½	3	3½	4	5½	3	2	2	2	1½	2½	Sputa ozs.
Day of Disease or Residence	22		24		26		28		30		32		34		36		38		40		42	Day of Disease or Residence

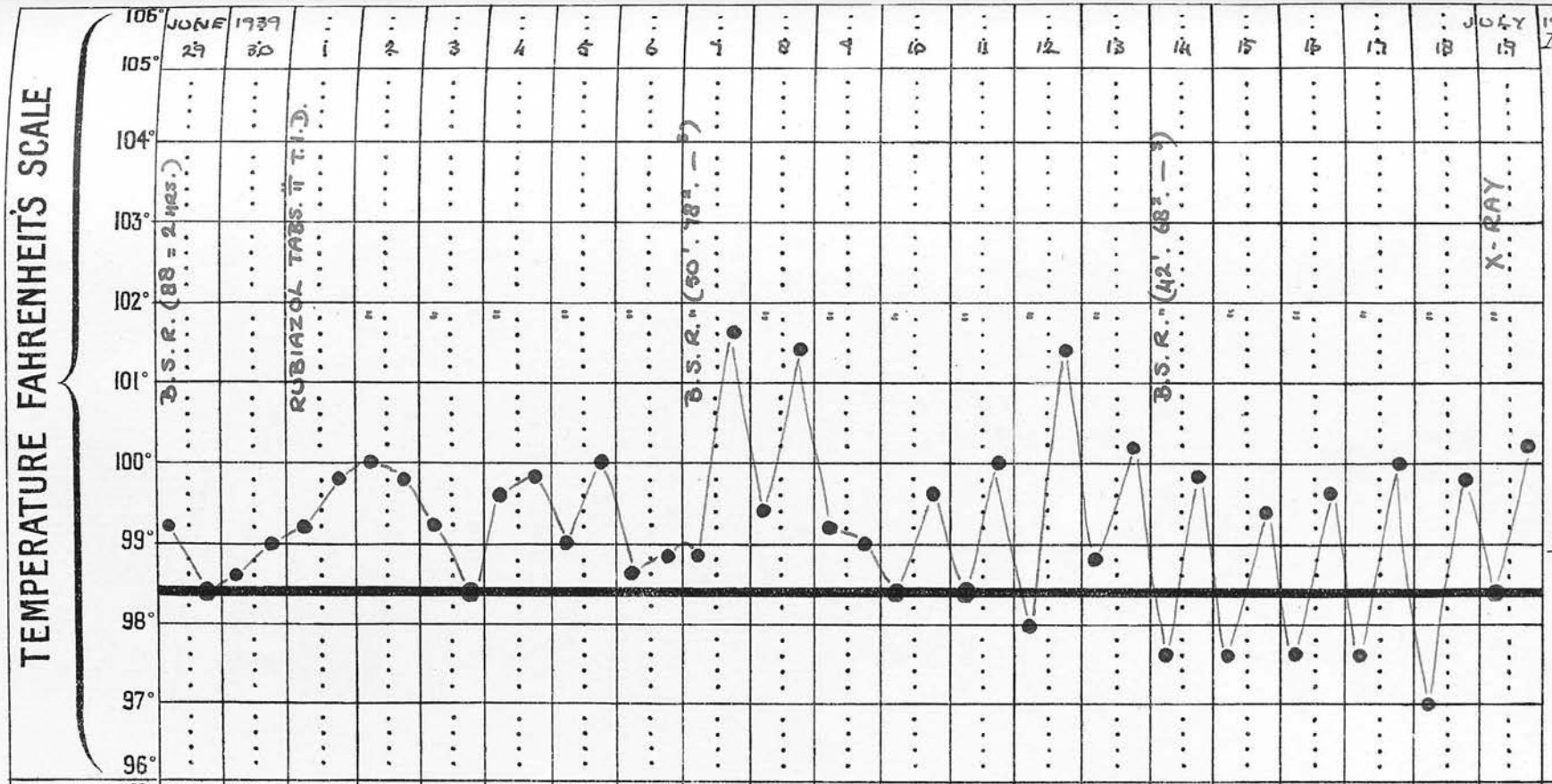
61/8A/14/55- 1M/7/40 Form C.H. 13

Name Private V. Coxe I. J.M.C. Age 18. Disease Suspected Pulmonary Tuberculosis. Admitted 27.4.39. Result –



JUNE 1939	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Medicines, etc.
Pulse m	100	96	96	100	96	92	96	106	92	98	98	98	98	100	98	98	98	100	96	100	98	Pulse m
Pulse e	104	112	100	94	100	104	112	108	108	100	104	108	100	106	96	108	100	84	100	106	100	Pulse e
Resp. m	22	20	20	22	20	22	20	22	20	22	22	22	22	22	22	22	22	22	22	24	20	Resp. m
Resp. e	22	22	24	20	20	24	26	20	24	22	20	20	22	22	22	22	22	20	24	20	22	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction														Acid								„ Reaction
„ Albumen														–								„ Albumen
„ Blood														–								„ Blood
WEIGHT C.S. Fluid																						WEIGHT C.S. Fluid
Sputa ozs.	1½	1¾	1½	¾	½	1	½	1	1½	1	1½	3⅛	1½	2	3	1½	2⅛	1	1	1	1	Sputa ozs.
Day of Disease or Residence		44		46		48		50		52		54		56		58		60		62		Day of Disease or Residence

Name Case I. J.M.C. Age 18 Disease Tuberculosis Admitted 27. 4. 39. Result —



Medicines, etc.

Diet

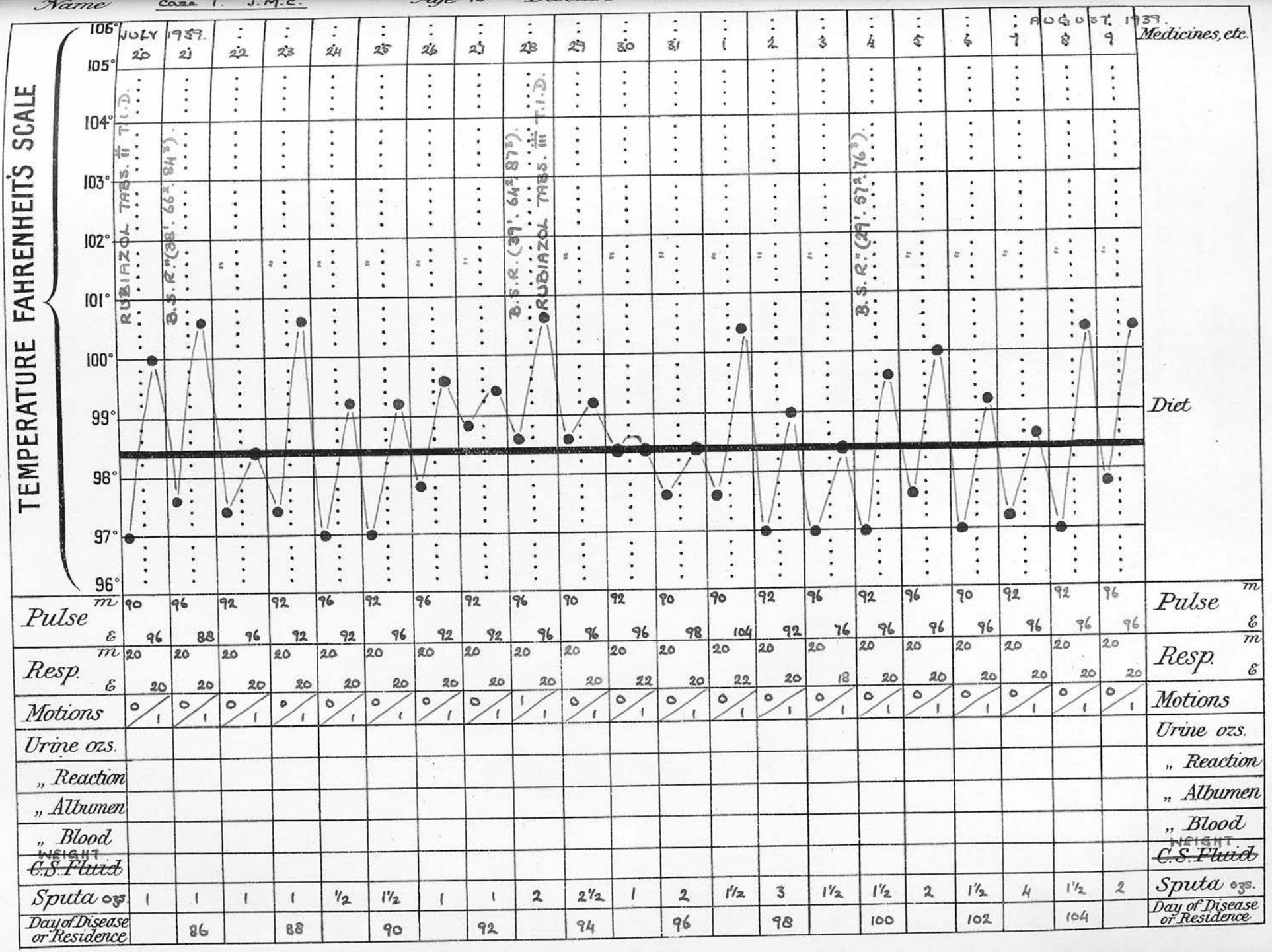
Pulse m	88	96	92	96	100	96	96	100	92	96	92	92	92	92	92	92	84	90	88	88	92	Pulse m
Pulse e	102	100	104	100	96	100	104	96	92	96	92	98	96	92	96	96	102	96	92	98	92	Pulse e
Resp. m	20	20	22	22	22	22	20	22	20	22	22	20	20	20	20	20	20	20	20	20	20	Resp. m
Resp. e	22	24	20	20	20	22	22	20	20	22	20	20	20	20	20	20	22	22	22	22	20	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~C.S. Fluid~~																						~~C.S. Fluid~~
Sputa 038	1	1	2	2	3	2	1½	2½	1	2	1½	1¾	1	1½	½	1	1	1	1	½	½	Sputa 038
Day of Disease or Residence	64		66		68		70		72		74		76		78		80		82		84	Day of Disease or Residence

WEIGHT

WEIGHT

61/8A/14/55 - 1M/7/40 Form C.H. 13

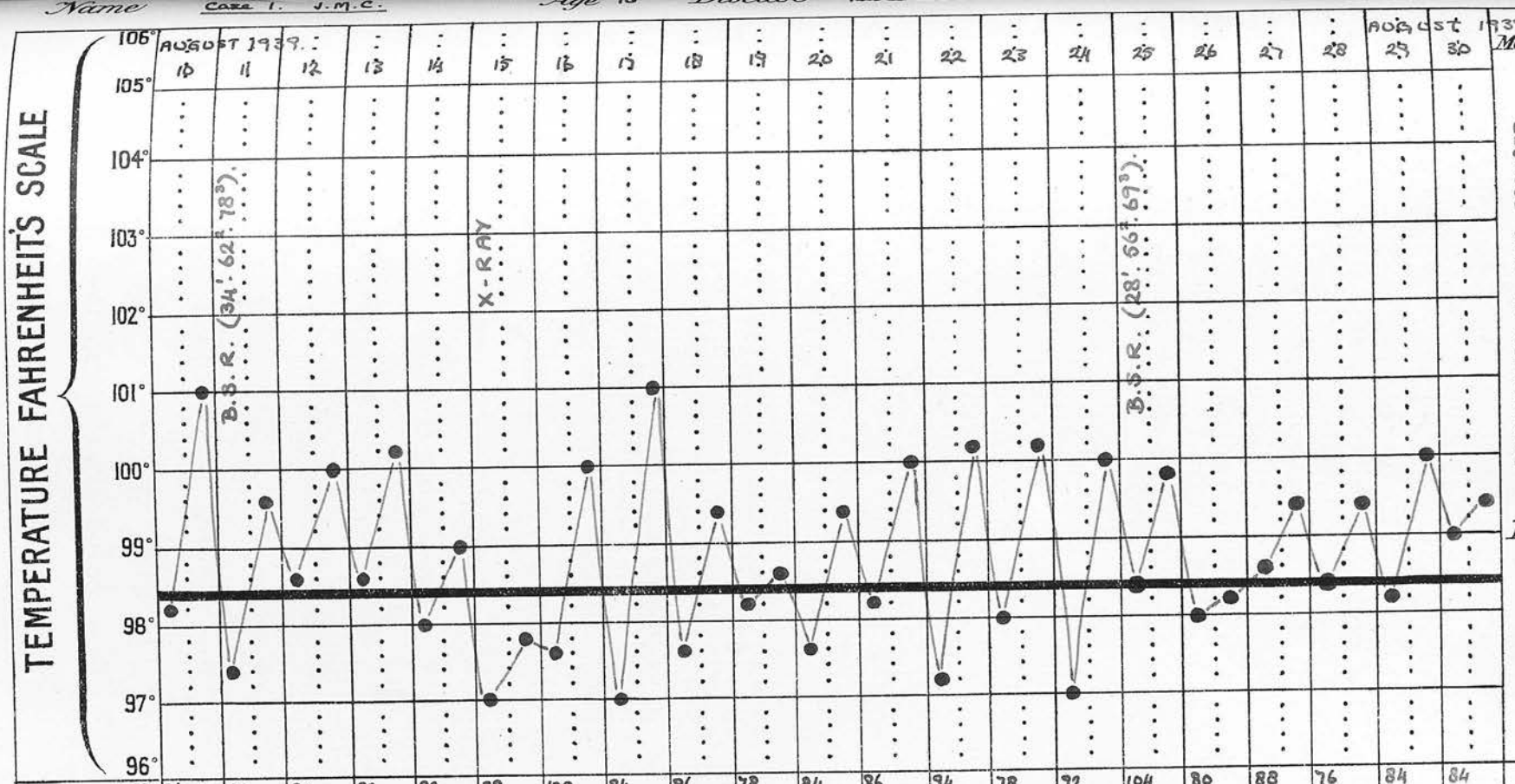
Name Case 1. J.M.C. Age 18 Disease Tuberculosis. Admitted 27.4.39. Result —



Pulse m	90	96	92	92	96	92	96	92	96	90	92	80	90	92	96	92	96	90	92	92	96	Pulse m
Pulse e	96	88	96	72	92	96	92	92	96	96	96	98	104	92	76	96	96	96	96	96	96	Pulse e
Resp. m	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	Resp. m
Resp. e	20	20	20	20	20	20	20	20	20	20	22	20	22	20	18	20	20	20	20	20	20	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~C.S. Fluid~~																						~~C.S. Fluid~~
Sputa ozs.	1	1	1	1	½	1½	1	1	2	2½	1	2	1½	3	1½	1½	2	1½	4	1½	2	Sputa ozs.
Day of Disease or Residence		86		88		90		92		94		96		98		100		102		104		Day of Disease or Residence

61/BA/14/55- 1M/7/40 Form C.H. 13

Name Case 1. J.M.C. Age 18 Disease Tuberculosis. Admitted 27. 4. 39. Result —



Pulse m	96	92	92	92	92	88	100	84	96	78	84	86	94	78	92	104	80	88	76	84	84	Pulse m
Pulse e	104	104	96	92	96	100	90	96	88	88	100	96	92	96	100	90	100	98	92	98	100	Pulse e
Resp. m	20	20	20	20	20	20	20	20	20	18	20	20	20	18	20	22	20	22	18	20	20	Resp. m
Resp. e	20	22	20	20	20	20	20	20	20	20	20	20	20	20	22	20	22	20	20	20	22	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~WEIGHT C.S.Fluid~~																						~~C.S.Fluid~~
Sputa ozs.	3	1	2¼	3⅛	3¼	2	1	1	1¾	½	1½	1½	1	1½	1¼	2	1½	2	1	1¼	2	Sputa ozs.
Day of Disease or Residence	106		108		110		112		114		116		118		120		122		124		126	Day of Disease or Residence

61/8A/14/55- 1M/7/40 Form C.H. 13

Plate VI.

See accompanying Temperature Charts.

Tubercle bacilli were present on all and every occasion (each week) that I examined the sputum, and there was no significant alteration in the cellular or saprophytic content. In particular streptococci remained present in moderate numbers in the films.

There was a definite decrease in moist accompaniments following rubiazol; indeed, in many areas where râles had previously abounded, they could be detected subsequently only after the stimulus of a cough. This improvement, like that in the sedimentation rate, was maintained up to the time of discharge from hospital.

The patient was too ill to be weighed, but, though he ate well, I think there is little doubt that he continued to lose weight.

On the third day that he was given rubiazol he

developed a morbilliform rash on the face, body and limbs. The drug was not discontinued, despite slight febrile accentuation, and within a further four days the rash had faded and completely disappeared.

Night-sweats, which had been very troublesome during his first two months in hospital, were less severe when he was having rubiazol, and at times even absent for several days. However, three weeks after rubiazol had been started, the night-sister reported that she had detected what she termed "The death-smell" - that odour of sweat so characteristic of moribund patients. Subsequently it seemed that the prognosis might not be so extremely unfavourable. The continued fall in sedimentation rate, gradual settling of temperature, less frequent night-sweats and dimunition in moist râles gave some grounds for hope, but when war was declared the patient chose to be moved from hospital to his home.

He was to live in a shelter in the garden but it was never built. A steady deterioration took place and he died about sixteen weeks after leaving hospital.

How far he behaved indiscreetly on reaching home I do not know. He might have hastened the fatal issue by such means. But certain facts stand out. His downward progress, though not arrested, was at least retarded while he was in the sanatorium and in particular after he began the rubiazol.

He died eight months after the date foretold by the radiologist, i.e. nine and not one month from the time the diagnosis was established. Radiologically

there was little alteration in appearance of films taken when rubiazol was started and two months later when the patient left hospital; extension of the diseased areas was insignificant and there was even a suggestion of commencing fibrosis in the left upper lobe. The change was howvever too slight to warrant inclusion of a plate in contrast to plate V.

There was no change in the size or appearance of the tuberculous gland in the left groin. It remained enlarged but did not break down and form an abscess.

Finally, though streptococci as well as tubercle bacilli remained present in the sputum, it did not follow that the streptococci originated in the lung. They may have come from the throat etc. Also they may have been of a type which was unaffected by sulphanilamide or rubiazol e.g. non-haemolytic streptococci.

Case 2. S.B. male, aged 19, a van-boy, who had been in good health until January 1938 when he sustained two blows which resulted in the appearance of a swelling in the scrotum. In spite of local treatment the swelling persisted.

During October 1938 he began to feel listless, and tired. He was off work for a few days on several occasions. His doctor treated him for what was termed tonsilitis. He became breathless on exertion, his appetite was poor, he sweated easily, and he seemed to have a continual cold.

By Christmas 1938 he had become thin and lost a great deal of weight; but still much valuable time elapsed before it was thought that the swelling in the scrotum might be connected with the general condition of the patient, and before x-ray examination established the presence of extensive left-sided pulmonary tuberculosis.(Plate VII.)

Plate VII.

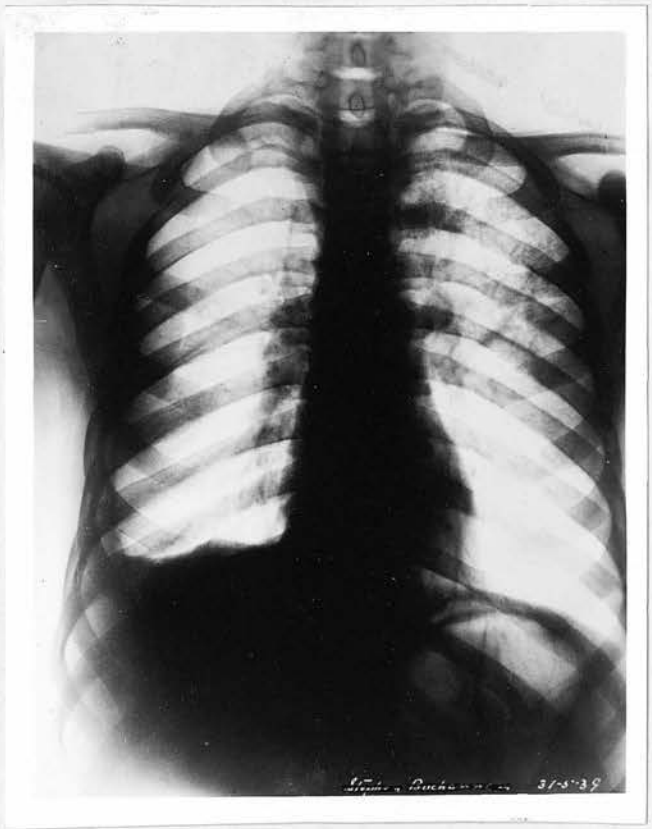
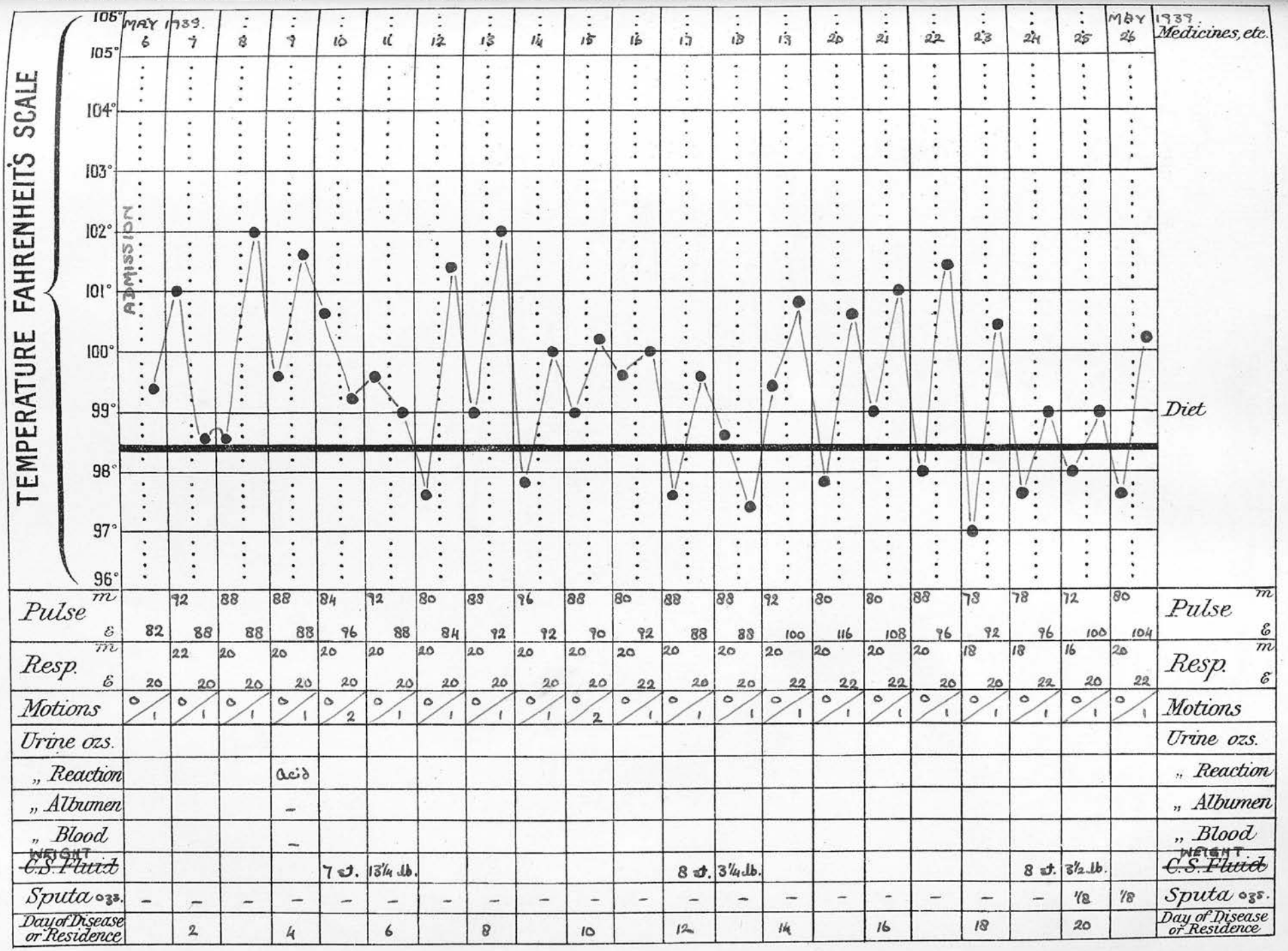


Plate VII: S.B. aged 19, showing ill-defined patches of tuberculosis involving the upper half of the left lung field.

He had had pleurisy five years before, but that was on the opposite side of the chest. Otherwise there was nothing in his own or his family history to suggest tuberculosis,

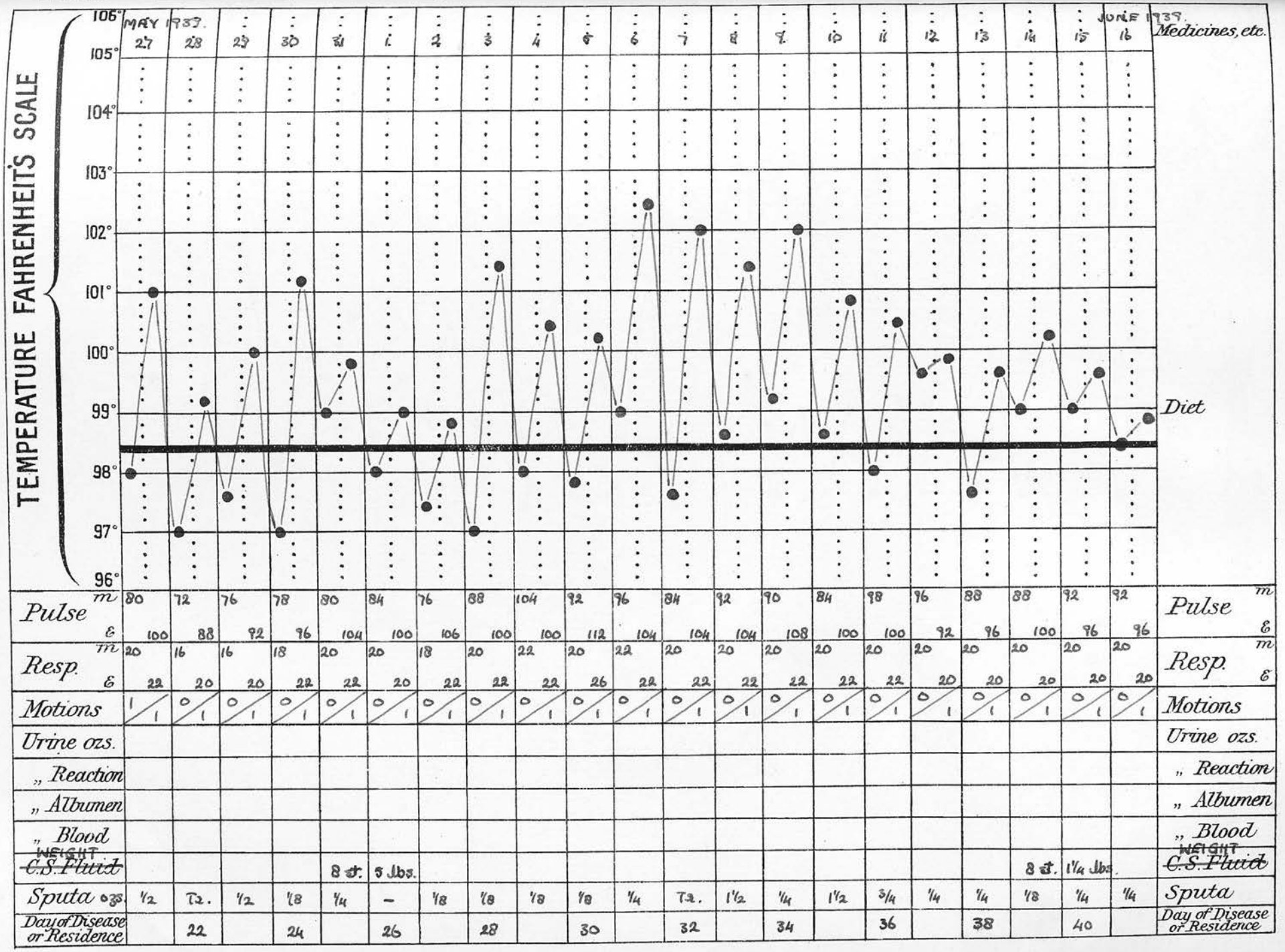
He was admitted to the Royal Victoria Hospital in May 1939 and by this time he was acutely ill. For

Name [illegible] Ward 2. S.B. Age 19. Disease Tuberculous Epididymitis. Admitted 6. 5. 39. Result —



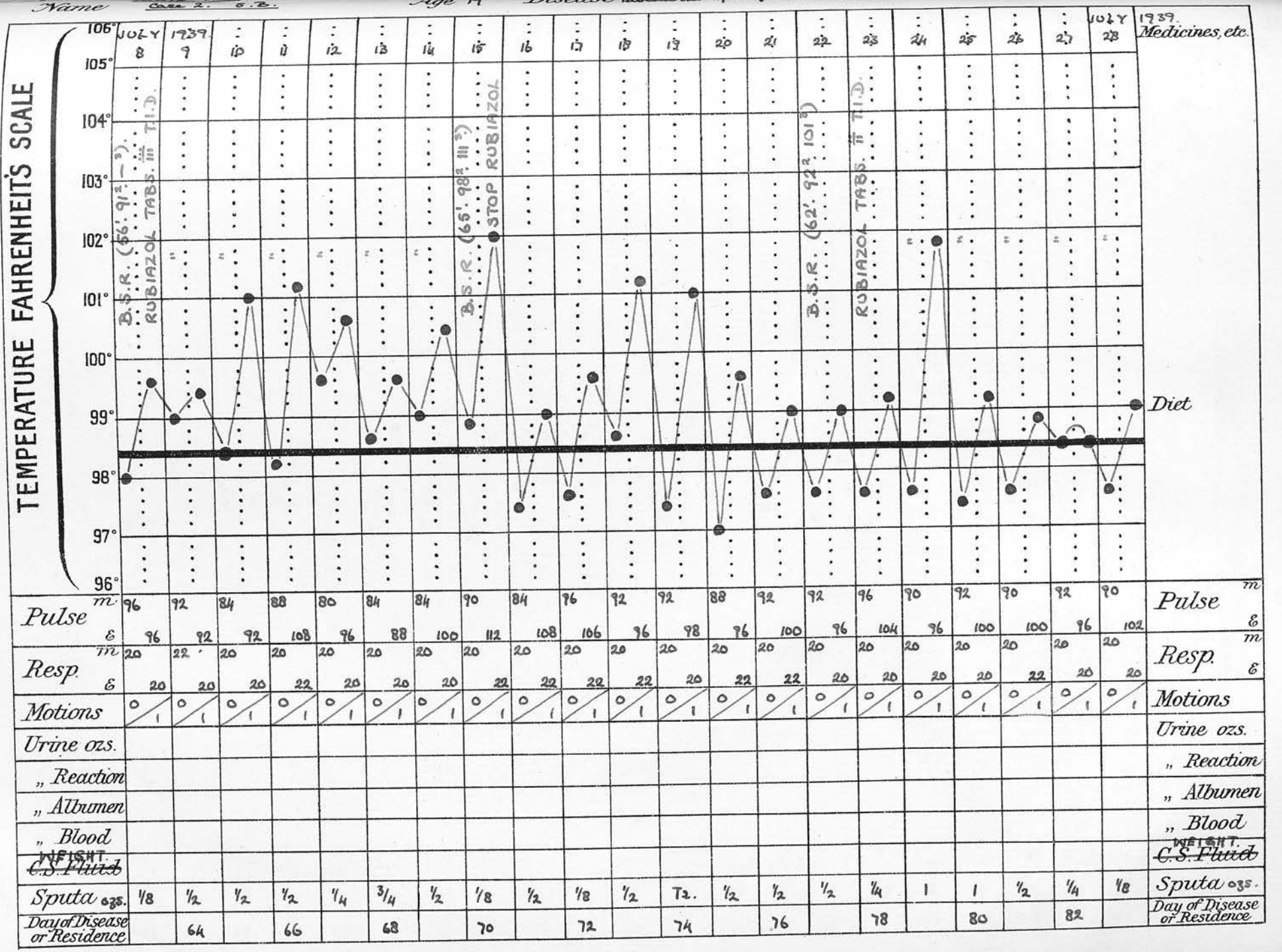
Name [illegible] Case 2. S.B. Age 19. Disease Tuberculous Epididymitis. Admitted 6.5.39. Result —

61/8A/14/55– 1.M/7/40 Form C.H. 13



	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Pulse m	80	72	76	78	80	84	76	88	104	92	96	84	92	90	84	98	96	88	88	92	92	Pulse m
Pulse e	100	88	92	96	104	100	106	100	100	112	104	104	104	108	100	100	92	96	100	96	96	Pulse e
Resp. m	20	16	16	18	20	20	18	20	22	20	22	20	20	20	20	20	20	20	20	20	20	Resp. m
Resp. e	22	20	20	22	22	20	22	22	22	26	22	22	22	22	22	22	20	20	20	20	20	Resp. e
Motions	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~C.S. Fluid~~ WEIGHT					8 st.	5 lbs.													8 st.	1¼ lbs.		~~C.S. Fluid~~ WEIGHT
Sputa 038	½	T2.	½	⅛	¼	—	⅛	⅛	⅛	⅛	¼	T2.	1½	¼	1½	¾	¼	¼	⅛	¼	¼	Sputa
Day of Disease or Residence		22		24		26		28		30		32		34		36		38		40		Day of Disease or Residence

Name [illegible] Ward Case 2. S.B. Age 19 Disease Tuberculous Epididymitis. Admitted 6.8.39. Result —

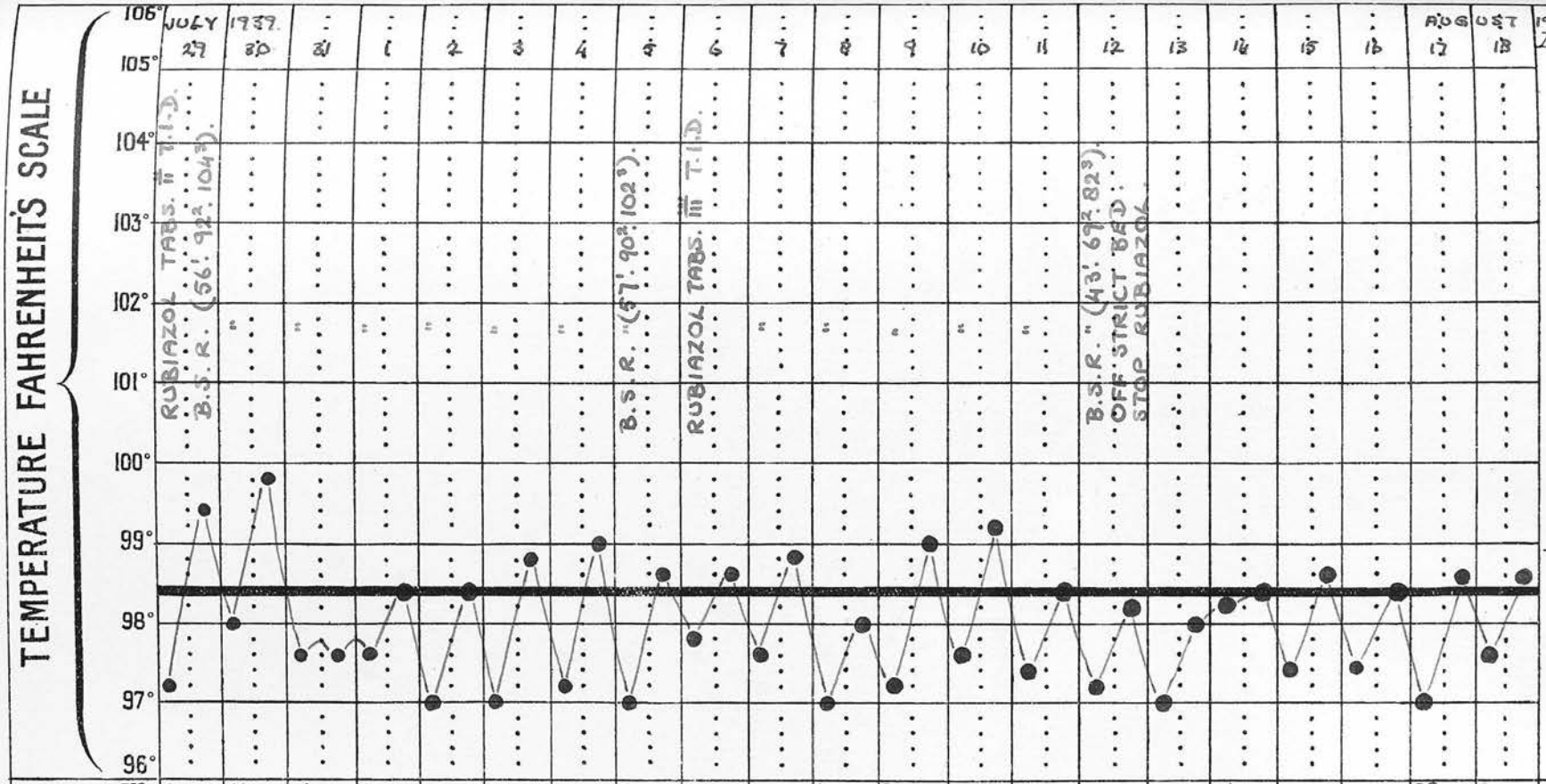


	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Pulse m	96	92	84	88	80	84	84	90	84	96	92	92	88	92	92	96	90	92	90	92	90	Pulse m
Pulse e	96	92	92	108	96	88	100	112	108	106	96	98	96	100	96	104	96	100	100	96	102	Pulse e
Resp. m	20	22	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	Resp. m
Resp. e	20	20	20	22	20	20	20	22	22	22	22	20	22	22	20	20	20	20	22	20	20	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~C.S. Fluid~~																						~~C.S. Fluid~~
Sputa ozs.	1/8	1/2	1/2	1/2	1/4	3/4	1/2	1/8	1/2	1/8	1/2	T2.	1/2	1/2	1/2	1/4	1	1	1/2	1/4	1/8	Sputa ozs.
Day of Disease or Residence		64		66		68		70		72		74		76		78		80		82		Day of Disease or Residence

WEIGHT.

Medicines, etc.

Name Miss VIII Case 2. S.B. Age 19 Disease Tuberculous Epididymitis. Admitted 6. 8. 39. Result –



Pulse m	90	96	96	92	92	92	90	90	92	90	90	90	90	90	90	88	86	88	76	88	92	Pulse m
Pulse e	92	100	92	96	92	98	96	92	92	92	92	92	92	92	88	80	92	92	96	84	88	Pulse e
Resp. m	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	18	20	20	Resp. m
Resp. e	20	20	20	20	20	22	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~C.S. Fluid~~ WEIGHT														8 st. 7¾ lbs.						8 st. 11 lbs.		~~C.S. Fluid~~ WEIGHT
Sputa ozs.	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	1/8	Sputa ozs.
Day of Disease or Residence	84		86		88		90		92		94		96		98		100		102		104	Day of Disease or Residence

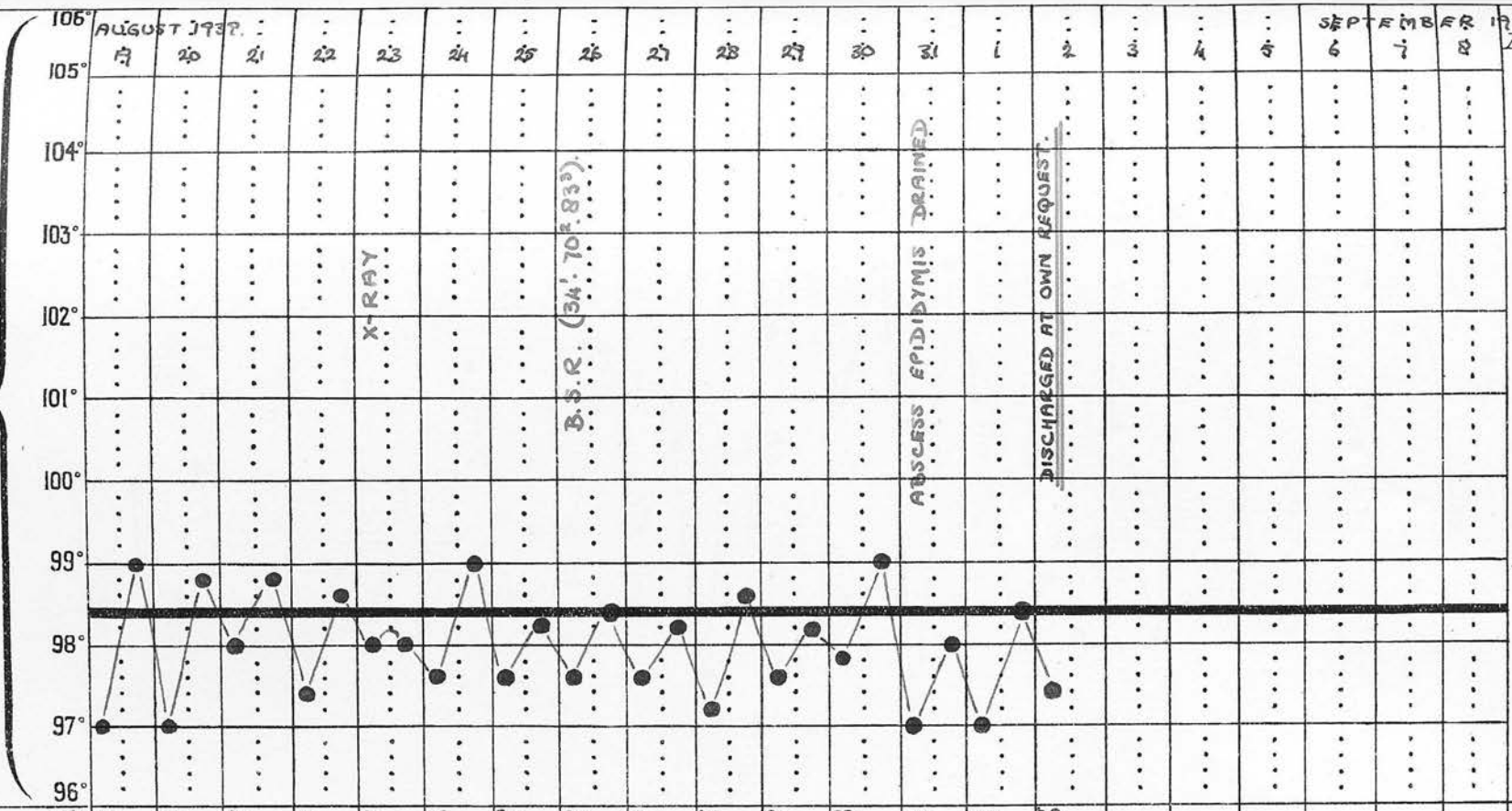
Medicines, etc.

61/8/14/55– 1M/7/40 Form C.H. 13

Name [illegible] Ward VIII. Case 2. S.B. Age 19 Disease Tubercu[illegible] Tuberculous Epididymitis. Admitted 6.8.39. Result —

61/8x/14/55– 1x/7/40 Form C.H. 13

TEMPERATURE FAHRENHEIT'S SCALE

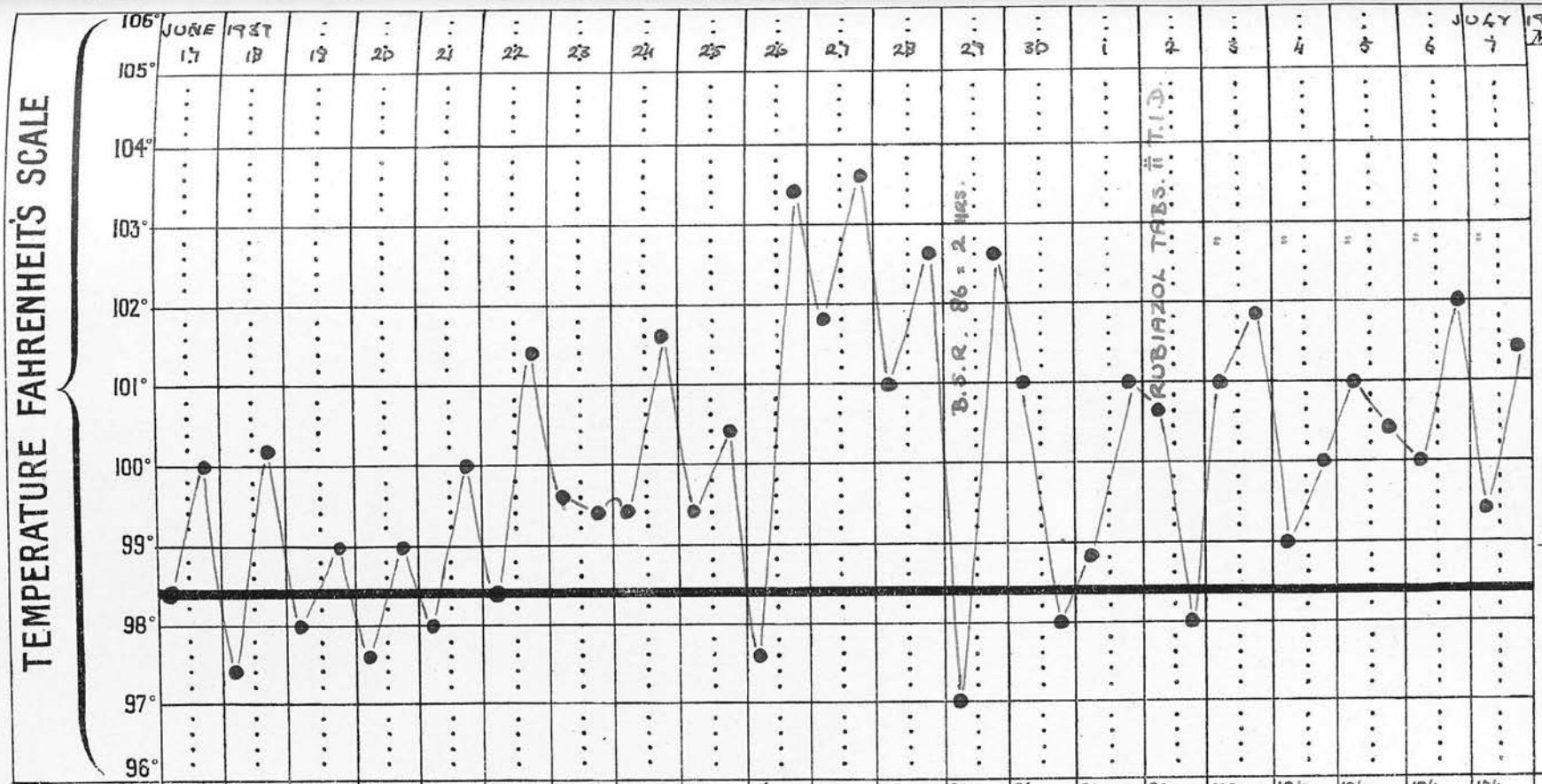


Medicines, etc.

Diet

	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6	7	8
Pulse m	84	68	84	76	80	78	80	80	92	76	84	88	100	100	78						
Pulse e	96	84	80	78	80	78	80	78	88	100	88	90	88	96							
Resp. m	20	18	20	18	20	18	20	18	20	18	20	20	22	20	18						
Resp. e	20	20	20	18	20	18	20	18	20	20	20	22	20	20							
Motions	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0	/	/	/	/	/	/
Urine ozs.																					
„ Reaction																					
„ Albumen																					
„ Blood																					
~~WEIGHT C.S. Fluid~~						9 st. 0½ lbs.								9 st. 3½ lbs.							
Sputa ozs.	—	1/8	Tr.	—	—	—	Tr.	1/8	Tr.	1/8	Tr.	—	—	—	—						
Day of Disease or Residence		106		108		110		112		114		116		118							

Name Mrs. Case 2. S.B. Age 19 Disease Tubercular Meningitis and Tuberculous Epididymitis. Admitted 6.6.39. Result —



	JUNE 17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	JULY 7	1939. Medicines, etc.
Pulse m	92	88	96	96	92	96	96	90	94	96	100	104	90	96	92	92	100	104	104	104	104	Pulse m
Pulse e	98	106	96	96	100	92	104	98	96	120	116	104	100	100	104	100	106	96	104	112	96	Pulse e
Resp. m	20	20	20	20	20	20	20	22	20	22	24	26	20	20	20	22	22	22	24	22	22	Resp. m
Resp. e	20	24	20	22	20	20	26	22	22	28	26	24	20	22	26	22	22	20	22	24	22	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction						Acid																„ Reaction
„ Albumen						–																„ Albumen
„ Blood						–																„ Blood
~~C.S. Fluid~~ WEIGHT																			8 ℥.	2½ lbs.		~~C.S. Fluid~~ WEIGHT
Sputa ozs.	¼	⅛	⅛	⅛	⅛	1	¼	⅛	½	½	½	¼	1	¼	¼	1½	½	1¼	⅛	1¼	1	Sputa ozs.
Day of Disease or Residence	42		44		46		48		50		52		54		56		58		60		62	Day of Disease or Residence

Diet

weeks (plate VIII.) he ran a febrile course. Far

Plate VIII.

See accompanying Temperature Charts.

from improving, he seemed to be going downhill.

He was thin, pale and anaemic and his prominent cheeks bore a cyanotic flush. He sweated profusely both day and night and, as he lay in bed, he seemed too weary or exhausted to attempt to sit up.

Not only was there flattening, diminished expansion and impaired percussion resonance below the left clavicle, but in the same area there was harsh, cog-wheel breathing, with prolonged expiratory murmur, and much increased conduction of the heart sounds towards the left apex.

Moist accompaniments were plentiful. They were audible at the left apex and in the second, third and

fourth left interspaces. They were increased by the act of coughing.

But the signs of tuberculosis were not confined to the left lung. The presence of left-sided tuberculous epididymitis was confirmed on admission, and a fortnight later enlargement of the left jugular group of cervical glands appeared. Further, a month after admission to hospital, he began to complain of persistent abdominal pain. His abdomen was tumid, doughy and tender. Ill-defined resistances suggestive of matted omentum could be felt, and the associated febrile disturbance left little doubt as to the nature of the abdominal condition. In the abdomen, lung, neck and epididymis active tuberculosis was present, and I therefore considered that he also would be a suitable subject for the experiment with rubiazol, although the drug was intended primarily for trial in pulmonary disease.

Rubiazol was administered only after the patient had been in hospital for a couple of months without making noteworthy progress. Then it was given for two weeks, stopped for one week, and resumed for another three weeks. The interruption during the third week was made because, although the patient appeared to be better, the sedimentation rate had risen and the white blood count was rather low.

The temperature charts (plate VIII) are included, but in tabulated form, as in the previous case, results are more readily appreciated.

Table 2.

T A B L E 2.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sputum (ozs)	-	-	¼	1½	2½	3⅜	2	3⅛	5⅞	3⅛	2¼	3⅝	⅝	⅝	⅞	¼	⅜	-
Evening Pulse Rate	88	92	102	98	105	97	99	105	103	96	101	98	95	93	89	82	90	-
B.S.R.	-	-	-	-	-	-		?/86		56/91	65/98	62/92	56/92	57/90	43/69	-	34/70	-
Weight	7 st.	13¼	8.3¼	8.3½	8.5.	-	8.1¼	-	-	8.2½	-	-	-	-	8.7¾	8.11	9.0½	9.3½	-

Effect of rubiazol on the quantity of sputum, pulse-rate, sedimentation rate (B.S.R.) and weight.

.Weeks underlined in red indicate weeks in which rubiazol was given.

The total quantity of rubiazol given was 50.4 gm. in the following amounts:- during the first, fourth and fifth weeks of treatment he received 1.2 gm. daily, during the second and sixth weeks 1.8 gm., and during the third week none.

The first fortnight he was in hopsital the patient had no sputum; thereafter the quantity increased gradually until the ninth week, during which he began to have rubiazol. In this week the amount was maximal, but there followed a decrease which was most marked after three weeks of rubiazol and was maintained even after cessation of the drug.

The temperature subsided slowly but was indeed still subfebrile at times shortly before discharge; the pulse-rate was appreciably slowed when and after the rubiazol was given. The terminal rise in pulse-rate was due to the patient not remaining strictly at rest during the tense days immediately preceding outbreak of war.

The sedimentation rate, after rising for two weeks with rubiazol, began to fall when the drug was interrupted, and this fall was subsequently maintained when the drug was resumed and after it was stopped. If the two-hour administration figure be taken as the index the result was not very impressive, falling, as it did, from 86 to 70 between the eighth and seventeenth weeks; on the other hand, between the eleventh and fifteenth weeks it had fallen from 98 to 69. The reason for the increase during the first fortnight of treatment remained obscure, particularly as the patient

felt and looked better by the end of that time.

The patient was notweighed every week because at times he was unfit to leave his bed. However the weights which were recorded latterly appeared to show a beneficial effect from the rubiazol.

The comments of the patient are worthy of mention. He said that he felt sick for the first two days, but the nausea had then passed away and subsequently he "seemed to sort of thrive" on the tablets. He had noticed a great difference. Sweating ceased, abdominal pain and discomfort vanished, his appetite improved and weight increased correspondingly; cough and sputum were much lessened. He sat up and took a new interest in life. Instead of looking pale and toxic he became bronzed and seemed the picture of health. The swollen glands in his neck subsided and the focus in the epididymis began to calcify. Indeed, even the sceptical onlooker was much impressed by the change that came over the patient.

Not only however did the patient look and feel better, but with commencing subsidence of the sputum, (after two weeks of rubiazol) tubercle bacilli disappeared; also elastic tissue, pus cells and saprophytes, such as streptococci, decreased and vanished while the sputum became scanty and mucoid.

Moist accompaniments in his chest were so far diminished that coughing was necessary to make them audible, and radiologically there was also much improvement.

War broke out. Many patients left hospital.

Much against advice he also decided to go home. He promised faithfully that he would rest in bed all day. A month later he called back at the hospital looking very well and having gained further weight. He announced that a week after discharge he had resumed his old job - lifting heavy objects as a van-boy. How true it is that you cannot hope to cure a fool of tuberculosis !

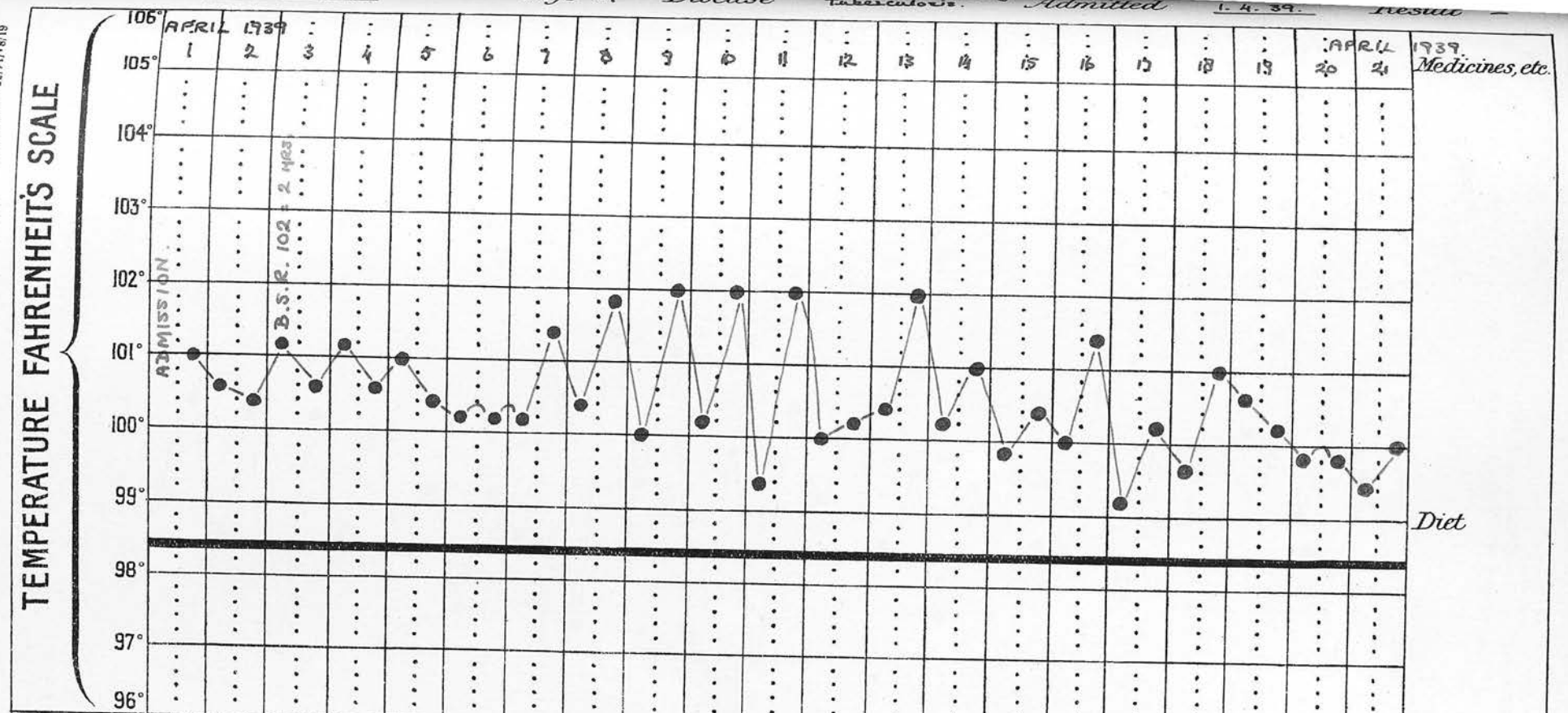
Case 3. A.D. male aged 24 : his occupation had for nine years consisted of loading lorries with lemonade bottles, and it entailed the lifting of weights sometimes in excess of an hundredweight. He was uncertain how long he had been feeling off-colour, but three months before admission to hospital he realized that he was unwell. He had no appetite, was tired in the evenings, desired only to get to bed, and seemed always to be feeling cold and shivery. A cough, which had previously been attributed to smoking, became more troublesome, and his weight fell in six months from 10 st. 7 lbs. to 9.st. 4 lbs.

At length he felt too ill to work and went to see his doctor. He was referred to the Tuberculosis Dispensary and admitted to hospital a week later.

Six years previously, following the death of a sister from tuberculosis, he had been examined as a contact case and declared to be free from disease. No other relatives were found to be suffering from tuberculosis and his wife and two-year-old child appeared to be in good health.

Name PLATE III. Case 8. A.D. Age 24 Disease Bilateral Pulmonary Tuberculosis. Admitted 1. 4. 39. Result —

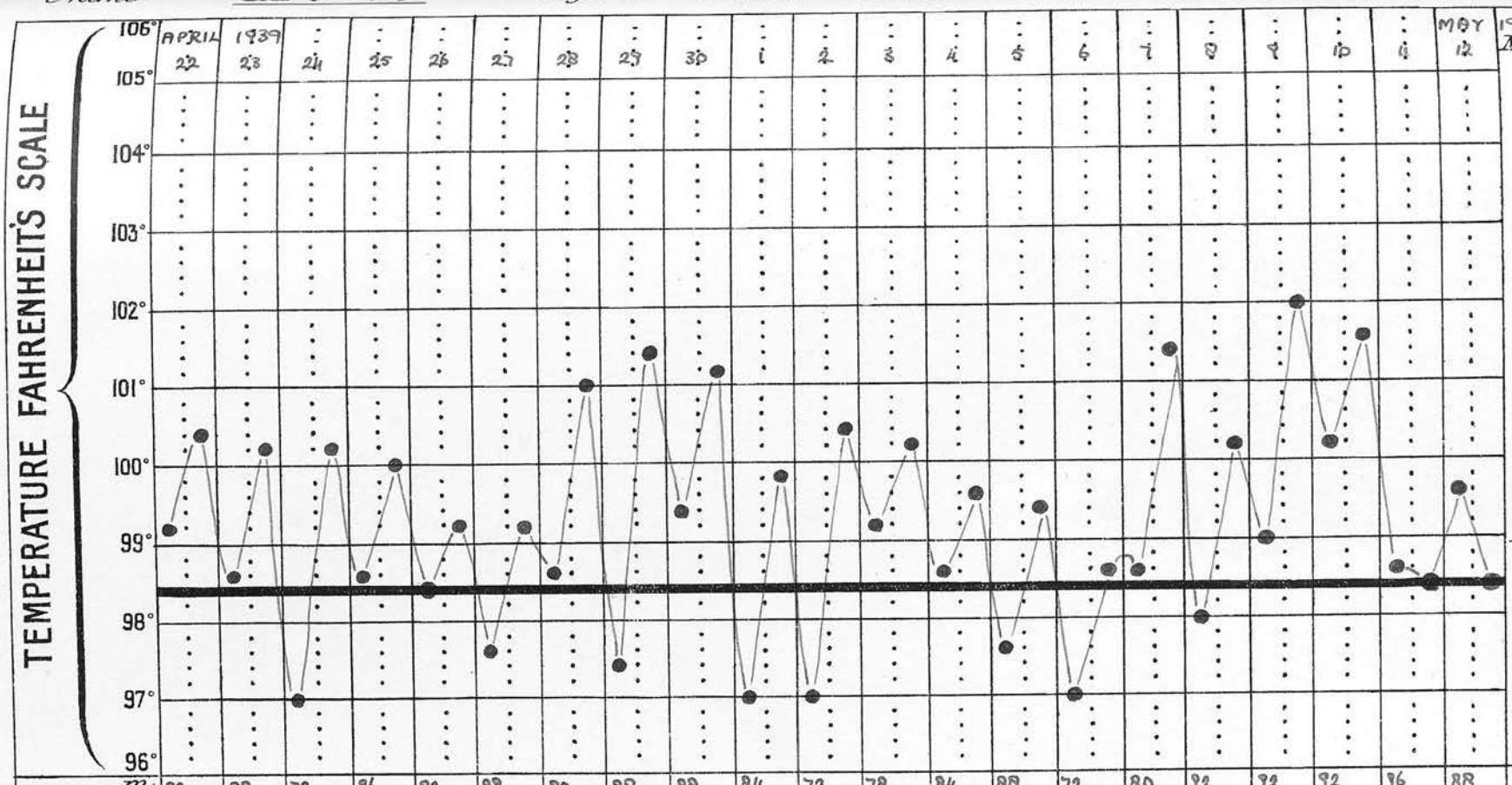
61/8A/14/55– 1M/7/40 Form C.H. 13



		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Pulse	m		88	80	86	88	96	88	80	80	88	88	88	88	88	80	88	88	72	92	88	78	Pulse
	e	92	96	88	98	88	88	96	90	86	104	90	80	96	100	100	98	96	96	80	92	88	
Resp.	m		20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	14	20	20	18	Resp.
	e	20	20	20	20	20	20	20	20	20	22	20	20	20	22	20	20	20	22	20	20	20	
Motions		0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	Motions
Urine ozs.																							Urine ozs.
„ Reaction																							„ Reaction
„ Albumen																							„ Albumen
„ Blood																							„ Blood
~~C.S. Fluid~~ WEIGHT.																							~~C.S. Fluid~~ WEIGHT.
Sputa ozs.			2½	5½	4½	4½	5	5	4	4	4½	6½	5	3¼	6	5½	4¾	8	8	6	7	4½	Sputa ozs.
Day of Disease or Residence			2		4		6		8		10		12		14		16		18		20		Day of Disease or Residence

Name [illegible] Case 8. A.D. Age 24. Disease Tuberculosis. Admitted 1.4.39. Result —

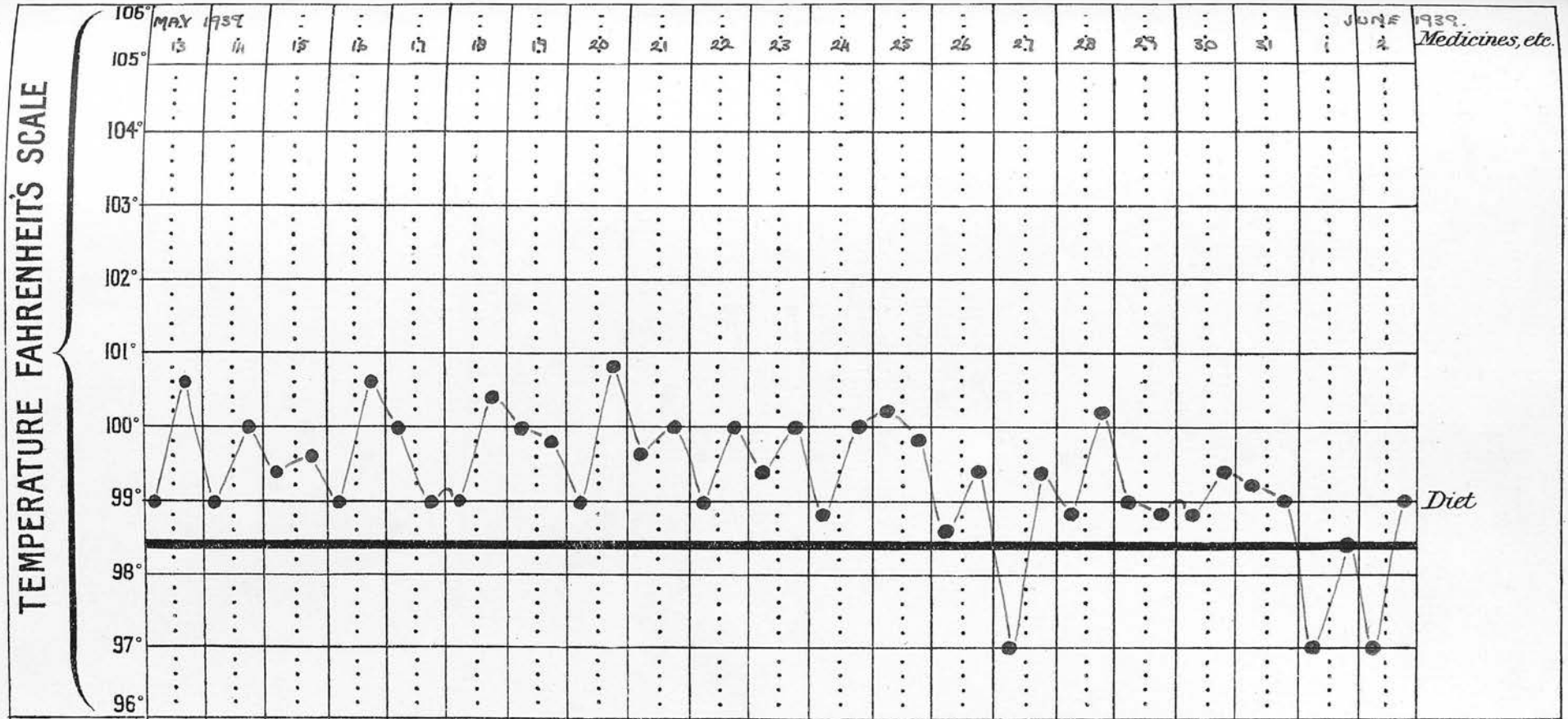
61/8/14/55– 1M/7/40 Form C.H. 13



	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12	
Pulse m	82	88	72	96	92	88	80	88	88	84	72	78	84	88	72	80	92	92	92	96	88	Pulse m
Pulse e	92	100	96	96	96	92	96	100	102	82	86	96	96	84	92	96	92	96	100	92	92	Pulse e
Resp. m	20	20	16	20	20	20	20	20	20	20	16	18	20	20	18	20	20	20	20	22	20	Resp. m
Resp. e	20	24	22	22	20	22	20	22	22	20	20	22	20	20	20	22	20	20	22	20	20	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
~~C.S. Fluid~~ WEIGHT																						~~C.S. Fluid~~ WEIGHT
Sputa ozs.	5½	8	4½	5	6	6	6	7	9	7½	6	6	6	6	6½	4½	6	7	6½	6½	7	Sputa ozs.
Day of Disease or Residence	22		24		26		28		30		32		34		36		38		40		42	Day of Disease or Residence

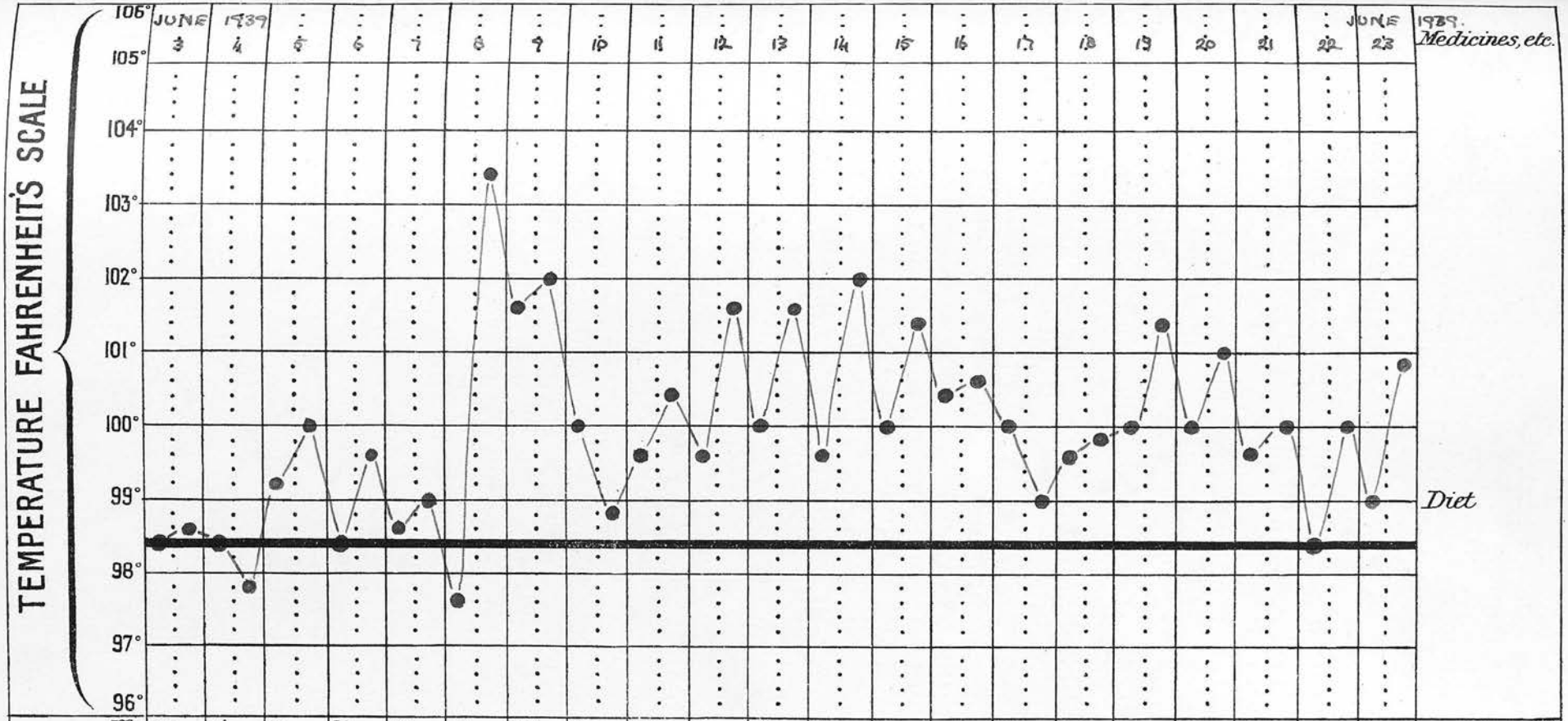
Name PLATE IX. Case 3. A.D. Age 24. Disease Bilateral Pulmonary Tuberculosis. Admitted 1.4.39. Result —

61/84/14/55- 14/7/40 Form C.H. 13



Pulse m	84	92	84	84	88	92	100	84	92	84	84	72	84	84	76	80	82	84	104	72	100	Pulse m
Pulse e	96	92	94	92	92	92	88	88	92	92	96	96	96	96	88	88	100	112	102	100	100	Pulse e
Resp. m	20	20	20	20	20	20	22	20	20	20	20	16	20	20	16	20	20	20	22	16	20	Resp. m
Resp. e	20	20	22	20	20	22	20	20	20	20	20	20	20	20	20	20	20	24	20	20	22	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction			Acid																			„ Reaction
„ Albumen			—																			„ Albumen
„ Blood			—																			„ Blood
~~C.S. Fluid~~ WEIGHT																						~~C.S. Fluid~~ WEIGHT
Sputa ozs.	6½	5½	5½	6	6	6	2¾	5	3¼	4	4½	4½	5½	5½	5½	4½	9	6	6	6½	5½	Sputa ozs.
Day of Disease or Residence		44		46		48		50		52		54		56		58		60		62		Day of Disease or Residence

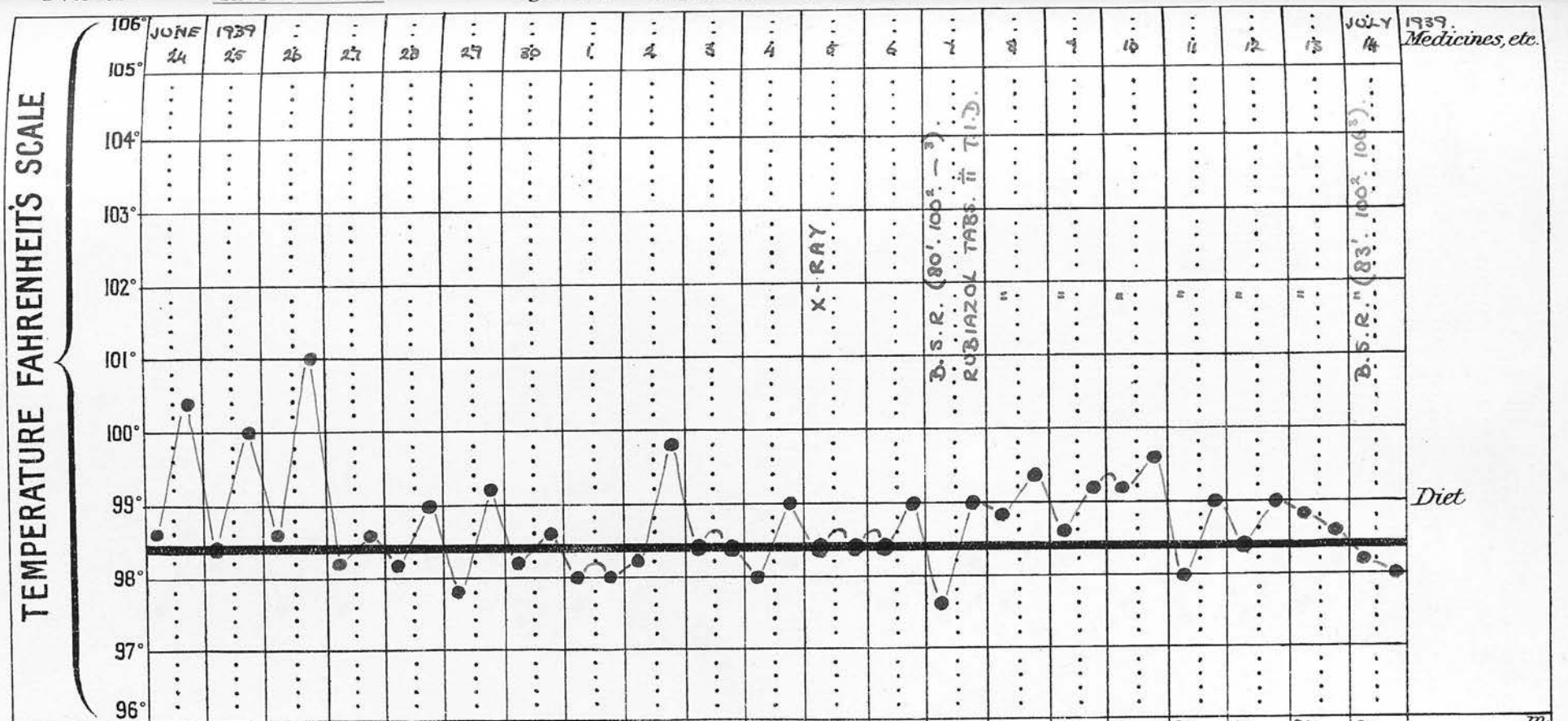
Name [illegible] IN. Case 3. A.D. Age 24. Disease [illegible] Tuberculosis. Admitted 1. 4. 39. Result –



Pulse m	100	96	92	84	92	92	100	100	100	100	96	96	96	100	104	100	100	102	100	100	100	Pulse m
Pulse e	100	100	112	112	102	102	100	106	100	104	104	116	104	106	88	108	102	100	100	104	96	Pulse e
Resp. m	22	22	22	20	20	20	24	22	22	24	24	22	24	24	22	20	22	22	22	20	22	Resp. m
Resp. e	22	22	22	24	22	24	24	22	22	24	26	30	24	24	20	22	24	22	22	24	22	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/0	Motions
Urine ozs.																							Urine ozs.
„ Reaction								Acid		Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid	„ Reaction
„ Albumen								T2.		–	–	–	–	–	–	–	–	–	–	–	–	„ Albumen
„ Blood								–		–	–	–	–	–	–	–	–	–	–	–	–	„ Blood
~~C.S. Fluid~~ WEIGHT.																						~~C.S. Fluid~~ WEIGHT.
Sputa ozs.	5	5½	3½	8	5½	7	5½	5	5½	5	6	6	5½	4¾	6	7	3½	5½	5½	3½	3	Sputa ozs.
Day of Disease or Residence	64		66		68		70		72		74		76		78		80		82		84	Day of Disease or Residence

Name [illegible] Case 3. A.D. Age 24. Disease [illegible] Tuberculosis. Admitted 1.4.39. Result —

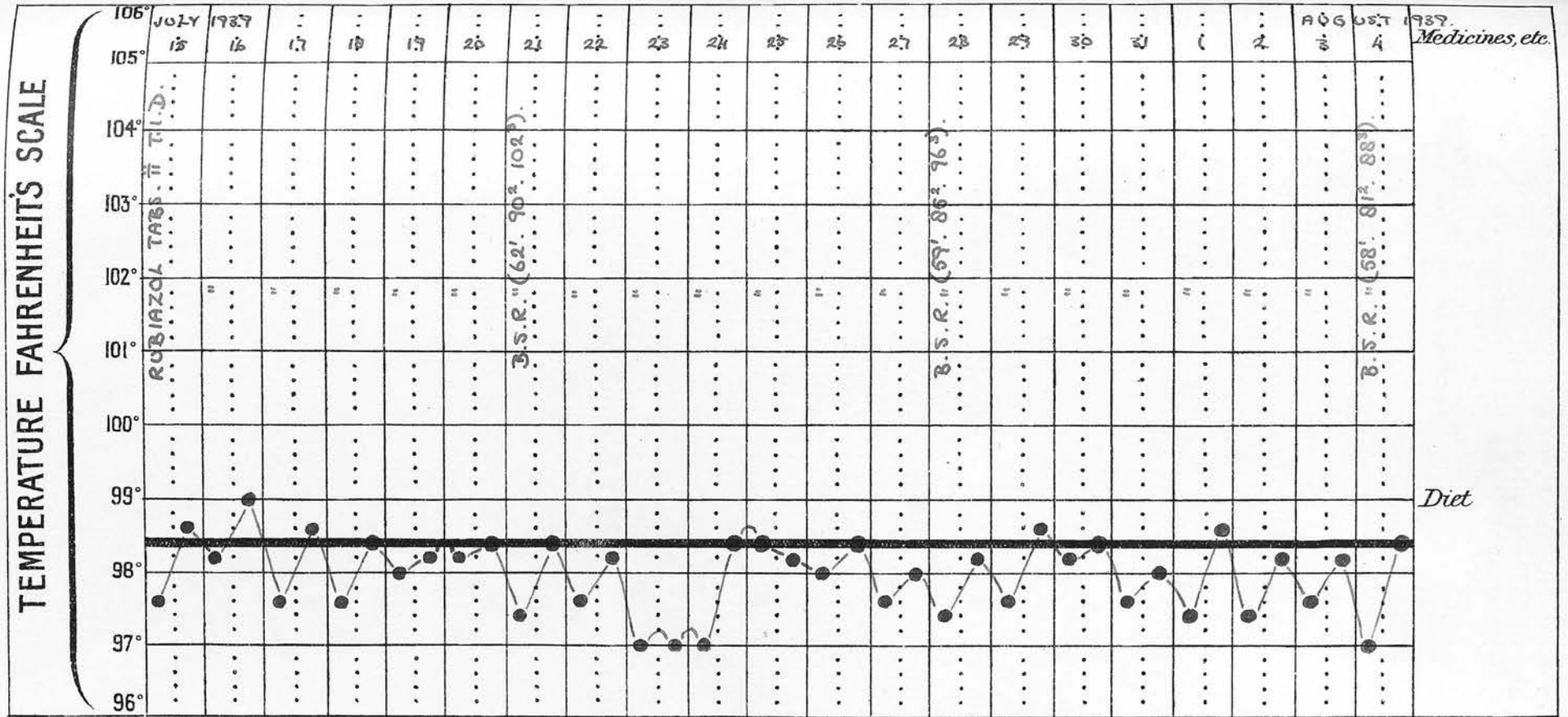
61/8/14/55- 1x/7/40 Form C.H. 13



	JUNE 24	1939 25	26	27	28	29	30	1	4	3	4	5	6	7	8	9	10	11	12	13	JULY 14	1939. Medicines, etc.
Pulse m	98	98	96	100	92	92	96	92	92	92	100	100	96	96	88	98	92	84	92	80	92	Pulse m
Pulse e	98	102	108	88	98	96	100	104	104	104	92	96	98	100	92	96	88	100	96	92	100	Pulse e
Resp. m	20	22	22	22	20	20	20	20	20	20	22	24	20	20	20	22	20	20	20	20	20	Resp. m
Resp. e	22	22	24	20	22	20	22	22	20	22	20	20	20	20	22	20	20	20	20	20	20	Resp. e
Motions	0/1	0/0	0/1	0/2	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction				Acid																		„ Reaction
„ Albumen				—																		„ Albumen
„ Blood				—																		„ Blood
~~C.S. Fluid~~ WEIGHT																						~~C.S. Fluid~~ WEIGHT
Sputa ozs.	4 1/2	5 1/2	5 1/2	6	4	5 1/2	4	4 1/2	4	5	4 1/2	5	3 1/2	3 1/2	4 1/2	4	3	3 3/4	3 1/2	4 3/4	4	Sputa ozs.
Day of Disease or Residence		86		88		90		92		94		96		98		100		102		104		Day of Disease or Residence

Name [illegible] M. Case 8. A.D. Age 24. Disease Tuberculosis. Admitted 1. 4. 37. Result —

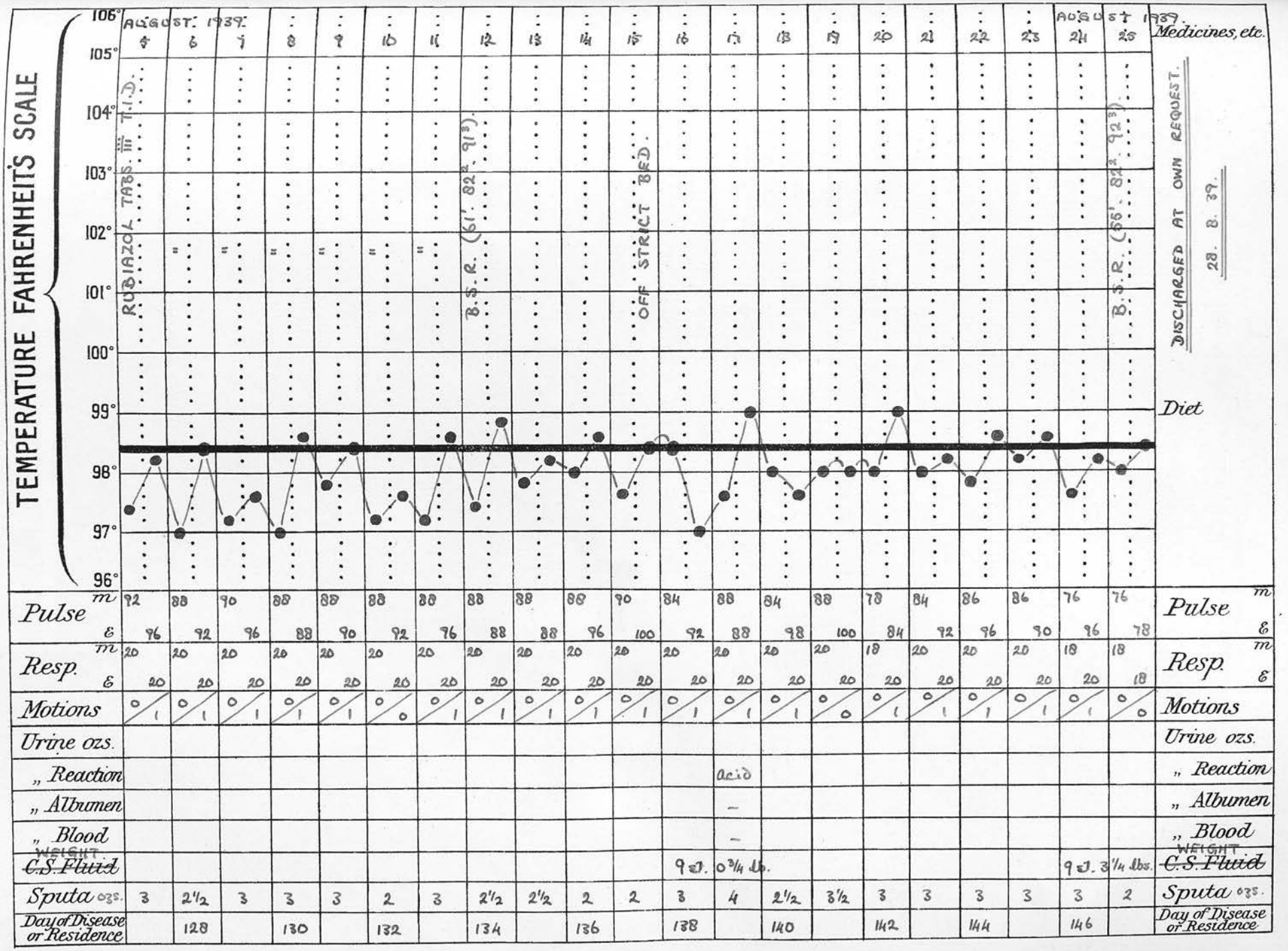
61/8/4/14/55– 1M/7/40 Form C.H. 13



Pulse m	90	92	88	90	92	92	92	92	92	88	90	92	96	88	88	88	92	88	92	92	90	Pulse m
Pulse &	90	98	96	96	92	96	96	92	96	96	92	92	92	96	92	92	92	96	96	100	96	Pulse &
Resp. m	20	20	20	20	20	22	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	Resp. m
Resp. &	20	20	20	20	20	20	20	22	20	20	20	20	20	20	20	20	20	20	20	20	20	Resp. &
Motions	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	Motions
Urine ozs.																						Urine ozs.
„ Reaction																						„ Reaction
„ Albumen																						„ Albumen
„ Blood																						„ Blood
WEIGHT C.S. Fluid																						WEIGHT C.S. Fluid
Sputa ozs.	4	2	3½	3	3	1¾	2½	3	3	3	3	2	1½	1½	2	1½	1½	3	1½	1½	2	Sputa ozs.
Day of Disease or Residence	106		108		110		112		114		116		118		120		122		124		126	Day of Disease or Residence

Name [illegible] Case 8. A.D. Age 24. Disease Bilateral Pulmonary Tuberculosis. Admitted 1.4.39. Result —

61/84/14/55- 1m/7/40 Form C.H. 13



Pulse m	92	88	90	88	88	88	88	88	88	88	90	84	88	84	88	78	84	86	86	76	76	Pulse m
Pulse e	96	92	96	88	90	92	76	88	88	96	100	92	88	98	100	84	92	96	90	96	78	Pulse e
Resp. m	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	18	20	20	20	18	18	Resp. m
Resp. e	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	18	Resp. e
Motions	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/0	Motions
Urine ozs.																						Urine ozs.
„ Reaction													Acid									„ Reaction
„ Albumen													—									„ Albumen
„ Blood													—									„ Blood
~~WEIGHT~~ ~~C.S.Fluid~~												9 ℈.	0 3/4 lb.							9 ℈.	3 1/4 lbs.	~~WEIGHT~~ ~~C.S.Fluid~~
Sputa ozs.	3	2 1/2	3	3	3	2	3	2 1/2	2 1/2	2	2	3	4	2 1/2	3 1/2	3	3	3	3	3	2	Sputa ozs.
Day of Disease or Residence		128		130		132		134		136		138		140		142		144		146		Day of Disease or Residence

On admission he was acutely ill. He coughed a great deal and produced copious sputum. Sweating was troublesome both during the day and night, and fever was very persistent (plate IX.) He was breathless and cyanosed, and examination of his chest showed evidence of widespread disease. There was flattening of both subclavicular areas with impaired percussion resonance, medium-pitched bronchial breathing, abundant moist râles - some coarse and consonating, some medium or fine subcrepitant - and whispering pectoriloquy was located along the lower half of the vertebral border of the right scapula. In the latter area there was also post-tussic suction.

Radiologically extensive tuberculosis of the broncho-pneumonic form was seen to affect the upper two-thirds of both lung fields (plate X.)

Plate X. A.D. aged 24, showing broncho-pneumonic type of tuberculosis affecting extensive areas in both lungs,

The sputum was purulent and contained large numbers of tubercle bacilli.

With such evidence the prognosis appeared very black, and indeed it seemed that he should have been admitted to a hospital for advanced cases rather than to the sanatorium.

When, after thirteen weeks, pyrexia was still present, (though admittedly rather less marked than on admission), I thought he might be considered suitable for the experiment with rubiazol. But there were also several other reasons for deciding to give him the drug.

Besides the continued pyrexia, the sputum was quite as profuse as on admission and still loaded with tubercle bacilli. Also, moist adventitia were not appreciably diminished in quantity.

There was no doubt that a change occurred following the rubiazol. Sputum became less, and after three weeks examination failed to reveal the presence of tubercle bacilli. The results obtained in examination of the sputum are shown in Table 3a.

Table /

TABLE 3a.

Date	Examination of Sputum.	Treatment.
21st April -	Tubercle bacilli +++.	-
17th May -	" " ++.	-
27th June -	" " +++.	-
8th July -	" " ++	Rubiazol started
14th July -	" " +	Having Rubiazol
19th July -	" " +	" "
28th July -	" " -	" "
6th August -	" " -	" "
17th August -	" " -	Rubiazol discontinued on 12th.
28th August -	" " -	-

It was of course no proof that the sputum had become sterile: neither enrichment nor cultured methods were used in reaching the above results, but the apparent disappearance of the tubercle bacilli certainly coincided with the administration of rubiazol, and saprophytes became very scanty though they did not entirely disappear.

The pulse-rate slowed but only to about the same rate as on admission.

Table /

TABLE 3b.

Weeks	1	2	3	4	5	6	7	8	9	10	11
Sputum (ozs)	26½	33¼	43¾	41	47½	43½	38¼	32½	43	40	37¾
Evening pulse rate	92	92	93	95	93	94	92	94	99	104	106
B.S.R.	?/102	-	-	-	-	-	-	-	-	-	-
Weight	-	-	-	-	-	-	-	-	-	-	-

Weeks	12	13	14	15	16	17	18	19	20	21	22
Sputum	34	35	30	27½	19¾	17	13	19½	18½	20½	16½
Evening Pulse-rate	100	99	100	95	95	94	95	92	93	92	87
B.S.R.	-	-	80/100	83/100	62/90	59/85	58/81	61/82	-	55/82	-
Weight	-	-	;	-	-	-	-	-	9st.0¾lb	9.3¼	-

Effect of rubiazol on the sputum, pulse, blood, sedimentation rate and weight.
Red lines indicate weeks in which rubiazol was given.

The sedimentation rate, which was 102 (for two hours) on admission, was still 100 after fourteen weeks in hospital. The fall to 90 after two weeks on rubiazol and to 81 after four weeks was surely, if not sensational, at least not mere coincidence. No further fall occurred, but whereas previously the patient had been too ill to leave his bed for the purpose of weighing, now, following the rubiazol, he was able to do so and actually gained two and a half pounds in one week.

His evening temperature altered from usually febrile to become usually normal though sometimes subfebrile. Possibly the most remarkable of all evidence of improvement was the diminution of moisture. Instead of abundant and widespread, the rales were everywhere very scanty except at the right apex. Here however they persisted in a rather obstinate manner, while the whispering pectoriloquy and apparent cavitation in the right lower lobe also remained.

Asked whether he thought he was better, worse or just the same, the patient said that "he never felt better" than he now did. His sputum was much lessened and in particular he was no longer troubled by the "incessant cough, cough, cough" on waking in the morning.

Radiologically there was also evidence of some improvement. Areas of infiltration were diminished in extent and rather more sharply defined, and there was commencing fibrosis.

When there were so many signs to suggest

improvement and one began to hope that the fatal outcome might be averted, it seemed sheer tragedy that the patient, on the outbreak of war, should decide to go home. Two months later he was said to be "keeping about the same," but since then nothing has been heard of him. It would not be surprising to learn that he also has started to work.

Case 4 : A. McD. male, aged 27, an engraver, who had been under treatment with insulin for diabetes for seven years. Two years after the diabetes was discovered he was found to have developed left-sided pulmonary tuberculosis. He was admitted to the Royal Victoria Hospital and an artificial pneumothorax was induced. During this stay in hospital he also received a course of gold injections - a total of 5 gm. of sanocrysin being given.

Twelve months later he was discharged, feeling well apart from slight dyspnoea on exertion. He attended hospital for pneumothorax refills for a further two years. Thereafter he enjoyed reasonably good health until October 1938 when he had an attack of 'Influenza'. His cough and sputum returned, breathlessness was aggravated, he became easily tired and lost more than a stone in weight. When readmitted to hospital in May 1939 he weighed only 9 st. 5 lbs. His height was 6 feet.

He was then pale and anaemic with toxic palate and atonic muscles. There was hollowing above and below both clavicles, bilateral impairment of percussion,

medium-pitched bronchial breathing and multiple moist râles, these being coarse and consonating in the right upper lobe. Bilateral fibrocaseous disease with cavitation was shown on x-ray (plate XI.) examination.

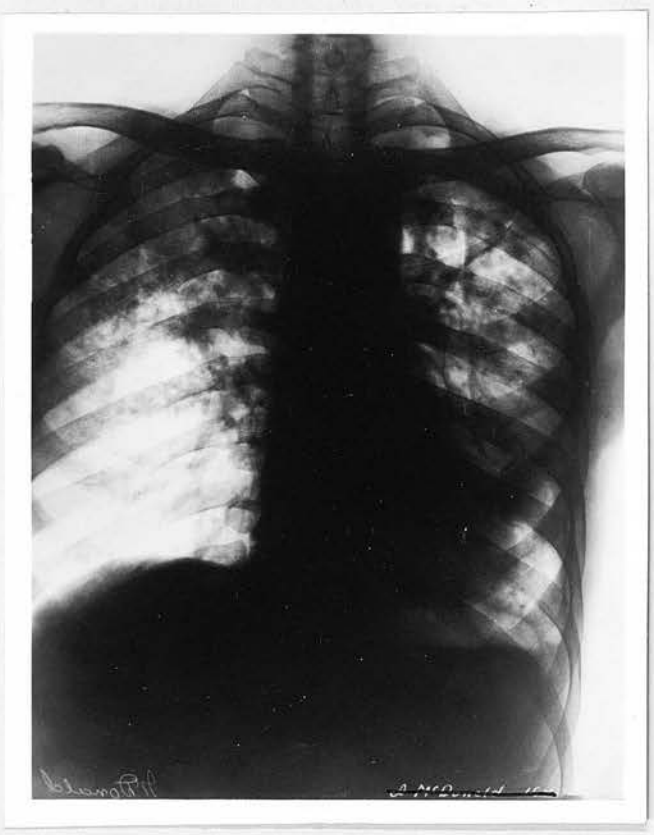


Plate XI. A.McD. aged 27, showing bilateral fibrocaseous tuberculosis with displacement of heart and trachea to the left. Old standing disease on left (treated by A.P.) and recent infiltration on right side.

In addition his voice was husky, and it was found that there was tuberculous infiltration in the interarytenoid region of the larynx without actual ulceration.

From the long history, comparative absence of pyrexia, shifting of heart trachea and mediastinum to the left and general clinical picture, he was classed as a case of chronic tuberculosis - in contradistinction to the previous three cases which were of acute variety.

Under the influence of a strict diet and insulin he gradually put on weight; he gained more than ten pounds in the course of six weeks. That however was practically the only evidence of improvement.

During the same period his pulse-rate quickened, his sputum remained positive for tubercle bacilli and increased in quantity, and sedimentation rate rose from 88' to 99 (for two hours). He was therefore given an experimental course of rubiazol.

Table /

TABLE 4.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sputum (ozs)	1 oz	6¼	5¼	8¾	11½	12	15½	11	13¾	12	12	8½	10½	11½	16½	12½
Evening Pulse-rate	81	87	92	97	93	90	95	93	91	88	88	87	89	90	90	87
B.S.R.	-	-	? 88	-	-	-	-	62 99	53 87	53 85	58 90	56 88	-	? 92	-	-
Weight	9st.5	9-5¾	9-7	9-10½	9-12	10-0½	10-1¾		10-0¾	9-13¾	10-1¼	10-0¾	10-2¾	10-2¾	10-1½	10-2

Effect of rubiazol on the sputum, pulse-rate, blood sedimentation rate and weight.

Red lines indicated weeks during which rubiazol was given.

Briefly the result was disappointing (table 4). The previous increase in weight was not maintained, the sputum remained tubercle laden and approximately the same in amount. The initial drop in sedimentation rate from 99 to 87 (after one week), and 85 (after two weeks), was likewise not continued, and the pulse-rate was slowed by only a negligible degree.

That he was an unsatisfactory patient, who constantly broke rules and fought against discipline, may have contributed to the negative result in his case. As Kingston Fowler, (1921) wrote "No fool ever gets rid of tuberculosis of the lungs. He may be no fool in relation to literature, science or art, but if he is in relation to his own well-being he is doomed for certain."

His throat remained the same, and his general condition was not altered materially either for better or for worse by the course of rubiazol. Like most of the other patients, he was discharged on the outbreak of war and since then he has steadily deteriorated.

Case 5: Mrs E.D. aged 22, whose father had died of pulmonary tuberculosis five years previously. Married at 20 she had a baby a year later. Following parturition she was in bed for three weeks, but on getting up she felt ill. Her appetite was poor, she had night-sweats, became tired easily, had palpitation and was extremely breathless.

A week later she felt a pleuritic pain on the right side, and this was accompanied by an irritating

dry cough. Tuberculosis was suspected and the diagnosis confirmed by sputum analysis and radiological examination. The prognosis was thought to be hopeless and she was admitted to a hospital for advanced cases in August 1937.

She made surprising progress. Her weight rose from 6 st. 9 lbs. to 8 st. 4 lbs. in eight months, and although suffering from bilateral disease (plate XII.)

Plate XII.

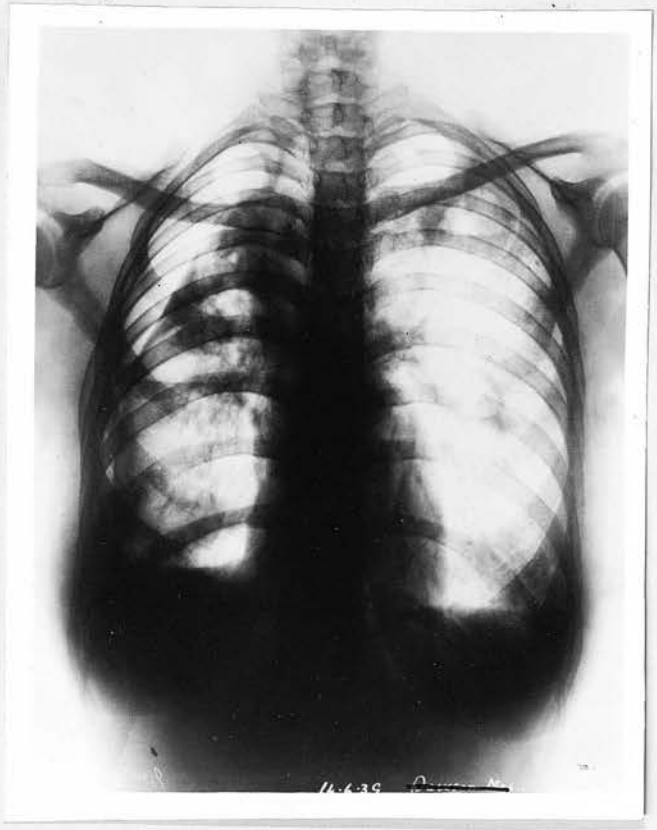


Plate XII: Mrs E.D. aged 22, showing bilateral pulmonary tuberculosis with multiple cavities and right-sided A.P. (discontinued.)

it was decided to risk inducing an artificial pneumothorax on the more diseased right side. This was done successfully in March 1938, and crysotherapy was started shortly afterwards. Progress continued. Diarrhoea, thought to be due to gold intolerance, was

followed in July 1938 by a febrile disturbance and appearance of an effusion complicating the pneumothorax.

Signs of increased activity were evident at both apices, and she lost 8 lbs in weight in little more than a month. Then she began once more slowly to improve. At length, in March 1939, she was transferred to the Royal Victoria Hospital considerably better.

In her new environment, apart from a slight initial gain in weight, there was little alteration in her condition. She was allowed up for gradually extended periods, beginning on 9th May 1939. Her progress seemed however to have stopped. In twenty weeks she only gained 1½ lbs. and for eleven weeks her weight remained at 7 st. 12 lbs, so I decided to give her rubiazol.

The result (Table 5) was not startling, but at least appreciable, because she promptly gained 4 lbs. in the next five weeks.

Table /

TABLE 5.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Weight	7.11	7.12	7.12	7.12½	7.12½	7.12½	7.12	7.12	7.12½	7.12	7.12	7.12	8.-	8.-
Evening Pulse Rate	95	95	84	83	87	99	100	95	90	93	90	76	78	77
B.S.R.	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Weeks	15	16	17	18
Weight	8.1	8.1½	8.2	8.2
Evening Pulse Rate	80	79	82	77
B.S.R.	29/55	32/67	-	26/67

Effect of rubiazol on the weight, pulse-rate and blood sedimentation rate.
Red lines indicate weeks during which rubiazol was given.

No less perceptible was an apparent slowing of the pulse. Her pulse-rate had admittedly been variable, but the drop from 90 to 76, which was subsequently maintained, was noteworthy.

She had no sputum, but it was surprising to find a lack of confirmation of improvement in the sedimentation rate, which was lowered for one week and then rose again. Menstruation may have been responsible for the rebound. It did not however explain the subsequent failure to fall.

In her general appearance there was improvement and onphysical examination there was no doubt that the moist accompaniments were much less prominent. Even though she was allowd to be up for eight hours each day there was no relapse, and when war broke out she was evacuated to her home where she continued to progress.

Case 6: Miss J.G.: aged 23, a factory-worker. Two years previously she had developed a cough which did not improve with medicine. She also became breathless, lacking in energy and sweated at night. For six months she was treated for "bronchial catarrh", but at length, following an haemoptysis, her doctor ordered an x-ray of her chest and found the true diagnosis was bilateral tuberculosis.

On admission to hospital she was thin and anaemic, and had that freckled appearance described by some as portraying an exudative diathesis. Her hair was of fine texture and eyelashes were abnormally

long, but her expression was one of weariness and exhaustion.

Muscular atony, drooping shoulders, flattening and retraction of the chest below the clavicles with impairment of percussion note, diminished air-entry and bilateral medium subcrepitant râles - these were the main physical signs of disease.

Very scanty sputum contained numerous tubercle bacilli, and for about nine weeks her temperature was subfebrile before eventually settling and becoming normal.

She was confined strictly to bed, yet in spite of this, after five months, she had four ~~xxxx~~ sharp haemoptyses in quick succession. An artificial pneumothorax was induced on the left side and succeeded in controlling and preventing further haemorrhage. Unfortunately signs of activity on the right side became pronounced, and a month later a pneumothorax was induced also on that side.

Owing to adherent pleura on the right side and to pleural adhesions on the left side, neither lung was collapsed in a really satisfactory manner. Some of the adhesions were divided by electro-cautery but still others remained (plate XIII.,)and could not be severed.

Plate XIII.

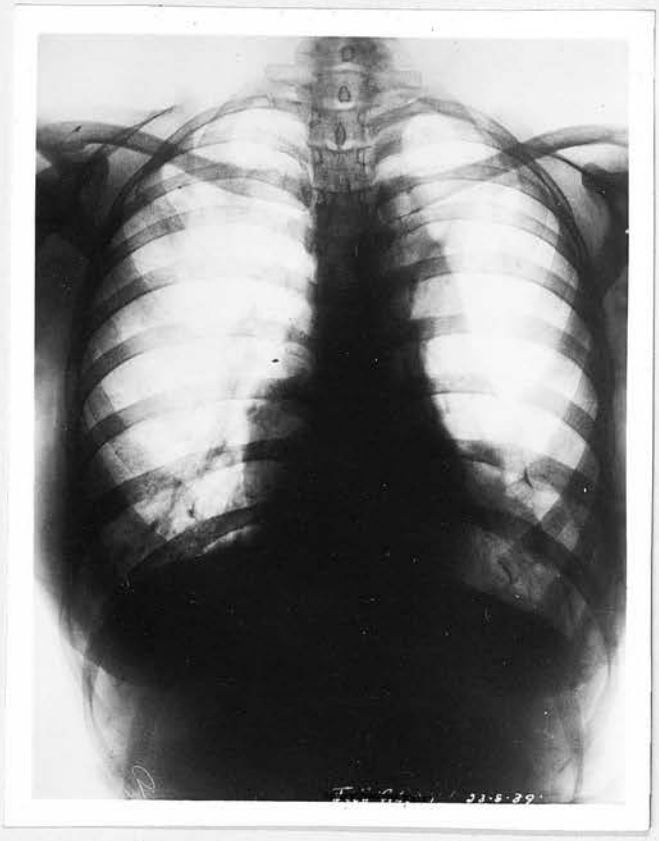


Plate XIII. Miss J.G. aged 23, showing A.P. with incompletely collapsed left lung held out by adhesions, and infiltration of right inter-cleido-Hilar zone.

After six weeks the pneumothorax on the right side was abandoned. Cough and other symptoms had seemed to be aggravated by the bilateral pneumothorax, and diarrhoea in particular had troubled her for four weeks, while she became febrile and lost eight pounds in weight.

Slowly she began again to improve. She regained the lost weight after three months. At length after a whole year in bed, she was allowed up for half-an-hour each day. This was increased later to one and then two hours, but immediately the moisture at the

right-apex, which had almost vanished, returned, and the sedimentation rate rose from 77 (after two hours) to 86.

With such a high sedimentation rate after prolonged rest the prognosis seemed pretty hopeless. Therefore, as an alternative to sending the patient back to bed all day, it was decided to try the effect of rubiazol - to see whether it could succeed, where rest had failed, in checking the activity on the right side. On the left, with the pneumothorax, no moisture could be detected, but owing to the adhesions only 150 to 200 ccm. air could be given at each refill. This resulted in an intra-pleural pressure of ±0:+8.

She was given two tablets of rubiazol three times a day for three weeks and three tablets thrice daily for the fourth week. The result was inconclusive. (Table 6.)

Table /

TABLE 6.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Weight	7.13	8.	8.	8.	8.1	8.2	8.2½	8.4	8.4	8.5	8.5	8.6	8.6	8.8	8.8	8.8½
Evening Pulse-rate	81.	78.	83	86.	81.	80.	79.	80.	79	80	81	78	83	80	79	81
B.S.R.	-	-	-	-	-	? 77	-	-	66/86	30/65	49/75	43/72	65/80	-	50/78	-
Sputum	-	¼oz.	⅛oz.	⅜oz.	¼oz.	⅜oz	⅜oz	½oz.	½oz.	⅞oz.	⅛oz.	-	-	-	-	-
Allowed up.	-	-	-	-	-	½hr	½hr	1 hr	2hrs	-	3hrs	4hrs	-	5hrs	--	6 hrs.

Effect of rubiazol on the weight, pulse-rate, blood sedimentation, and sputum.

lines marked in red indicate weeks in which rubiazol was given.

Case 7: M.M. male, aged 32, a clerk, who was suffering from chronic fibroid tuberculosis. He gave a history peculiarly similar to that of case 4.

During 1932 he consulted his doctor on account of loss of weight, thirst and polyuria, and was found to have diabetes. He was admitted to the Edinburgh Royal Infirmary and treated there by diet and insulin; the latter was steadily reduced from 50 units daily until he was having only 6 units each day.

After discharge he remained well for one year. Then he developed a cough with sputum and had a slight haemoptysis. Pulmonary tuberculosis was discovered on the left side, and he was admitted to the Royal Victoria Hospital in October 1933.

In March 1934 an artificial pneumothorax was induced on the left side and it was maintained successfully for 3 years. Much improved, he remained symptom-free till May 1938 when "he caught a chill" and was readmitted to the Royal Victoria Hospital. A phrenic nerve crush was performed and he stayed in hospital for six months. Then he was discharged at his own request but against medical advice.

On May 1939 his condition had so far deteriorated that he relented. He was again readmitted to hospital where a thorocoplasty was performed in 4 stages. The x-ray (Plate XIV.) was taken while he was convalescing from the last stage of this operation.

Plate XIV.

Plate XIV.: M.M. aged 32, showing displacement of trachea, heart and mediastinum towards collapsed lung following recently performed left-sided thoracoplasty.

He beganto feel better, but cough and copious sputum still persisted and, although reduced from 100, he was still receiving 65 units of Insulin daily.

His appearance was that of a cadaverous individual, with clubbing of the fingers, sunken cheeks, ~~xxx~~ prominent hollowing above and below both clavicles, trachea and heart displaced towards the left side, stony dullness on percussion, enfeebled air-entry and multiple medium or coarse moist râles all over the left lung field. The x-ray showed displacement of the heart and mediastinum to the left side,

fibroid tuberculosis with cavitation on the left and compensatory emphysema on the opposite side.

It was primarily with the object of observing whether or not there was any effect on the quantity of sputum expectorated that I placed him on rubiazol. The result was entirely negative as will be seen from the accompanying Table (7).

TABLE 7.

Weeks	1	2	3	4	5	6	7	8
Sputum	15¾	19	21⅜	24	21⅞	22	20½	-
Pulse	85	86	86	86	85	88	93	-
B.S.R.	-	-	-	20/45	22/49	23/50	20/45	-
Weight	-	-	-	-	-	9.7¾	9.10¼	

The observations in this case were started four weeks after the last stage of the thoracoplasty had been performed, and they ended abruptly as ten days only after he had finished having rubiazol he was evacuated from hospital on account of the war.

He was not fit enough to leave his bed for the purpose of weighing before the sixth week (Table 7), and the fact that he gained 2½ pounds in weight during the following week cannot be credited to the rubiazol. The drug produced no effect on the sedimentation rate, on the pulse-rate, nor on the quantity or quality of the sputum.

By way of explanation it should be noted that no benefit was anticipated in this type of case - one in which fibrosis was predominant. The lung was partly

collapsed and inexpansile, and circulating blood carrying the drug had minimal access to the diseased areas.

The negative findings, if not welcome, were at least expected.

Case 8: R.W. male, aged 21, a labourer, who was, judged by the result, possibly the most interesting of the cases in the experiment.

His father had died of pulmonary tuberculosis complicating diabetes, and he had a brother with bilateral tuberculosis who, nine months previously, had been discharged very much improved after ten months in hospital. His mother and five siblings were apparently in good health.

Some eight months before admission to the Royal Victoria Hospital the patient had pain in his chest in the region of the left scapula. With medicinal treatment this "muscular rheumatism" improved. It did not however disappear entirely, and six months later it became very acute.

Changing the diagnosis to "a little touch of catarrh", his doctor persisted in symptomatic treatment, reassured the patient, and allowed him to resume manual work.

At length, worried by pain, dyspnoea, cough and sputum, and particularly remembering his family history, he requested that an x-ray examination be made. This was done and the examination revealed extensive left-sided fibro-caseous tuberculosis.(Plate XV)

Plate XV.

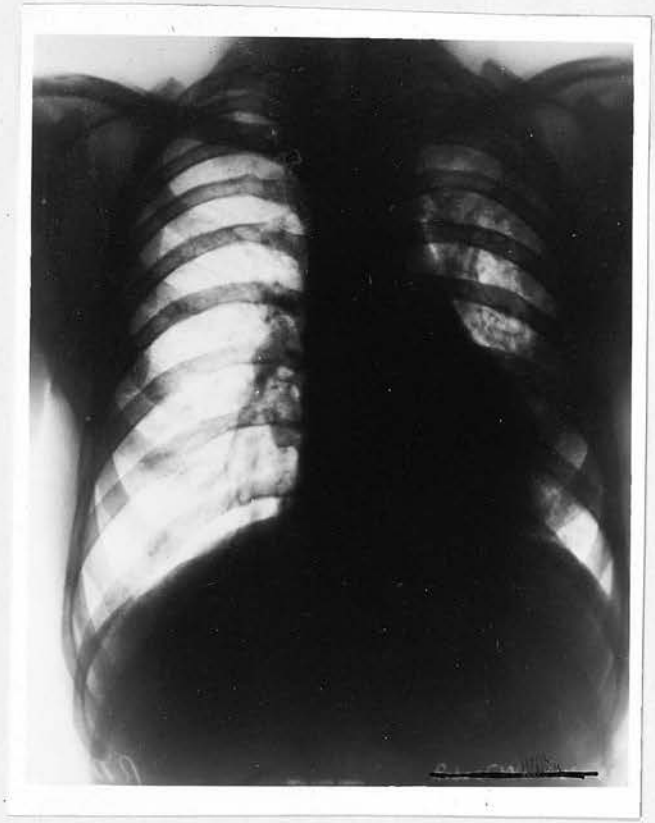


Plate XV.: R.W. aged 21, showing extensive left sided fibro-caseous tuberculosis with displacement of the heart to that side.

Within a fortnight he was admitted to hospital. He was then pale with a cyanotic malar flush, looked very ill, and became faint and collapsed on standing for a short while during examination. Musculature was flabby, pulse soft and accelerated in rate, blood pressure low - systolic pressure 108, diastolic 65 - and his palate was a toxic primrose-yellow colour.

Signs of disease were easily detected and just as extensive as the radiological examination led one to expect. There was drooping of the left shoulder with relative wasting of the left shoulder muscles, flattening below the left clavicle, diminished expansion and impaired air-entry and percussion note over

most of the left lung, and correspondingly widespread medium or fine subcrepitant râles. Friction was not audible, but evidence of old-standing disease was seen from the situation of the apex-beat. This was outside the left nipple, and since the heart was of normal dimensions it indicated retraction of the heart and mediastinum towards the diseased side.

Injections of sodium cacodylate gr.¾ produced both local and febrile reactions similar to those from an excessive dose of tuberculin. The injections were discontinued after two had been given.

An attempt to induce an artificial pneumothorax failed, owing, presumably, to the adhesions resulting from the old-standing pleurisy.

Crysotherapy was tried, and it was during this course of treatment that rubiazol was also given. The object here was to discover whether there was any symbiotic or allied effect of the two drugs together - gold (crisalbine) and sulphanilamide (rubiazol.)

I have already mentioned that both compounds have same structural similarity and that both are known sometimes to cause agranulocytosis.

TABLE /

TABLE 8a.

Weeks	1	2	3	4	5	6	7	8	9	10
Sputum	11½	19½	12	12	12½	14	14	10½	10¾	10½
B.S.R.	/44	-	-	-	-	-	14/37	14/38	14/39	2/5
Pulse Rate	84	75	76	81	83	86	80	81	81	74
Weight	9.3½	9.4¾	9.7	9.5¾	9.6½	9.7¾	9.9	9.9½	9.12¼	9.12%

Weeks	11	12	13	14	15	16	17	18	19	20
Sputum	8⅝	8¾	7½	4½	3¼	2½	2⅜	2⅝	2⅜	4
B.S.R.	0/¼	10/29	2/6	8/25	6/19	-	-	-	-	-
Pulse Rate	79	79	73	77	75	77	78	74	76	77
Weight	9.12	9.13	9.13¾	10	10-¼	10.2¼	10.3¼	10.3	10.4	10.4

Effect of rubiazol on sputum, pulse, weight and blood sedimentation rate in patient already having gold. Red lines indicate weeks in which rubiazol was given.

The result was instructive. There was no appreciable effect on the pulse-rate which was previously within normal limits, nor was there any noteworthy effect on the weight which had been slowly increasing since admission. The sputum began to decrease in quantity and this diminution continued after stopping the rubiazol. But the most profound effect was observed in the blood sedimentation rate. (Table 8a).

On admission his two-hour sedimentation reading was 44. With the rest in bed and general tonic treatment it fell, during the first six weeks, to 37. At this point injections of crisalbine were started. He received 0.01 gm. the first week, 0.02 gm. the next, and a further increase of 0.02 gm. in each subsequent weekly injection up to 0.1 gm.

After two weeks of gold the sedimentation rate had risen very slightly to 39. Then it was that rubiazol was started in addition to the gold. Inside a week the rate was down to 5, and after another week it was only ¼ after two hours. One wondered whether this phenomenal alteration would be maintained, but it was not so. Subsequent aberrations were puzzling.

The figures are shown in greater detail in Table 8b :-

TABLE 8b.

Date	Blood Sedimentation Rate			Treatment
	1 Hour	2 Hours	3 Hours	
22nd June	-	44	-	Bed - rest
1st August	14	37	50	Crisalbine 0.01 gm
8th "	14	38	54	" 0.02 gm.
15th "	14	39	60	" 0.04 gm. Rubiazol Tabs. ii t.i.d.
22nd "	2	5	9	" 0.06 gm. Rubiazol Tabs. ii. t.i.d.
29th "	0	¼	½	" 0.08 gm. Rubiazol Tabs. ii t.i.d Allowed up 1 hr.
5th September	10	29	44	" 0.1 g.m. Allowed up 1 hr.
12th "	2	6	12	" 0.2. gm. Rubiazol stopped.
19th "	8	25	36	" 0.3 gm. Allowed up 2 hrs.
26th "	6	19	32	" 0.4 gm.

Every precaution was taken to ensure that, as far as possible, extraneous factors, liable to influence the sedimentation rate, should be ruled out. Blood was withdrawn from the patient at the same hour of the same day each week and readings were obtained at the same temperature and under the same conditions.

Alterations in the sedimentation rate may have been influenced by improvement in the patient's condition, by the crisalbine, by the rubiazol, by the patient being allowed up, or by some other completely obscure factor.

Of these possibilities none is a wholly satisfactory explanation. There was an improvement in the patient's condition. He gained weight, sputum lessened, subfebrile elevations of temperature disappeared. He looked and felt better and moist accompaniments in the left lung became less prominent, but there was still abundant moisture and evidence of activity.

Crisalbine alone did not materially influence the sedimentation rate before rubiazol was started, nor have I ever observed such extreme undulations of the rate in other patients having crysotherapy.

An initial sharp fall in the sedimentation following rubiazol had been observed in some of the cases already described, but certainly it was always less dramatic than in the present instance.

Specimens of blood were obtained in the morning, whereas the patient was allowed up only in the afternoon. Exercise could therefore influence the sedimentation rate only indirectly, by causing a deterioration in the general condition of the patient. As has just been mentioned however, there was no deterioration but rather some improvement in the patient's condition, and though it might throw light on the rises in sedimentation rate it would not explain the fall.

The most likely explanation would seem to be that rubiazol and gold together have a symbiotic action profoundly disturbing to the mechanism which controls the blood sedimentation rate in an individual.

While it may have been a coincidence, rubiazol

seemed to mark a turn for the better in this patient. He had previously failed to make satisfactory progress and was on the verge of being transferred to another hospital for advanced cases. After rubiazol there was a steady improvement, so much so that four months later he was able to be up for eight hours daily without ill effect.

Tubercle bacilli became progressively more scarce and could not be found in the sputum six weeks after the rubiazol was started. Saprophytes, particularly streptococci, became very scanty, and from frankly purulent in character the sputum became mucoid with but a few clusters of pus cells.

Eight months later the patient was continuing to make good progress though now discharged from hospital.

With a view to investigating further the allied effect of gold and rubiazol, the following three cases were also given both forms of treatment.

Case 9: W.B. aged 18, a mill-worker, who had had pneumonia three times in infancy, including a pneumococcal empyaema on the right side, which had necessitated drainage. Breathless for about a year, he had been troubled by a cough and right-sided pleuritic pain for four months before he was admitted to hospital.

No accompaniments were audible, but there were delayed/ expansion, enfeebled vesicular breath sounds and impaired percussion resonance below the right clavicle, corresponding to a medium-sized zone of tuberculous infiltration observed radiologically in the right

inter-cleido - hilar region.

Adherent pleura prevented the induction of a pneumothorax and injections of crisalbine were begun. In sixteen weeks he gained a stone in weight, scanty sputum had disappeared, and his blood sedimentation rate had dropped from 21 to 9 (after 2 hours.)

At that time he had received a total of 5.67 gm. crisalbine and the gold was duly discontinued. Immediately however rubiazol was started in the dose of two tablets thrice daily. The already satisfactory sedimentation rate fell to 7 after one week, to 5 after two weeks and remained at that figure until and after rubiazol was stopped. The drug was given altogether for four weeks.

There was no noteworthy effect during this time on the weight, sputum, pulse-rate or temperature. The patient continued to progress.

Case 10: D.D., aged 30, a baker. In November 1938 he was admitted to hospital with a right basal pneumonia. Improvement was followed, after a fortnight, by a left-sided pleural effusion. Radiological examination showed bilateral tuberculous infiltration in the upper third of both lung fields. The total amount of parenchyma involved was relatively small. He was admitted to the Royal Victoria Hospital at the beginning of December 1939. In most respects he made excellent progress. He gained a stone inweight in seven weeks, another stone in a further sixteen weeks,and after twenty-two weeks his sedimentation rate had fallen from 55 to 14 (after two hours.) During part of this time

he had a course of gold injections - totalling in all 7.9 gm. crisalbine.

In June 1939 he began to get up and a second course of crisalbine was started. The sedimentation rate continued to fall - from 14 to 11 in ten weeks, - and this despite the fact that, when the latter estimation was made, he was remaining up all day. At this point rubiazol tablets were started. He had had 1.5 gm. of the second course of crisalbine. The result is shown in Table 9 :-

TABLE 9.

Date	Blood Sedimentation Rate			Treatment
	1 Hour	2 Hours	3 Hours	
1938 December 16th	-	55	-	
1939 June 2nd	-	14	-	
" August 22nd	4	11	20	Rubiazol Tablets ii t.i.d.
" " 29th	3	10	17	" " " "
" September 5th	2	6	11	" " " "
" " 12th	0	½	1	Rubiazol tablets stopped.
" " 26th	1	3	4	

In this case, after three weeks, a reading was obtained which was analagous to that seen in case 8 after two weeks of rubiazol. Like in the latter also there was no significant effect on the weight or pulse-rate, (sputum was absent), though moist accompaniments did decrease very markedly.

The last reading was obtained a fortnight after discharge from hospital. The improvement was apparently maintained. Eight months later the patient was still making favourable progress at home.

Case 11: Miss J.McN. aged 27, a typist. Unfortunately not an instructive case. Her father had died of phthisis eleven years previously and she had had suggestive symptoms for eight months.

Admitted to hospital as a case of pneumonia, she was found by x-ray examination to have bilateral apical tuberculosis with a small localised spontaneous pneumothorax near the right apex.

She was transferred to the Royal Victoria Hospital in May 1939, where she was given a course of crisalbine and kept at rest in bed. Her weight increased in fourteen weeks from 6 sto. 5 lbs. to 7 st. 12 lbs., and the sedimentation rate fell from 48 to 7 in the same period. At the same time there was no dimunition of moisture, there being still copious medium subcrepitant râles at both apices.

Rubiazol was started. At the end of a week the sedimentation rate had risen again to 25, while the patient had diarrhoea and also showed albuminuria. It was assumed that the disturbance was due to gold intoxication, but for safety both crisalbine and rubiazol were discontinued.

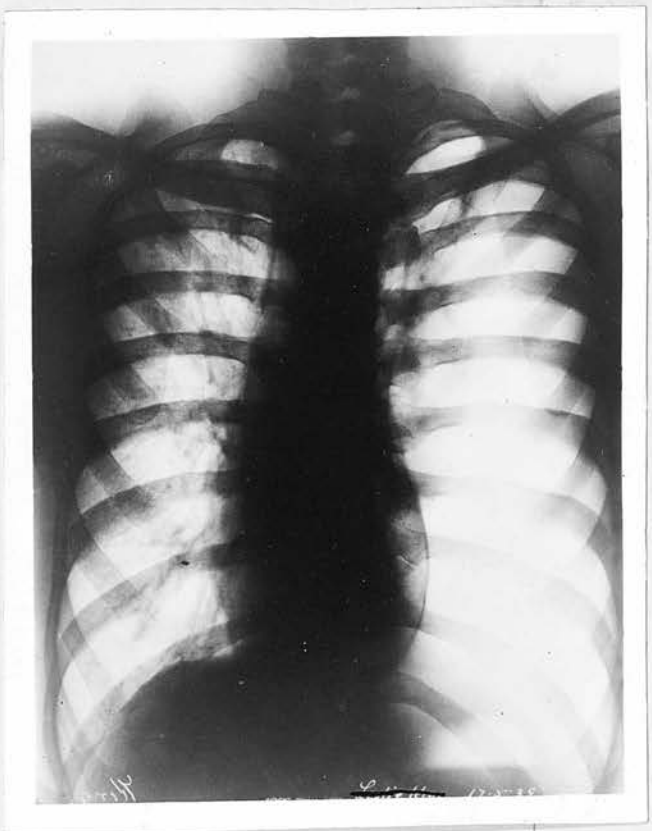
After a fortnight she began again to improve, but it was thought unwise to resume the crisalbine, and rubiazol given for a further fortnight was without definite effect.

Case 12. J.L.K. aged 25, a chemist, who was admitted to hospital for appendicitis and was found also to have extensive bilateral pulmonary tuberculosis. He

was transferred to the Royal Victoria Hospital in May 1937 after appendicectomy and treated at first only by strict rest in bed. In November of that year he began a course of gold injections but these were discontinued in February 1938, after 15 injections (total 4.4 gm. sanocrysin), owing to albuminuria.

In March 1938 an artificial pneumothorax was induced on the more diseased left side. It was fairly satisfactory, but a small cavity appeared near the right apex and during June 1938 an attempt was made to induce a bilateral pneumothorax. The attempt failed. Therefore the right phrenic nerve was crushed by operation, and the resultant temporary paralysis of the diaphragm led to successful obliteration of the cavity on that side.

To produce a more complete collapse in the left lung five adhesions were divided by electro-cautery, but there still remained others which were inaccessible. (Plate XVI.)



J.L.K. aged 25, showing left-sided A.P. with apical adhesions, displacement of heart towards opposite side and small area of infiltration below right clavicle.

Plate VI.

From the time of admission, two years previously, the patient had improved enormously, and this improvement was most marked in the x-ray examination. His weight however, though fluctuating, was actually less than on admission at the time rubiazol was started. (Table 10.)

TABLE 10.

Date	Weight	Treatment.
1937 May 27th	9 st. 5 lbs.	On admission,
" July 1st	9 st.10 lbs.	
" November 1st	10 st.	Allowed up one hour
1938 January 1st	9 st.13½ lbs	
" April 1st	9 st. 10 lbs.	Allowed up four hours
" June 1st	9 st. 13 lbs	
" September 1st	9 st. 8 lbs.	
" December 1st	9 st. 8¼ lbs	Adhesions cut.
1939 March 1st	9 st. 6 lbs.	
" June 1st	9 st. 3¼ lbs	
" July 1st	9 st. 3¾ lbs	Rubiazol started
" " 6th	9 st. 5 lbs	" tab. ii t.i.d.
" " 13th	9 st. 4¼ lbs.	" " " "
" " 20th	9 st. 5½ lbs	" " " "
" " 27th	9 st. 7 lbs.	" " " "
" August 3rd	9 st. 9¾ lbs.	Rubiazol stopped.
" " 17th	9 st. 9¾ lbs	
"September 1st	9 st. 6¼ lbs.	Discharged owing to war.

An increase in weight coincided with the rubiazol, but the fact that his weight again declined subsequently does not suggest there was lasting benefit

from the drug. He had no sputum and a normal sedimentation rate (5 after two hours) before the rubiazol was given. No alteration in the latter occurred, nor was it to be expected, but there was a slight though inconclusive slowing of the pulse-rate.

Little alteration was noted in physical signs, but the radiological appearance showed slight improvement. For his part the patient stated that his appetite had improved while taking the tablets. As, sulphanilamide, despite all its properties, is not acclaimed to be a stimulant to the gastric juice, one must conclude the increase in appetite and gain in weight were probably of psychic origin.

Case 13: Miss A.C. aged 19, shop-assistant. Became ill in October 1936 and was admitted to hospital. An artificial pneumothorax was induced and she was discharged much improved after ten months. Remained well and working until September 1938 when she developed a pleural effusion which proved to be purulent. There was now apparent activity at both apices (Plate XVII.)

She was re-admitted to hospital. Aspirations of the pus had to be made on four occasions. Her weight increased slowly but steadily and her general condition improved, but still there seemed to be no lessening of activity in the lungs. At length however when night-sweats, palpitation, dyspnoea and other untoward symptoms had largely disappeared, pulse-rate was slow and sedimentation rate normal, she was given rubiazol and allowed to get up.

Plate XVII.

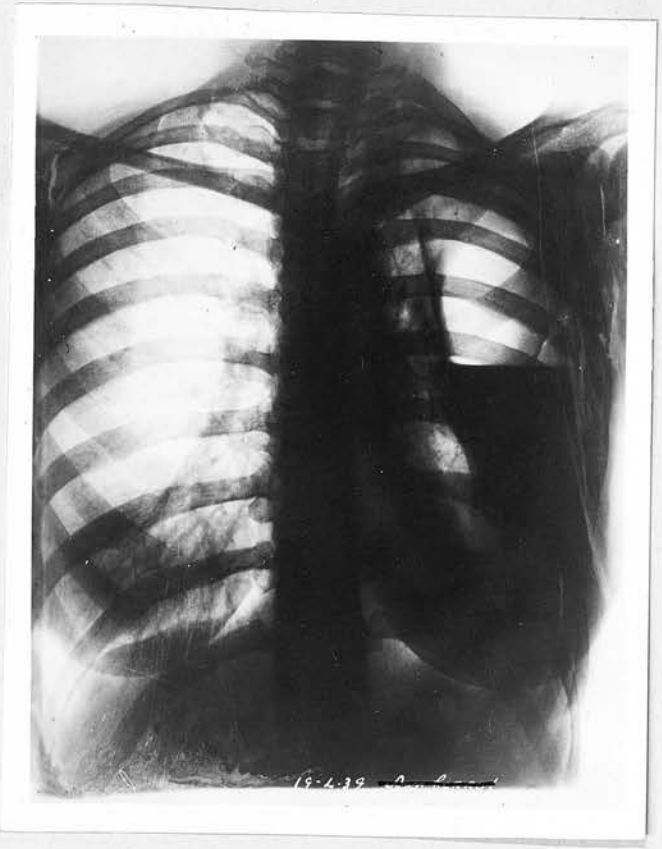


Plate XVII: Miss A.C. aged 19, showing left-sided pyopneumothorax with partial re-expansion of underlying lung ; also slight subapical infiltration on the right side.

Again one observed (Table 11) the counterbalancing effects of exercise and rubiazol as in case 6.

Table /

TABLE 11.

Date	Weight	Blood Sedimentation Rate 1 Hour	2 Hours	3 Hours	Treatment
July 5th	9 st.5½ lbs	-	-	-	Rest in bed.
" 10th	-	-	-	-	Allowed up 1 hour
" 12th	9 st.7½ lbs	6	12	28	Rubiazol tab ii t.i.d.
" 19th	9 st.6½ lbs	7	19	31	Allowed up 2 hours.
" 26th	9 st. 8 lbs	7	20	32	" " 3 "
August 2nd	9 st.9 lbs	-	-	-	" " " "
" 9th	9 st. 9 lbs	4	10	17	Rubiazol stopped.
" 16th	9 st. 10 lbs.	±	±	-	Allowed up 4 hours.
" 23rd	9 st. 11 lbs.	5	13	23	" " " "

In this instance the gain in weight was maintained, and a temporary rise in sedimentation rate was followed by an improvement. Physical signs were unaltered. It seemed that the rubiazol may have had a slight action off-setting the expected injurious effect of allowingthe patient to get up.

Case 14: Mrs A.T. aged 29, a housewife, who was not strictly speaking a case of pulmonary tuberculosis. At the beginning of March 1939 she was admitted to the Royal Victoria Hospital with abdominal tuberculosis. Her abdomen was distended and there was a large palpable mass in the epigastrium extending down to the umbilicus. After three weeks, during which she remained febrile and seemed to be making no progress, she was transferred to another hospital for advanced tuberculosis.

There she made unexpectedly good progress and by July 1939 was allowed up for two hours daily. She left hospital at that point and went home against medical

advice. Within a week she had relapsed, become acutely ill, and was found to have developed a left-sided pleural effusion (Plate XVIII.) A fortnight later she was readmitted to hospital.

Plate XVIII.

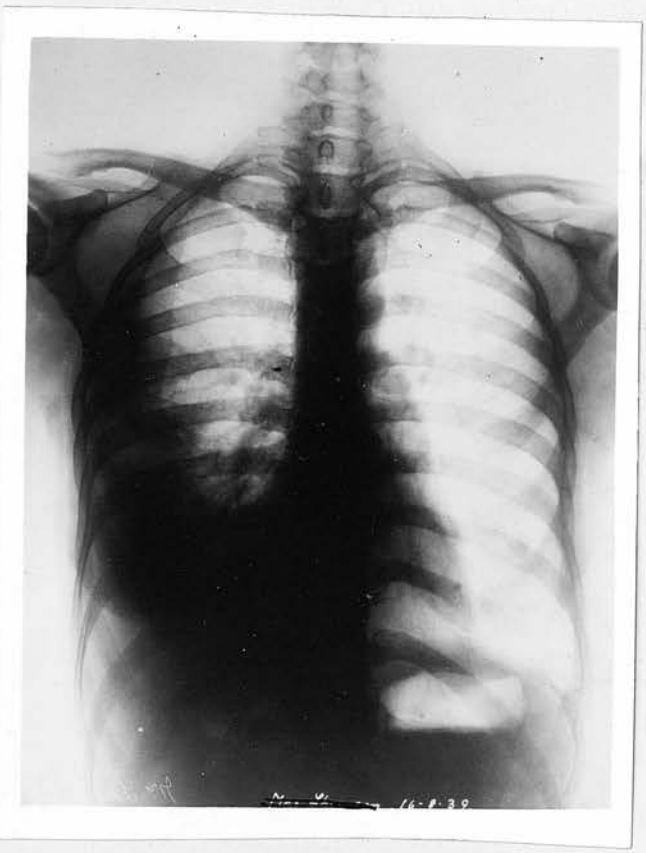


Plate XVIII: Mrs A.T. aged 29, showing right-sided pleural effusion in patient suffering from abdominal tuberculosis.

The fluid did not contain tubercle bacilli on examination, but there was no reasonable doubt that she had a tuberculous pleural effusion. Presumably there was, obscured by the fluid, a small underlying tuberculous focus in the left lung, which had been metastasised from the abdominal mass. Therefore, with the idea of combatting the pulmonary lesion in its early infancy, I decided to give her rubiazol.

It is impossible to dispute that the improvement which followed may have been due solely to fresh air

and rest in the sanatorium. Improvement was highly satisfactory (Table 12a). The ward-sister, with many years experience in the sanatorium, said that she "had never seen such a change in a patient"in her life. Always highly sceptical about the use of rubiazol in tuberculosis, that she should make such a statement, even if it were an exaggeration, gave some idea of the improvement in the appearance of this patient.

TABLE 12a.

Weeks	1	2	3	4	5	6	7	8
Pulse-rate	107	100	99	90	82	81	82	79
Sedimentation Rate	-	65	65	51	49	39	40	9
Weight	7.8.	-	-	-	7.10	7.12	7.12½	8
Temperature.	Febrile	Febrile	Subf.	Subf.	Subf.	Normal	Normal	Normal

TABLE 12b.

Date	Blood Sedimentation Rate. 1 hour	2 hours	3 hours	Treatment
August 15th	33	65	79	
" 22nd	31	65	72	Rubiazol Tab ii. t.i.d.
" 29th	24	51	66	" " " "
September 5th	23	49	62	" " " "
" 12th	16	39	55	Rubiazol stopped.
" 19th	19	40	54	
" 26th	4	9	16	

The sedimentation rate fell as soon as the rubiazol was started (Table 12b), continued to fall for the three weeks the drug was given, ceased to do so during the first week after stopping it and then fell ~~xxxxxxxx~~

remarkably in the following week. If, as I think, the drug exerted a favourable action in this case, it is hard to understand why the maximum fall in sedimentation rate occurred between seven and fourteen days after the drug was stopped.

Perhaps one might draw an analogy. A fracture will usually heal in course of time. If immobilized by a splint, healing is much more rapid. When the splint is removed stiffness and pain may temporarily be aggravated, but after a short time there is a return to normality. Did the rubiazol possibly behave like the splint - did it not expedite recovery ?

So greatly had the patient improved that she was considered one of the patients who could safely be sent home from the hospital on the outbreak of war.

Case 15: Miss J.McB., aged 13 Schoolgirl. Her mother was known to have active pulmonary tuberculosis and had for a time been in a sanatorium undergoing treatment. When therefore the patient became ill with pleurisy and had a slight haemoptysis the probable diagnosis was obvious. She was admitted to hospital and an x-ray plate (Plate IV) revealed infiltration of the parenchyma at the right base. The Mantoux tuberculin test (0.01 mg.) was strongly positive, but no sputum was available for examination. There was no reasonable doubt that her condition was tuberculous.

She was in hospital for ten weeks and her temperature still remained elevated and intermittent.

She was pale, toxic-looking and making little or no headway. I decided to try rubiazol.

The result (Table 13a) was contrary to hopes or expectation because after a week of improvement, there was an exacerbation. No cause could be found for this unless it was the rubiazol.

Rubiazol was discontinued after only a fortnight on this account. The drug certainly proved to be without benefit in this particular case.

The sedimentation readings of this patient help to stress one point, namely the variance which may exist between the readings for one and two hours.

TABLE /

TABLE 13a.

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Weight	5.11	5.12	5.13½	6	-	-	-	-	-	-	-	-	6.6½	6.9	6.10½	6.10½
Pulse-rate	101	95	91	93	93	94	87	91	107	103	88	89	86	87	99	91
Sedimentation Rate	-	-	-	-	63	-	63	52	85	-	60	-	40	-	-	-
Temperature	Feb.	Subfeb.	Subfeb.	Subfeb.	Subfeb.	Feb.	Feb.	Feb.	Feb.	Feb.	Sub-	Sub-	Sub-	Sub-	Sub-	Sub-

Effect of rubiazol on weight, pulse, blood sedimentation rate and Temperature.

Lines marked in red indicate weeks in which rubiazol was given.

TABLE 13b.

Date	Blood Sedimentation Rate 1 hour	2 hours	3 hours	Treatment.
July 12th	45	63	67	
" 25th	37	63	68	Rubiazol started
August 1st	19	52	62	" tab. ii t.i.d.
" 8th	56	85	89	Rubiazol stopped
" 22nd	29	60	71	
September 5th	14	40	52	

The same reading was obtained for two hours on July 12th and 25th yet the readings for one hour differed considerably. Still greater variance is seen on comparing the readings of these two dates with those obtained on 22nd August.

Case 16: R.H., aged 45, a clerk, who gave a history of having pleurisy on the left side in 1929 and four years later an attack of pleurisy on the opposite side.

During November 1938 he developed urinary symptoms - dysuria and haematuria - and in February 1939, following a cystoscopic investigation, a left-sided nephrectomy was performed. Extensive tuberculous caseation was found in the removed kidney.

Following the operation he stayed in hospital for five months but the urinary symptoms persisted. Radiological examination (Plate XIX.) showed quite extensive fibroid tuberculosis in the left lung, with a circumscribed and apparently quiescent focus at the right apex. He was then transferred to the Royal Victoria Hospital for sanatorium treatment.

Plate XIX:

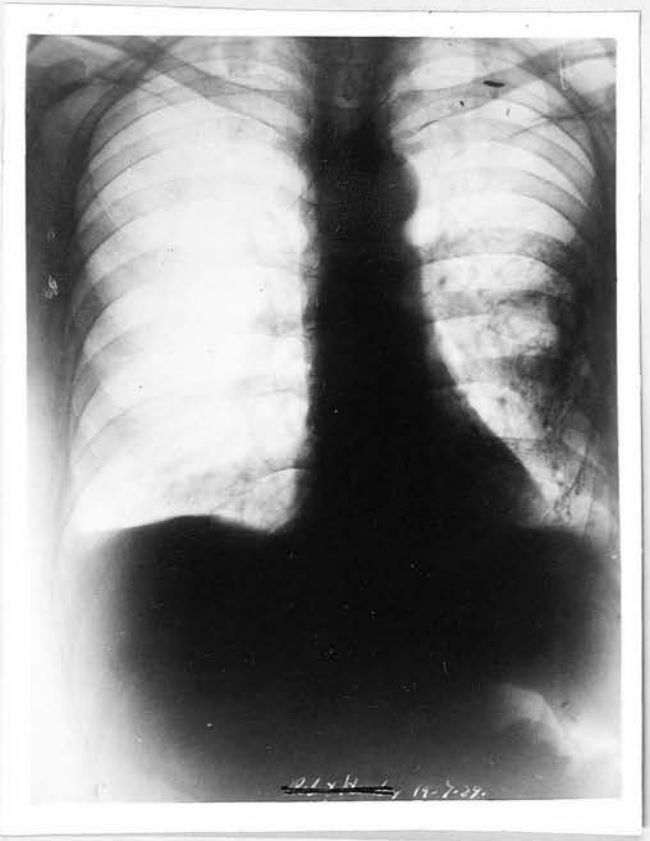


Plate XIX: R.H., aged 45, showing chronic fibroid tuberculosis of left lung with circumscribed lesion at right apex.

Moist accompaniments were extremely scanty on examination of the left lung. He seemed to be a case such as would be unlikely to benefit from the experiment, but since his sedimentation rate was high I decided to try giving him rubiazol.

He had no sputum, his temperature and pulse-rate were normal, and his weight was steadily increasing. This state of affairs continued while he received the rubiazol.

The action on the blood sedimentation rate is shown in Table 14.

area of the right lung, moist accompaniments were numerous and varied in type, and the x-ray examination (Plate XX)

Plate XX: D.McC, aged 18, showing multiple cavitation in the right lung.

showed the honeycomb appearance of multiple cavities in the right lung.

Not unexpectedly an attempted induction of an artificial pneumothorax was unsuccessful.

When I decided to try rubiazol he had been in hospital for ten weeks without making any headway and a sharp bout of pleurisy was just subsiding. The result of the rubiazol was negative (Table 15). Sputum remained positive for tubercle bacilli and did not diminish in volume; his weight was uninfluenced, and so also were his pulse-rate and temperature, the latter being persistently subfebrile.

TABLE 15.

Date	Blood Sedimentation Rate 1 hour	2 hours	3 hours.	Treatment etc.
July 14th	53	94	108	Acute Pleurisy.
" 25th	36	69	87	Pleurisy subsiding
August 1st	32	63	83	Rubiazol started
				" tab. ii t.i.d.
				Pleurisy returned also otorrhoea.
" 15th	55	94	103	Rubiazol stopped.
" 28th	29	48	60	

Rubiazol was given only for a fortnight. Far from improving with it, the pleurisy again became more acute and the drug, if not injurious, seemed to be serving no useful purpose. Cessation of the drug was followed by improvement.

Case 18, C.B., aged 22, a miner. The last of the cases, who, like the two preceding ones, gave a history of pleurisy a year before his present illness began. He had never got rid of the cough following that illness and also had some sputum in the mornings.

Early in 1939 he started to vomit. Although the vomiting was preceded by spasms of coughing his doctor attributed the sickness to indigestion. Treatment gave no relief.

Eventually, having lost nearly a stone in weight, the patient went of his own accord to the Tuberculosis Dispensary where the nature of his trouble was verified. He entered hospital at the beginning of March 1939. Both his lungs were affected with scattered tuberculous

foci (Plate XXI.), but the right one showing dense

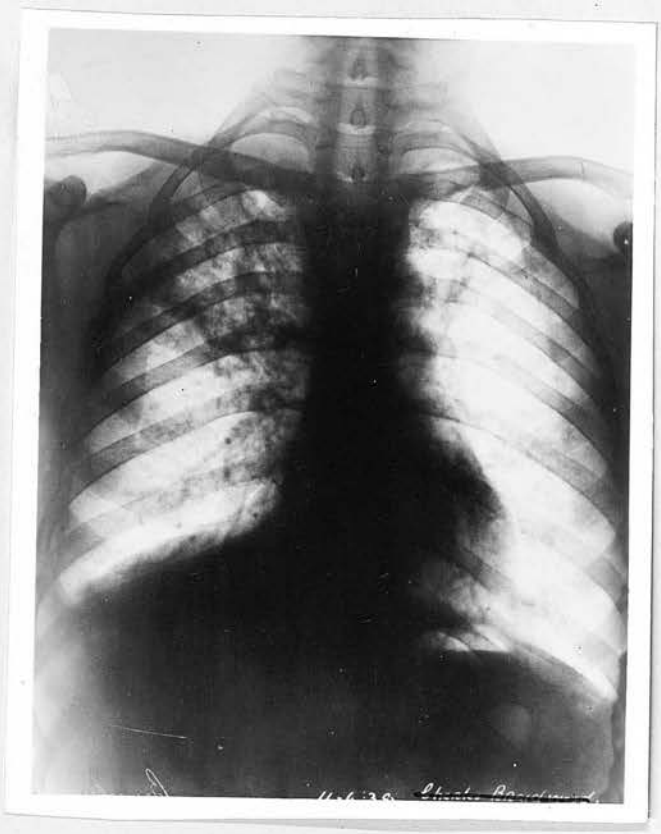


Plate XXI. C.B., aged 22, showing extensive tuberculous infiltration of both lungs but more severe on the right side.

mottling was much more seriously involved than the left. Moist râles were abundantly present on both sides.

Under sanatorium régime he made good progress. His weight increased from 8 st. 6 lbs. to 10 stones in seventeen weeks, the latter figure being slightly above his average expected weight. His sputum, at first positive, became negative for tubercle bacilli; and his temperature settled after a few febrile bouts. At the same time his pulse-rate slowed to approximately 80 beats per minute.

On the face of these facts it seemed rather superfluous to try out rubiazol and I confess it was done mainly out of curiosity. Before starting the drug

however he had lost three pounds in a like number of weeks and it seemed as if he were "sticking." In addition a very great deal of improvement was still required of the left lung before possible collapse therapy could be considered for the right side. Thirdly his sedimentation rate was still high and seemed to offer a good index for estimating improvement. He was given two tablets of rubiazol thrice daily for three weeks.

The pulse-rate remained uninfluenced. The weight increased by 2¾ lbs during the first week, and then returned to the previous level the following week and remained there.

The scanty sputum disappeared entirely. On the sedimentation rate there was singularly little effect. (Table 16.)

TABLE 16.

Date	Blood Sedimentation Rate 1 Hour	2 Hours	3 Hours	Treatment.
July 20th	51	86	99	
" 27th	49	76	89	Rubiazol started
August 3rd	45	75	89	Tabs. ii. t.i.d.
" 10th	41	69	81	" " "
" 15th	40	69	81	Rubiazol stopped.
" 22nd	43	72	85	

It had fallen considerably the week before the rubiazol was started, and though it did continue to fall while the drug was given the fall was not great, nor, when the drug was stopped, was the fall sustained.

In this case therefore there was no conclusive evidence of any improvement accruing from the rubiazol.

D I S C U S S I O N.

The late Dr Arthur Latham wrote 19 years ago in an article on the progress of pulmonary tuberculosis:- "The extent or character of physical signs is of little assistance in determining the activity of the disease: the important things are the degree of toxaemia and the response of the individual." Since he wrote that sentence considerable advances have been made, particularly in x-ray technique, enabling the extent and character of the disease to be gauged more accurately; also the sedimentation test has been introduced and widely used for measuring the degree of toxaemia. It is probably still true to say that the nature of the disease present can be assessed best by a study of the symptoms, but best of all is to utilize all available evidence, clinical, radiological and laboratory findings.

In the eighteen cases which have just been described it was my aim to observe closely all the most helpful aids to prognosis - the temperature, body-weight, pulse-rate, presence or absence of tubercle bacilli in the sputum, x-ray appearance and sedimentation-rate - and to note whether individually or collectively they testified to a brighter outlook for those tuberculous patients who were given rubiazol or sulphanilamide.

Effect on the Temperature:-

It used to be considered that a raised temperature, if it had been accurately taken, was a sure sign of active disease, and its absence an indication of quiescence. It was shown (Pearson 1909) that the progress could be

gauged with some degree of accuracy by reference to the height, character and persistence of the pyrexia, and that this was one of the best measures for estimating the degree of toxaemia. But it is now realized that occasionally disease may progress in the lungs and yet no fever be present, even of very minor degree. Nevertheless the following figures (Clarke 1922) are worthy of attention.

Of 448 patients in the Forster Green Hospital, Belfast, who had tubercle bacilli in their sputum (T.B. plus), 93 were admitted with febrile temperatures, 174 with subfebrile temperatures, and 181 with normal temperatures. At the end of 6½ years after discharge:- of the first group only 1.1 per cent. were alive - of the second 17.2 per cent.; and of the third 37.6 per cent.

In the present group of eighteen cases none had a normal temperature on admission to hospital. Five who were T.B. plus were admitted with febrile temperatures (cases 1, 2, 3, 8 and 13), ten with subfebrile temperatures (cases 4, 5, 6, 7, 9, 10, 11, 12, 17 and 18), and of the remaining cases two (14, 15) were febrile and one (16) subfebrile though no sputum could be obtained for examination. The cases to whom rubiazol was given were not therefore those for whom a good prognosis could be given and this fact is evident by the above figures.

As is commonly found among patients entering a sanatorium, the pyrexia began in most instances to subside spontaneously with rest in the airy surroundings. There was not consequently much opportunity for

observing the influence of rubiazol on pyrexia. No weight can be laid on the subsidence of occasional bouts of subfebrile pyrexia. The pyrexia should be persistent after weeks of rest in the sanatorium and despite all treatment. If such a temperature becomes normal under a new line of treatment it is suggestive, if not conclusive, that that treatment is beneficial.

The effect of rubiazol on a persistent temperature can be seen in the charts of the first three cases above described (plates, VI., VIII., and IX.) All three had bilateral disease and very rapid sedimentation rates. All had tubercle bacilli in their sputum and the sputum was particularly profuse in cases 1 and 3.

The findings were as follows:-

Case 1. The temperature altered slightly in character so that there was a greater disparity between the morning and evening readings: the continuous low-grade temperature became an intermittent one with normal readings in the morning and subfebrile or mildly febrile excursions at night.

Case 2. No effect apparent for a fortnight but there was a definite tendency to abate during the last three weeks, so that the morning temperature was normal and the evening one either normal or subfebrile.

Case 3. The temperature, which was previously apparently tending to settle, continued to subside but did not become entirely stable: slight evening rises of temperature often appeared though the morning reading was consistently normal. Before rubiazol the morning temperature was usually above normal.

The temperatures were taken by the oral method for a minimum period of five minutes. Each patient had a thermometer which he used exclusively for himself. Such routine was found to give more reliable records.

One may be justified in saying that there resulted from the rubiazol a slightly sedative action on the pyrexia in the above cases. And what is the explanation ?

Koch thought a temperature of over 100.4° was due to the presence of septic organisms (and consequently should be taken as a contra-indication for tuberculin), but it is questionable whether the advent of mixed infection can be diagnosed by the temperature chart. There is no doubt that typical hectic fever is seen in cases of tuberculous peritonitis, pleurisy etc., where post.mortem examination shows simply tuberculous disease. Kingston Fowler (1921) said, "The parrot cry of mixed infection does not come from the pathologists". And again "The term 'mixed infection' has no place in relation to pulmonary tuberculosis, but of course other organisms are present in the lungs when breaking down of the lesions and the formation of cavities is in progress."

The temperature did not settle completely in any of the three cases in question. The tuberculous lesions remained active, but if the thermometer be an accurate gauge of activity then the activity was reduced. Might not the reduction of activity be due solely to an action of the rubiazol on organisms other than the tubercle

bacillus ? I think this was probably the case.

In all three cases, particularly cases 1 and 3 with profuse sputum and clinical and radiological evidence of cavitation, septic organisms were not only suspected as being present but were also demonstrated in the sputum examination.

Following the rubiazol no alteration in the saprophyte content of the sputum was noted in Case 1 but a definite improvement was evident in Cases 2 and 3.

Effect on the Sputum:

By way of confirmation, in the latter two cases (2 and 3) there was marked decrease in the sputum pointing to lessened breakdown of tissue and probably lessened activity of septic organisms. This decrease in sputum was only temporary and not sustained in case 1, as if tissue destruction were but momentarily checked. Even so, perhaps that transient arrest accounted for the altered form of temperature which was noted.

It may have appeared in the description of the various cases that overemphasis has been laid on the quantity of sputum expectorated as opposed to the presence or absence of tubercle bacilli in the sputum. The reason is not far to seek. It was most exceptional to find tubercle bacilli disappearing after rubiazol.

The presence or absence of tubercle bacilli in the sputum is of course of great importance. For example returns from the Forster Green Hospital Belfast (Clarke), referring to 700 patients in the hospital over ten years ago, showed at the end of the sixth year after that of discharge that 72.5 per cent. of those without tubercle

bacilli in their sputum were alive, but only 22 per cent. of the rest.

At the time of giving rubiazol only ten of my eighteen patients had any sputum. Three of these had little but some had fairly profuse amounts containing tubercle bacilli in every instance. After rubiazol there was a significant reduction in quantity of the sputum whereever the disease was running an acute course, (cases 1, 2 and 3 who were febrile and 8 who were very toxic), but no alteration when the disease was chronic with a normal or subfebrile temperature (cases 4, 7 and 17.)

The latter three chronic cases all had cavities, while streptococci and other saprophytes were demonstrated in their sputa both before and after rubiazol. The acute cases likewise exhibited cavity formation, but though only one showed disappearance of tubercle bacilli, three out of the four showed disappearance of streptococci.

This rather anomalous finding was after all in keeping with what one had expected theoretically. As I have already pointed out, sulphanilamide or allied blood-borne drugs should act with maximum effect in acute or rapidly spreading disease: under such circumstances the invading organisms will be most accessible to the bactericidal influence of the drug as the latter circulates in the hyperaemic zones around the lesions.

The findings suggest that the action of the rubiazol was on the secondary infecting organisms and

particularly streptococci in the sputum and not on the tubercle bacilli. But whether or not this be true the conclusion is the same, namely that sulphanilamide causes a decrease in sputum in acute febrile cases with copious sputum yet has no effect in similar chronic cases who have normal or mildly subfebrile temperatures.

Effect on the Weight:

Gain in weight in afebrile patients with a good appetite is a good sign. But occasionally a patient holds his own, or even gains, despite fever. In such cases the thermometer should be the guide and not the scales.

Too much importance may be attached to the weight in forming a prognosis or in assessing the benefit of a particular line of treatment.

Of the patients who received rubiazol, six were gaining weight when the drug was started: and, of these six, four continued to gain at the same rate, one remained stationary, and one lost weight temporarily (due to intolerance to gold which was also being given). Out of ten patients who had not been gaining weight previously, six began to gain and continued to do so when the drug was stopped, two gained for one week but relapsed the next week, and two remained at the same weight.

On the whole therefore it may be said that rubiazol seemed to have a beneficial effect on the weight.

Effect on the Pulse-Rate:

Maurice Fishberg (1932) wrote:- "Excepting in heart disease and hyperthyroidism, no disease can be evaluated prognostically with the same degree of accuracy by the pulse-rate as chronic phthisis." Probably most people will agree with this statement, and few will dispute that "the outlook is good in chronic cases with slow pulse."

If the pulse be slowed under the influence of sulphanilamide - does that indicate an improved prognosis ? If the slowing remain after the drug is discontinued the answer should be in the affirmative. That, I think, is not an unreasonable conclusion.

In point of fact the pulse rate was noticeably slowed in only seven of the eighteen cases to whom the rubiazol was given, and these seven (cases 1, 2, 3, 5, 8, 12 and 14) were the more acute cases, all of whom were febrile on admission to hospital; all had bilateral exudative lesions except one (case 14), who had abdominal tuberculosis with pleural effusion. There was no slowing of the pulse in the more chronic cases.

The pulse-rate seemed to be a more accurate measure of improvement than did the sedimentation rate or any other index. It was indeed the same seven patients who, all things considered, seemed to benefit most from the rubiazol.

Of the remaining eleven cases, four had pulse-rates of approximately 80 beats per minute, a figure which might be considered within normal limits, but which

was not altered in any respect by rubiazol.

In every instance where the pulse-rate was persistently in the region of 100 or more per minute there was improvement with rubiazol. To quote an arbitrary figure it seemed that a pulse-rate in excess of 95 was an indication for the use of sulphanilamide. This conclusion is of course reaffirmation of the previous opinion that a febrile temperature, profuse sputum and actively spreading disease would probably improve under the influence of sulphanilamide.

Effect on the Radiological Appearance:

Tuberculosis being essentially a chronic disease, the x-ray appearances are unlikely to change rapidly unless there is a sudden change for the worse.

Startling alteration was not expected, nor was it seen, in the patients who were given rubiazol. X-ray plates were, in most instances, taken at the beginning and end of the time that the drug was given. So slight was the alteration that I adjudged it to be superfluous to inclued both plates in the description of any one case.

In the broncho-pneumonic or acutely spreading lesions the speed of dissemination seemed in the x-ray to be checked (cases 1 and 3), but there was little evidence of reactionary fibrosis. Otherwise there was nothing positive to report.

Effect on the Symptoms and Toxic Effects:

Sulphanilamide is not a symptomatic remedy. It may relieve multiple symptoms by destroying the causal organism. It may cause a number of undesirable

symptoms or side effects by way of its toxicity. But in the present series transient cyanosis in one case, and, incidentally in the same case, a scarlatinaform rash disappearing spontaneously after two days - these were the only untoward effects recorded which were probably attributable to the drug. None of the patients complained of feeling light-headed, dizzy, depressed or otherwise upset by the rubiazol.

Increased appetite and a sense of well-being were noted by several patients but such do not form convincing evidence of improvement.

Effect on the Physical Signs:-

The physical signs in pulmonary tuberculosis do not undergo a rapid change, but a periodic examination of the chest can furnish certain useful information. Attention should be focussed particularly on the number, type, situation and extent of the accompaniments, since the presence of these is evidence of active disease. Increase in number, appearance over a wider area or in a new site, these are indicative of adverse progress. Conversely, diminution in number or extent of adventitia is suggestive of improvement. All kinds of râles - sonorous, sibilant, crepitant, subcrepitant, consonating etc - are met with during the course of the disease, and each variety has some significance, indicating various pathological conditions of the lung.

With the onset of softening, the crepitant and, at times, the fine subcrepitant râle can be discovered at the affected area. With advance of the disease

and with increased softening and liquefaction, the secretions become more and more copious, the size of the râles increases and one hears medium, large and coarse bubbling râles and gurgles.

Consonating râles arise under the same circumstances as does bronchial breathing. They indicate that the area over which they are heard is either consolidated or excavated.

It must have struck the reader how often I mentioned that the moist accompaniments had become less pronounced after rubiazol. This was particularly noticeable in six patients (cases 1, 2, 3, 5, 8 and 10) and was certainly circumstantial evidence of improvement being attributable to the drug. That it indicated a favourable effect there can be little doubt.

Effect on the Blood Picture:

Many workers attach importance to the appearance of the blood picture in tuberculosis. They note in particular the indentations or number of individual nuclei in the polymorphonuclear neutrophil leucocytes.

In healthy individuals there is a predominance of forms with two or three nuclei, but in tuberculosis the predominance is of forms with one or with two nuclei. The findings are represented im a variety of ways. Arneth counted the percentage of mononuclears or forms with two, three, four or five nuclei present. Von Bonsdorff's modification of this method is to count the nuclei of 100 polymorphonuclear leucocytes. He takes the normal as 275 nuclei per 100 cells. When there less than this it is called a shift to the

left and the prognosis is bad, whereas a shift to the right indicates a good prognosis.

Further, an increase of monocytes and decrease of lymphocytes indicate activity. Increase of eosinophils indicates a good prognosis.

Lymphocytes increase with healing, monocytes increase with tubercle formation, and polymorphonuclear leucocytes when there is breaking down of tissue and suppuration.

Such observations require considerable technical skill and they must be made solely by one observer if the maximum degree of accuracy in comparing a number of films be desired.

The writer does not claim to ba a highly skilled haematologist, and partly for this reason alterations in the blood picture are not included as showing favourable effects from sulphanilamide. In addition as has already been noted, sulphanilamide is apt to alter the differential white cell or Arneth counts even in normal persons. But all the observations were made solely by the writer, and as they include more than one hundred estimations each of the white-cell count, differential white cell count, von Bonsdorff index, haemoglobin estimation, and a considerable number of red-cell counts, I feel it is justifiable to give a short summary of the findings obtained from this mass of figures.

In the accompanying chart (table 17) figures are given for the von Bonsdorff index, in every case the figures obtained both before and after rubiazol being

shown: otherwise increase, decrease or no change is recorded. Under the heading of haemoglobin percentage, "unaltered" signifies a change of less than 5 per cent, "slightly" increased or decreased a change of 5 to 10 per cent., "increased" or "decreased" a change of 10 to 20 per cent., and "marked" an alteration of over 20 per cent.

Similarly an alteration in white blood cell count of 1000 to 3000 is designated as a "slight" change: less is considered "unaltered" and more than 3000 is called simply "increase" or "decrease". In no instance did the white cell count alter by more than 5000 cells per cmm; consequently no "marked" change is shown.

Table /

TABLE 17.

Apparent influence of rubiazol on the blood haemoglobin content (Hb), total white blood cell count (W.B.C.), polymorphonuclears (P), lymphocytes (L) large monenuclear (M) and von Bonsdorff (V.B.) (1) before and (2) after rubiazol.

	Hb.%	W.B.C.	P.	L.	M.	V.B. (1)	V.B. (2)
Case 1.	Slightly decreased	Slightly Decreased	Decreased	Increased	Decreased	175	207
Case 2.	Increased	Slightly Decreased	Decreased	Increased	Decreased	186	270
Case 3.	Slightly Increased	Slightly Decreased	Decreased	Increased	Decreased	199	235
Case 4.	Slightly Increased	Slightly Increased	Unaltered	Unaltered	Unaltered	228	208
Case 5.	Slightly Decreased	Decreased	Unaltered	Unaltered	Unaltered	242	285
Case 6.	Slightly Increased	Slightly Increased	Increased	Decreased	Unaltered	272	260
Case 7.	Unaltered	SlightlyIncreased	Decreased	Increased	Unaltered	298	300
Case 8.	Markedly Increased	Decreased	Unaltered	Increased	Decreased	256	310
Case 9.	Unaltered	Slightly Increased	Decreased	Increased	Decreased	300	330
Case 10.	Increased	Slightly Decreased	Decreased	Increased	Unaltered	256	281
Case 11.	Increased	Slightly Increased	Increased	Decreased	Unaltered	285	232
Case 12	Unaltered	Slightly decreased	Unaltered	Unaltered	Unaltered	274	284
Case 13.	Unaltered	Slightly Decreased	Unaltered	Unaltered	Decreased	288	292
Case 14.	Increased	Unaltered	Decreased	Increased	Decreased	204	228

	Hb.%	W.B.C.	P.	L.	M.	(i) v:B: 1 (2)	
Case 15.	Slightly decreased	Slightly increased	Increased	Decreased	Increased	246	275
" 16.	Unaltered	Slightly Increased	Increased	Unaltered	Decreased	275	314
" 17.	Unaltered	Unaltered	Unaltered	Unaltered	Unaltered	248	257
" 18.	Increased	Slightly decreased	Decreased	Increased	Decreased	240	262

The predominant findings were slight decrease in total white cell count, polymorphonuclear and large monounclear cells, with a slight increase in haemoglobin percentage , lymphocytes and von Bonsdorff index, i.e. a shift to the right.

Such evidence suggested improvement and might be taken to imply lessened suppuration and breakdown of tissue, lessened tubercle formation and increasing healing.

It is dubious however whether this was the correct interpretation. Only six patients had total white cell counts exceeding 9000 cells per cmm. The others had white counts which were approximately normal, and yet, under the influence of rubiazol, which dropped to levels approaching leucopenia. The lowest figure recorded was 3600 (case no. 16), but even without discontinuing the drug, after a further week, the reading was 4800. Similar fluctuations with recovery were seen in other cases.

It seemed that, although the white cells and polymorphonuclears in particular were decreased under rubiazol, there was no grave danger of agranulocytosis with this particular drug. The latter fact is of course claimed by the manufacturers.

It has already been mentioned that one of the fractions which make up the tubercle bacillus is a saturated fatty-acid that stimulates connective tissue cells to produce monocytes and tubercles. It was also mentioned that studies of the action of sulphanilamide in normal persons showed monocytosis to occur in about

44 per cent. of cases (Burton and Howkins 1938). Thus both sulphanilamide and the tubercle bacillus tended to cause an increase in monocytes. But in the figures shown above there was normally a reduction of monocytes (table 17)

What is the explanation ?

It was noted that sulphanilamide was more soluble in fatty than in aqueous solution (Finklestone-Sayliss 1937). I suggest that herein may like the key to the explanation. Might not the adsorption of sulphanilamide (or rubiazol) by the fatty-acid fraction of the tubercle bacillus interfere with its stimulus to the produ ction of monocytes and tubercles ? Might not this hypothesis explain the findings of Rich and Follis - that sulphanilamide in the guinea-pig retarded the appearance of macroscopie lesions in the spleen ? The experimental work of Birkhaug (1939) supports my findings and hypothesis up to a point: he found that sulphanilamide caused a reduction of monocytes, increase of lymphocytes and retarded tubercle formation in guinea-pigs suffering from tuberculosis.

I think it is probable that sulphanliamide does exert an action directly on the tubercle bacillus and that the altered blood findings are not merely toxic effects of the drug or haematopoiesis.

Effect on the Blood Sedimentation Rate.

Before discussing the effect of rubiazol on the blood sedimentation rate in tuberculosis it is essential to review briefly the factors which control the mechanism of sedimentation.

The technique used at the Royal Victoria Hospital was that of Westergren. 1.6 c.cm. of blood is drawn into a syringe containing 0.4 c.cm. of a 3.8 per cent. solution of sodium citrate as anticoagulant. The mixture is emptied into a specimen tube and some of it drawn up into a standard Westergren tube (2.5 mm. in diameter) to the zero mark, 200 mm. from the tip. The tube is set vertical in a stand and the level of the red cell column read after each hour for several hours. In men the normal rate is 3 to 5 mm. at the end of one hour, and in women and children 4 to 7 mm. In active infections these rates are much increased and the investigation is of value in assessing the activity of an infection, particularly tuberculosis, chronic rheumatism and rheumatoid arthritis.

There are many causes of error. In the first place the length of the column of blood should always be the same, because calculations based on the fall of the red cells as a percentage of the height of the column are not accurate during the first few hours.

Miller (1936) states (1) That the fall is not equal in tubes of different lengths in the first few hours; (2) That the fall is only proportional to the length of the tube when a proportionately long time has been allowed; (3) That there is an optimum time at

which each tube should be read, and after this the increase in the fall occurs not because of the factors affecting the sedimentation rate, but owing to packing of the red-cells from their own weight.

If the tube is not absolutely vertical the reading is misleading, for a slant in the tube of 5 degrees may make a difference of over 20 per cent. Again, the sedimentation rate is affected by the red cell count and so an increase or decrease in the rate of fall may be due to variation in the number of red corpuscles. After haemorrhage there is an increased rate of fall in direct proportion to decrease in red corpuscles. Temperature has an effect on the sedimentation rate, so that the turning on or off of a radiator in the room may make a great difference. A fall of 40 mm. in a tube kept at 37° C was found to be only 22 mm. in a column of the same height and of the same sample of blood kept at 12° C.

Lockett (1937) has described the variation of the erythrocyte fall under various conditions, and certain sources of error. For example, digestion affects the test considerably. She found that the blood taken from one patient half an hour before a meal showed a drop of 24 mm. in the first hour, but blood of the same patient half an hour after the meal showed a drop of 36 mm. Exercise must be taken into account. Burrell (1937) quotes the case of a lady medical student who showed a fall of red cells of 35 mm. in two hours in a column of 200 mm., but of 52 an hour later after half an hour's tennis. The drop of 35 mm. in

two hours is high, but, he says, not uncommon in women who are apparantly healthy and who remain in good health.

In another young women in apparent health the sedimentation rate was taken every day for a month to show the effect of the menstrual cycle. At the onset of menstruation the fall after two hours was 60 mm., at the finish 55, and at mid-period 50, in a column of blood of 200 mm.

Roche (1932) states that altitude renders the fall slower. He regards the test as a valuable guide to treatment and prognosis, and considers a fall of 4 to 15 mm. from a 200 mm. column in one hour in men, or 6 to 15 mm. in women, as a slight increase, a drop of 15 to 30 as medium and 30 to 50 a great increase of the normal.

Heaf (1926) noted that the rate of sedimentation was increased in cases in which the disease was obviously progressing and decreased in cases in which the lesion was healing.

Of 150 patients whom he watched for from six to ten months it was found that prognosis based on a series of sedimentation tests was correct in 82 per cent.

Cummins and Acland (1927) consider the sedimentation test is a useful guide in treatment, because if conducted carefully it gives a rough indication of the patient's progress forwards or backwards, but that it is not a delicate test and may easily be misleading.

Fishberg (1932) remarks that the extent of the lesion in tuberculosis is not per se a factor in

increasing the sedimentation rate; even when an entire lobe is involved with cavities, the rate may be low as long as the process is quiescent. On the other hand, even with limited involvement, but of the exudative type of lesion, the acceleration will be pronounced. In general in patients with healed lesions the rate is normal; in quiescent cases slightly accelerated, while in acutely progressive cases, in exudative lesions tending to spread, the sedimentation rate is rapid.

If this statement were strictly true and if rubiazol were most efficacious in exudative forms of tuberculosis one would have expected to note the maximum benefit from the drug in all patients with very high sedimentation rates. But in the cases described this was not conclusively shown. Those who benefited most from the drug had indeed rapid sedimentation rates (cases 1, 2, 3, 8 and 14), but others (cases, 4, 6, 7, 15, 16, 17 and 18) with equally rapid rates of sedimentation did not appreciably improve.

The blood sedimentation rate seems dependent chiefly on the fibrinogen in the plasma, on the globulin to a smaller degree and on the red-cell content to some extent.

No case suffered from haemoptysis during the investigation and the red-cell count and haemoglobin content were found to vary but little from week to week. The third factor was therefore relatively constant and could not be held responsible for marked fluctuations in the rate.

Taking of food, exercise, alterations in temperature, not setting the tube vertical, and other factors, mentioned as erroneously influencing the rate, were also excluded as far as possible.

It would have been helpful to know whether sulphanilamide caused any alteration in the fibrinogen content of the blood but such investigation is beyond the scope of this Thesis. The only enquiry, as I have mentioned, into the effect of sulphanilamide on the normal blood sedimentation rate (de Caires), suggested that it produced an acceleration.

An inference that one must draw is that the sedimentation test is less valuable than are the pulse-rate, temperature or even quantity of sputum, as a guide to those cases which will respond to the use of sulphanilamide (rubiazol). Not only were there cases with rapid sedimentation rates which did not improve with the drug, but there were other cases (e.g. cases 6 and 10) in whom remarkable reduction of the rate occurred under rubiazol - reduction out of all proportion to the degree of clinical improvement - and a reduction often not maintained for more than one or two weeks.

This finding leads naturally to consideration of the combined effect of gold and sulphanilamide on the sedimentation rate in particular and on pulmonary tuberculosis in general.

The Combined Effect of Gold and Rubiazol:

This theoretically unsound association of chemotherapeutic drugs was the source of most interesting results. Four patients (cases 8,9,10 and 11) were

given both gold and rubiazol, but the trial was a fair one in only two cases. To summarize:-

(1) Case 8, showed profound slowing of the sedimentation rate after a fortnight of the combined therapy; he also showed other signs of progress - lessened moist accompaniments, settling of temperature, decrease in sputum, disappearance of tubercle bacilli and great decrease in streptococci etc., continued gain in weight - indeed only his pulse-rate was unaltered and that was within normal limits.

(2) Case 9: Rubiazol was started the day that gold was given for the last time (the patient having completed his course of crysotherapy). The sedimentation rate fell from 9 to 7 and 7 to 5 after one and two weeks respectively. Thereafter, perhaps because the effect of the gold had worn off, there was no further fall though the rate remained at the same level. There was no significant effect on this patient's progress. He had neither sputum nor moist râles in the chest to act as indices of improvement.

(3) Case 10: Showed a profound slowing of the sedimentation rate after three weeks of gold and rubiazol. He had previously had a complete course of crysotherapy alone. His weight and pulse-rate (about 90) were unaffected, but the moist adventitia in his chest were markedly decreased. The sputum which was small in amount remained negative for tubercle bacilli.

(4) Case 11., whose sedimentation rate had been falling very well with gold alone, and who had gained much weight without any sign of lessened activity

(moisture) in the lungs. The starting of rubiazol coincided with the appearance of symptoms indicating gold intolerance. Gold had to be discontinued, and although restarted after a week's interval rubiazol given alone was without significant effect.

It is ridiculous to generalize from two cases, but cases 8 and 10 certainly suggest that gold and sulphanilamide used conjointly will, after two or three weeks, produce a remarkable and deceptive depression of the sedimentation rate. It is doubtful whether this forebodes an improved outlook for the patient.

If these two drugs, both with some experimental evidence in support of their action on the tubercle bacillus, are given together - does one enhance the bacteriostatic action of the other? The idea leads to another speculation.

Rheumatoid arthritis is a disease whose etiology is much disputed. The trend of modern opinion favours the view that the haemolytic streptococcus is, of all organisms, most probably that which plays a leading part in causation of the disease. Gold is widely used in treatment. Sulphanilamide has been tried. But has anyone ever tried the two drugs together? Sulphanilamide is a specific for the haemolytic streptococcus: gold acts in a questionable manner - perhaps by causing perifocal hyperaemia, perhaps as a catalyst, perhaps in some other way. Gold might facilitate the action of sulphanilamide on the streptococcus. The allied use of the two drugs might, I believe, support my findings regarding the action on the sedimentation rate and might

produce a surprising therapeutic discovery.

John Hunter said: "Don't think, try", and Hazlitt said, "Prejudice is the child of ignorance". I suggest it is worthy of a trial.

S U M M A R Y.

(1) The present investigation was stimulated by the absence of any publication concerning the use of sulphanilamide in pulmonary tuberculosis.

(2) The pathology of tuberculosis is reviewedbriefly including a description of the tubercle bacillus and the process taking place in the lung after infection by the bacillus.

(3) The avascular nature of the tubercle is a bar to successful chemotherapy, and forthe same reason fibroid lesions are resistant.

(4) Adequate contact between the focus and remedial agent can only be achieved by means of hyperaemic lung tissue: such conditions are fulfilled best by rapidly spreading exudative lesions with or without cavitation.

(5) When there is rapid tissue destruction there is almost certainly mixed infection and this contributes to systemic disturbance.

(6) Acute forms of Tuberculosis, particularly if bilateral, are the most lethal and least responsive to treatment.

(7) The composition of sulphanilamide and allied drugs, their favourable action on various micro-organisms including an incomplete bacteriostatic action on the tubercle

bacillus are described: their toxic effects, influence on the blood and mode of action are discussed.

(8) Present day treatment of tuberculosis is reviewed. The results obtained are recorded and mention is made of the possibility of combining each method with sulphanilamide. Collapse Therapy is relatively ineffective in bilateral disease, gold of doubtful use and often too toxic, and tuberculin is both useless and dangerous if there is much systemic upset.

(9) The eighteen cases to whom rubiazol was given are described, and the effect of the drug is estimated by reference to its action on the temperature, pulse, weight, sputum, sedimentation rate etc.

(1) Toxic effects were minimal - transient cyanosis and a scarlatiniform rash - both disappearing without stopping treatment. Rubiazol is probably the safest form of sulphanilamide for use over a prolonger period, but frequent examinations of the blood are essential to avoid possible agranulocytosis.

(11) Certain blood changes occurred and it is suggested that these may have resulted indirectly from action of rubiazol on the tubercle bacillus itself.

(12) The sedimentation rate is not a very precise measure of improvement. Profound alterations in the rate follow the use of gold and rubiazol together.

(13) It is suggested that trial of gold and sulphanliamide should be made in treatment of rheumatoid arthritis.

(14) The action of sulphanilamide in tuberculosis is mainly on the secondary infecting organisms - especially the streptococci.

(15) Presence in the sputum of streptococci or other organisms than the tubercle bacillus is not, per se, an indication for use of sulphanilamide. There must be evidence of their activity.

(16) Indications for sulphanilamide are: rapidly spreading exudative tuberculosis, with or without cavities, a pulse-rate in excess of 95, temperature 100°F or more, copious sputum containing streptococci etc., numerous moist râles and a rapid sedimentation rate.

(17) Speedy improvement in recent tuberculous pleural effusion suggests a possible use for sulphanilamide in this condition, and other early lesions which evoke pyrexia and tachycardia.

(18) Sulphanilamide is useless in chronic and indolent forms of tuberculosis unassociated with systemic disturbance.

CONCLUSION.

Eighteen cases of pleuro-pulmonary tuberculosis were treated with rubiazol a compound closely similar to sulphanilamide. Some of the cases seemed to derive benefit. It is suggested that sulphanilamide is of most use in active lesions with mixed infection. The drug may be of special service in patients for whom collapse therapy, gold and other forms of treatment cannot be used.

BIBLIOGRAPHY.

Alexander J. (1937) Collapse Therapy of Pulmonary Tuberculosis, London.

Archer H.E. and Discombe G. (1937) Lancet II., 432.

Ballon, H.C. and Guernon A. (1938) Jour.Thor.Surg. VIII., 188.

Banks, S.H. (1938) Lancet. II. 7.

Barer M. (1937) Ibid. II. 964.

Batchelor C.L. and Lees R. (1938) Brit.Med.Jour. I., 1100.

" " " " Murrall M., and Braine G.I.H. (1938) Ibid. II., 1142.

Becker W. (1937) Derm. Wschr. Feb. 221.

Bentley F.J. (1936) Med.Research Council - Special Report Series No. 215.

Birkhaug, K. (1939) Acta. Tuberc. Scand. XIII..45.

Blacklock J.W.S. (1938) Med. Research Council - Special Report Series No. 172.

Bliss E.A. and Long P.H. (1937a) Jour.Amer. Med.Assoc. CVIII. 32.

" " " (1937b) Sth. med Journ. Nashville XXX. 579

" " " (1937c) Canad.Med. Assoc. XXXVII. 457

" " " (1937d) Journ.Amer.Med.Assoc. CIX.1524.

" " " (1937e) Bull. Johns. Hopk. Hosp. LX. 149

" & " (1939) Proc. Soc. exp. Biol. N.Y. XL. 32.

Bohlman S.R. (1937) Jour.Amer.Med.Assoc. CIX. 254.

Bowie, F.J.T. (1938) Brit.Med.Journ. II. 283.

Boyd, W. (1937) Text-book of Pathology, Toronto.

Britton C.J.C. (1938) Brit.Jour.Exp.Path. XIX. 140.

Bryant J and Fairman H.G. (1939) Lancet. I. 923.

Burrell L.S.T. (1937) Recent Advances in Pulmonary Tuberculosis, London.

Burton, C.J.C. and Howkins J. (1938) Lancet II. 718.

Buttle G.A.H. (1937) Proc. Roy.Sco.Med. XXXI. 154.

" " Stephenson D. Smith S. Dewing T., Foster G.E. (1937) Lancet I. 133.

" and Parish H.J. (1938) Brit.Med.Jour. II. 776.

" (1939) Ibid. II. 270.

Calmette A. (1929) Journ.Amer.Med.Assoc. XCII. 1674.

Campbell, A.D. (1937) Amer.Journ.Syph. XXI. 524.

Carman, J.A. (1937-8) E.Afr.Med.Jour. XIV. 362.

Clark B.R. (1932) Ulster, Med.Jour. Oct. 32.

Colebrook L. Buttle G.A. O'Meara R.A.Q. (1936) Lancet II. 1323.

" and Kenny M. (1936a) Ibid I. 1085.

" " " (1936b) Ibid I. 1279.

" " " (1936c) Ibid II. 1319.

" and Purdie A.N. (1937) Ibid II. 1237.

" (1937) Ibid II. 286.

Cook E.N. and Butchel H.A. (1937) Proc.Mayo.Clin. XII., 24.

Cooper A.T. (1928) Amer.Rev. Tuberc. XVIII., 66.

Cooper A. and Dow D. (1928) Lancet II. 859.

Crean T.F. (1937) Ibid II. 895.

Cummins S.L. and Acland C.M. (1927) Tubercle IX. 1.

Davies H. Morriston (1933) Pulmonary Tuberculosis. London.

Dees J.E. and Colston J.A.C. (1937) Jour.Amer.Med.Ass.

Domagk G. (1935) Dtsch.Med. Wschr. LXI. 250

" (1936) Klin.Wschr. XV.)

" (1937) XVI. 1412.

Dundas J. (1937-8) E.Afr. Med.Jour. XIV. 208.

Dunlop, D.M. Davidson, L.S.P., McNee, J.W. (1939) Text-Book of Medical Treatment, Edinburgh.

Durran G.B. and Sierra A.N.(1938) Rev de Tuberc. di Cuba. L. 179.

Dyke S.C. and Harvey E. (1937) Practitioner. Nov. 574.

Edwards P.W. and Stevens, J.S.T. (1938) Tubercle. Mar. 252.

Eisenberg P. (1913) Zbl. Bakteriol Parasiten, u. Infektkr. LXXI., 420.

Ellman P. (1939) Brit.Med. Jour. I. 1024.

Elyan M. (1938) Ibid. I. 146.

Epstein E. (1922) Jahrb. f. Kinderheilk XCVII. 99.

Faget G.H. Palmer A.E. and Sherwood W.D. (1938) U.S. Pub. Health. Rep. LIII., 1354.

Feldman W.H. and Hinshaw H.C. (1939) Proc.Mayo.Clin. March 15th. 174.

Finklestone-Sayliss H, Payne C.G., and Patrick L.B. (1937) Lancet II. 792

Fishberg, M. (1932) Pulmonary Tuberculosis Vol. II. New York,

Foerster O. (1933) Zbl. Haut-u, Geschl.Kr LXV. 549.

Fowler Sir J. Kingston (1921) "Pulmonary Tuberculosis", London.

Francis A.E. (1938) Lancet. I., 496.

Frost, L.D.B.(1937) Ibid I., 510.

Fuller, A.T. (1937) Ibid. I., 194.

Gaisford W.F. and Evans, G.M., (1939) Proc.Roy.Soc. Med. XXXII., 1070.

Garrod, L.P. (1935) Jour. Infect. Dis. LVII., 247.

Gauvain, Sir H. (1930) Jour. State. Med. XXXVIII, 468.

Gay, F.P. and Clark A.R. (1937) Jour. Exp. Med. LXVI., 535.

Gelmo, P. (1908) J. prakt. Chem. LXXVII, 372.

Ghon A. (1921) Das primäre Lungenhard bei der Tuberculose der Kinden. Berlin.

Ginard, A. and Gley P. (1936) Presse-méd. XLIV. 1775.

" " " (1937) Tr. méd. XLV., 1291.

Gjurié, N.J. (1938) Münch.Med. Wschr. LXXXV., 334.

Goldberg, B. and Gasul B.M. (1930) Amer.Jour. Med. Sci. Dec. 824.

Greey, P.H., Campbell H.H., and Cullen, A.W. (1938) Proc.Soc.Exp.Biol. N.Y. XXXIX, 22.

" " Boddington, G.D.M., and Little M.H. (1939) Ibid. XL. 418.

Griffiths S. (1924) Tubercle. V., 569.

Grütz, O. (1937) Munch. Med. Wschr. LXXXIV.

Hageman, P.O. (1937) Proc.Soc.Exp.Biol. Med. XXXVII. 119.

" " and Blake F.G. (1938) Amer.Jour.Med. Sci. CXCV. 163.

Hansen L. (1939) Jour.Pharmacol. LXV. 372.

Harper, F.R. (1938) J.Thor. Surg. April, VII., 398.

Harrison G.A. (1930) Chemical Methods in Clinical Medicine, London. 294.

Harvey, A.M. and Janeway C.A. (1937) Jour.Amer.Med.Ass. CIX. 12.

Heaf, F.R.G. (1926) Tubercle. VIII. 97.

Heintzelman, J.H.L. Hadley P.B. and Mellon R.R. (1937) Amer.J.Med.Sci. CXCIII. 759.

Helmholz, H.F. and Osterberg, A.E. (1937) Proc.Mayo. Clin. XII., 377.

Hill, R.A. and Goodwin, M.H., (1937) Sth. Med.J.Nash-ville. XXX. 1170.

Hoare, E.D. (1938) Lancet T., 655.

Hoerlein, H. Dressel. O. and Kothe E. (1909) Deutsches Reichspatent, 226.

" (1937) Practitioner. Dec. 641.

Holmes E.M. (1935) Proc.Roy.Soc.Med. XXIX. 1669.

Huber, H.G. (1936) Münch. Med. Wschr. LXXXIII. 2014.

Jennings, G.H. and Southwell-Sander G. (1937) Lancet, II. 898.

Johnston F.D. (1938) Ibid. II. 1944.

Johnstone, R.W. (1938) Brit.Med.Jour. I., 562.

Kayne G. and Hounslow A.G., (1939) Ibid I. 1170.

Kenny M. Johnston F.D., Haebler T. Vom. (1937) Lancet II. 119.

King N. and Rosario P.S. (1938) Jour.Roy.Army Med. Corps. Dec. 404.

Klee P. and Römer H. (1935) Dtsch. Med.Wschr. LXI. 253.

Koch 1822 - Berl. Kln. Wehnschr.

Kolmer J.A. Raiziss, G.W., and Rule A.M. (1938) Proc.Soc. exp. Biol. N.Y. XXXIX, 581.

Lancefield R.C. (1938) Jour.Exp.Med. LVII, 571.

" and Hare R. (1935) Ibid LXI. 335.

Lee A.C. (1938) Proc. Soc.Exper.Biol. & Med. XXXVIII. 78.

Levaditi C. and Vaisman A.C.R. (1935a) C.R.Acad.Sci. Paris CC. 1694.

" " " (1935b) Soc.Biol.Paris CXIX. 946.

" " " (1938) Ann.Inst.Pasteur LXI. 635.

Levaditi C.et al (1937) Comptes rend. =Soc.de. Biol. CCVI 1018.

Levin N. (1939) Acta. med. Scand. XCVIII, 422.

Lloyd, V.E. Erskine, D. and Johnson A.G. (1938) Lancet II. 1160.

Lockett M.F. (1937) Brit.Jour.Tub. XXXI. 31.

Lockie M. (1939) Jour.Roy.Army Med.Corps. May. 334.

Long P.H. (1933) Amer.Jour.Med.Sci. CLXXXV. 749.

Lucas C.F. (1937) Brit.Med.Jour. I. 557.

Lyth H. (1937) Ibid. I. 584.

McIntosh J. and Whitby L.E.H. (1939) Lancet I. 431.

McIntosh R, Wilcox D.A. and Wright F.H. (1937) Jour.Paediat. I. 11.

McKinley E.B. (1939) Jour.Infect.Dis. LXIV. 36.

Marshall E.K. Emerson K. and Cutting W.C. (1937a) Jour.Amer.Med.Assoc. CVIII. 953.

" " " (1937b) Jour.Pharmacol. LXI. 191.

Marshall E.K. and Walzl E.M. (1937c) John's Hopk. Hosp Bull. LXI. 140.

Marshall E.K. Bratton A.C. and Litchfield J.T. (1938a) Science LXXXVIII, 597.

" " Emerson K and Cutting W.C. (1938b) Jour.Amer.Med.Assoc. CX. 252

Marshall E.K. (1939a) Physiol. Rev. XIX., 240.

" and Long (1939) Jour.Amer.Med.Assoc. CXII, 1671.

Mason, G.A. (1937) Tubercle. XVIII, 255.

Maurer A. and Savitsch E.de (1938) / Lancet II. 1468.

Medlar E.M. (1926) Amer.Jour.Path. II. 275.

Menendez F. (1938) Rev. de. Tuberc. di Cuba April. 218.

Michie A.M. and Webster M.H. (1938) Lancet II. 371.

Mietzsch F. and Klarer I. (1932) Deutsches Reich-patent. 607, 537.

Miller, A.K. (1936) Brit.Jour.Tuberc. XXX. 39.

Morin, J. (1931) Archl.Med.Chir.de l'app.resp. VI. 229.

Müller H. (1939) Med.Klin. May 5th. 604.

Munro, W.T. (1930) Edin.Med.Jour. March. 141.

Nayer H.R. and Steinbach M.M. (1939) Amer.Rev.Tuberc. XLIV. 470.

Neal J.B. and Appelbaum A. (1938) Amer.Jour.Med.Sci. CXCV. 175.

Nissen R. (1937) Schweiz. med. Wschr. LXVII. 334.

Oakley C.L. (1938) Brit.Med.Jour. I. 895.

O'Hanlon O.J. (1938) J.Roy.Army Med.Cps. LXX. 183.

Palmer W.H. (1937) Brit.Med.Jour. I. 472.

Paterson M. (1911) Autointoxication in Pulmonary Tuberculosis, London.

Paton J.P.J. and Eaton J.C. (1937) Lancet I. 1159.

Pearson S,V, (1909) Ibid. II. 852.

Peters B.A. and Harvard R.V. (1937) / Ibid. I. 1273.

Preisz H. (1909) Xbl. Bakt. f. Orig. XLIX. 341.

Prest, E.E. (1922) Brit.Med.Jour. I. 53.

Rich, A.A. (1933) Lancet. II. 521.

" and Follis R.H. (1938) Johns Hopk. Hosp. Bull LXII. 77.

Robinson G.L. (1937) Lancet. I. 1273.

Roche H. (1932) Brit.Med.Journ. I. 466

Römer G. (1920) Handb.d.Tuberkul. I. 247.

Rosenheim M.L. (1935) Lancet. I. 1032.

Sauerbruck F. (1930) Chiz. der. Brustorgane. Berlin.

Saugman A and Graveson J. (1925) Surgical Treatment of Pulmonary and Pleural Tuberculosis, London.

Schmidt W. (1936) Beitr. Klin. Tuberk. LXXXVIII, 689.

Schmidt P.W. (1937) Munch. Med.Wschr. LXXXIII. 2122.

Schultz H. (1939) Lancet. I. 266.

Schwabacher H.(1937) Brit. J. Urol. IX. 272.

Secher K. (1938) Lancet. T. 996.

Smithburn K.C. (1938) Proc.Soc.exp.Biol. N.Y. XXXVIII. 574.

Snodgrass W.R. and Anderson T. (1937) Brit.Med.Jour. II. 101.

Somers R.B.V. (1939) Lancet. I. 921.

Southwark H. (1937) Proc.Soc.Exp.Biol. N.Y. XXXVI. 58.

Thomson A.R. (1939) Brit.Med.Jour. II. 13.

Tréfouel J. and Mme. Nitti F. and Bovet D. (1935) C.R. Soc.Biol. Paris. CXX. 756.

Türk, H. (1937) Münch. Med.Wschr. LXXXIV. 1259.

Walker O. (1938) Lancet. I. 1219.

Whitby, L.E.H. (1938a) Ibid I. 1210.

" " (1938b) Ibid. II. 1095.

Wilkie, C.H. (1939) Brit.Med.Jour. I. 57.

Wilson, W.H.M. (1939) Ibid. I. 749.

Wingfield R.C. (1929) Textbook of Pulmonary Tuberculosis, London.

Wood, Burton (1930) Lancet. II. 726.

Young, C.J. (1937) Brit.Med.Jour. II. 105.

Zarod W.A. (1937) Jour.Amer.Med.Assoc. CIX. 1693.