ASPECTS OF RESOLUTION IN PNEUMONIA

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SUMMARY

P R E F A C E

For any merits that this thesis may possess I wish to express my indebtedness to my chief, Dr. Thomas Anderson, Knightswood Hospital. He inspired me to tackle the subject and his constant interest and guidance awakened and maintained my enthusiasm and made the work a very real pleasure.

I must also thank Miss Jean Small of the Biochemistry Laboratory, Stobhill Hospital, who performed the plasma protein estimations.

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INTRODUCTION

In 1938, the discovery of the antipneumococcal effects of sulphapyridine marked a real advance in the treatment of pneumococcal pneumonia. Moreover, it seemed that, in sulphonamides, scientists had at last discovered the chemotherapeutic substance which they had been seeking so long, namely a drug which had a selective action on bacteria with no seriously harmful effect on the human body cells.

Now in any evaluation of sulphonamides as a therapeutic remedy it would appear necessary to demonstrate not only the effect of the drug on the immediate outcome of the disease, but also its influence in stimulating or depressing the body's defensive mechanism, that is, its effect upon the host's response to the infection.

In respect of the immediate outcome, the results of sulphonamide chemotherapy have been carefully studied. The most apparent benefit is the general reduction in the fatality rate. Anderson and others, in the Glasgow report on pneumococcal pneumonia (1938-42), demonstrated that this effect of the drug is in no way dependent on the type of the infecting organism. They found that, for the three commonest types of pneumococcal pneumonia, I, II, and III, the fatality rates are ranged in the same order as in pre-sulphonamide days. Another beneficial feature of sulphonamide treatment is that the clinical course of the disease during the acute stage of the illness assumes a milder form, and

does not correspond with older descriptions. Thus, in the great majority of cases, there is a rapid disappearance of the signs of toxaemia. After twenty-four hours' treatment the general condition of the patient is much improved: the respirations have become easier, and the tongue is less coated. In addition, by the end of this time, the temperature is generally beginning to fall. A further difference is seen in this subsidence of fever, for it is now uncommon to see the typical crisis, which previously was so characteristic of pneumonia.

These results certainly establish the value of sulphonamides so far as the immediate effect of treatment is concerned. When we turn to the other side of the picture, namely the effects of sulphonamide on the body's response to the infection, we find that very little investigation has been performed. The effect of the drug on the actual pathology of the pneumonic consolidation and the subsequent progress of resolution has received scant attention outside the Glasgow school. In this respect, the occurrence of delayed resolution is of some importance. Clearly before the introduction of the sulphonamides this complication was of little moment. Thus, in 1910, McCrae from a study of 805 cases at Johns Hopkins Hospital, estimated the occurrence of delayed resolution at 3.7 per cent. The Glasgow report on pneumococcal pneumonia treatment by sulphonamides placed the incidence much higher - at 28.6 per cent. over all age groups, or in 19.8 per cent. of patients under 40 years of

age, and in 37.1 per cent. of those over 40 years of age. It thus seems that delayed resolution has increased since the introduction of sulphonamides. Indeed, it is now the commonest complication of lobar pneumonia.

Now, of course, a treatment which saves life in a deadly disease by maiming the causal organism must save some patients whose chances but a few years ago were negligible, and one might well expect such individuals to show a poor response to the infection. Can this reason in itself account for the increased incidence of delayed resolution? When reference is made to the figures for delayed resolution under chemotherapy, it is found, however, that they are too high to be explained in this way: the fatality rate, in the Glasgow report, has only dropped from 14.2 per cent. before sulphonamide treatment to 10.9 per cent. under sulphonamide chemotherapy, whereas the percentage number of cases showing delayed resolution is now more than seven times the presulphonamide figure. This would seem to indicate that sulphonamides do actually favour delayed resolution, although there have been few exact scientific observations on the subject. Indeed, the condition of delayed resolution has been assessed chiefly on clinical impressions and clinical signs which are dependent on the individual observer. Even the period of time required for normal resolution has not been defined so that the very term "delayed resolution" has had varying interpretations.

My purpose in the present study was to investigate the effect of sulphonamide chemotherapy on the progress of resolution, and to discover if the drug does in itself inhibit resolution. In addition, if delayed resolution were indeed a more common condition, the factors concerned in its incidence might be studied more closely. Finally, from these findings I hoped to deduce the reason behind the inhibitory effects of sulphonamides.

For a proper understanding of the subject, a study of the pathological sequence of events involved in the pneumonic process seemed the first essential. As, however, various eminent pathologists have had differing views, it has been found necessary to give a brief outline of several accepted theories.

The next step was to analyse the cases in respect of the progress of resolution, and a convenient method of classification was to divide its progress into three types according to the period of time required for clearing of the pulmonic consolidation. For this purpose radiographic findings were employed since they provided the most reliable indication of the intensity of the underlying consolidation and the subsequent progress of resolution.

In respect of the factors concerned in the incidence of delayed resolution, Anderson and others have shown that the age of the patient, the presence of a positive blood culture, the number of days ill prior to admission and the type of the infecting organism all play a part. My findings

supported his results. In addition, the radiographic study revealed another factor of importance, namely the density of the initial consolidation. It was found that "intense" opacities were responsible for a higher proportion of cases showing delayed resolution than were "hazy" opacities. A simple explanation of this finding seemed forthcoming by postulating that the more severe the infection, the greater would be the outpouring of exudate into the alveoli, and the longer would be the period of time required for resolution. However, this explanation did not suffice, for I found that the age of the patient was still an all-important factor. Thus, in older individuals, intense consolidations were certainly associated with a high incidence of delayed resolution: but in the younger age group, equally dense opacities usually showed normal resolution.

This study of the density of the opacity in relation to resolution led to a further consideration. It was obvious that, in the pulmonic consolidation, the great outpouring of plasma into the pulmonary alveoli must result in a withdrawal of plasma proteins from the blood stream. Had the blood plasma protein levels any relation to the progress of resolution? The answer to this question involved a study of the plasma protein values in pneumonia, and this investigation revealed that low plasma proteins were a common finding not only in delayed resolution but also in patients of the older age group.

The importance of the age of the patient was thus a constantly recurring theme, for not only was age the chief factor in the incidence of delayed resolution, but also it was the most important finding in relation to low plasma proteins in pneumonia. It seemed, therefore, that the secret of delayed resolution lay hidden in some concomitant condition of old age. Now, perhaps the most pronounced pathological feature of advancing years is a process of degeneration which affects all tissues. This degeneration is especially marked in its effect on the blood vessels. So the hypothesis of vascular impairment as a possible cause of delayed resolution led me to investigate the progress of resolution in respect of cardio-vascular efficiency. And now the solution of the problem seemed close at hand, for I found that, where cardio-vascular inefficiency was present, delay in resolution resulted. Further, the various factors concerned in the incidence of delayed resolution, namely the age of the patient, the density of the consolidation and the presence of low plasma proteins, might all be explained by cardio-vascular impairment.

But how could the effects of sulphonamide chemotherapy be related to circulatory inefficiency? In this connection a study of sulphonamide blood levels proved of great interest. Hitherto the concentration of the drug in the blood in relation to clinical progress had been very inconstant and had puzzled many observers. I found, however, that this inconstancy could readily be explained in relation to the

circulation, and that it also served to confirm the close relationship between the efficiency of the cardio-vascular system and the progress of resolution.

Finally, from all these various aspects, a more complete picture depicting the influence of sulphonamide chemotherapy on the progress of resolution was gradually produced.

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CHAPTER I.

PLAN OF THE STUDY.

Section (i) : General Survey of the Investigation.
- (1) Investigation on admission.
- (2) Treatment.
- (3) Subsequent investigation.

Section (ii) : Description of Methods Employed.
- (1) Identification of the pneumococcus
  - (a) Typing of pneumococci
  - (b) Blood culture
- (2) Sulphonamide blood concentration.
- (3) Estimation of plasma proteins.
- (4) Blood sedimentation rate.
- (5) Differential white cell count.

The following chapter will consist of a description of every step taken from the admission of the patient till his dismissal. A general survey of the procedures adopted will first be given, and this will be followed by a more detailed description of the methods employed in the investigation.

SECTION (i)
General Survey of the Investigation

(1) Investigation on admission

Each patient on arrival at hospital, and before proceeding to the ward, was first examined by the doctor in the ambulance. The degree of illness was roughly assessed so that any special emergency treatment could be carried out straightway. Thus, if very cyanosed and dyspnoeic, oxygen would be administered as soon as the patient was in bed. Again, if very severely ill, the customary blanket bath, which each patient received on admission, would be omitted. The temperature, pulse rate, and respiratory rate were recorded by the nursing staff. In about half an hour after admission to hospital, he was ready for a full examination by the doctor.

A history of the illness, as detailed as circumstances permitted, was obtained from the patient. Particular attention was paid to the following points:- type of onset, whether sudden or gradual, and if preceded by a "cold". The

occurrence of such symptoms as rigor, pain in the chest, vomiting, cough, and the presence of rusty sputum was also noted.

A careful clinical examination was then performed. The presence of herpes, cyanosis, dyspnoea, or the grey toxic appearance often characteristic of a severe attack of pneumonia was noted. The condition of the tongue was carefully observed, for a dry, heavily-furred tongue invariably denoted a severe illness. A detailed assessment of the physical signs in the lungs was made, and any cardio-vascular involvement noted. In some cases no definite physical signs of consolidation could be detected in the lungs. However, if the illness was of sudden onset with rigor and pain in the chest, and the patient showed a dry, coated tongue with rapid respirations and elevation of temperature and pulse rate, the case was regarded as pneumonia and treated as such. In such cases later examination usually confirmed the diagnosis.

Before commencing chemotherapy, 22 cc. of the patient's blood was withdrawn by venipuncture under aseptic conditions and utilized as follows:-

(i) In order to cultivate any pneumococci which might be present in the blood, a blood culture was performed by injecting 5 cc. of the blood into sterile digest broth.

(ii) To estimate the degree of any bacteriaemia present and to study the growth characteristics of the organism, a pour plate was made by adding 2 cc. of the blood to

melted agar.

Both blood culture bottle and pour plate were placed in the incubator for 18 to 24 hours.

(iii) The remainder of the blood was put into two heparinized containers, one holding 10 cc. and the other 5 cc. The former was used for the estimation of the plasma proteins. An admission sulphonamide blood level and, in addition, a total white cell count were performed from the latter.

(iv) Two thin blood films were made on glass slides for an estimation of the differential white cell count.

A specimen of sputum was obtained from the patient at the earliest opportunity and sent to the laboratory for bacteriological examination.

The methods adopted for these various estimations will be described in detail in Section (ii)

(2) Treatment.

I shall not here discuss the symptomatic treatment which can be found in any textbook. All my cases received chemotherapy. The particular sulphonamide used was sulphathiazole, although on very rare occasions when the drug was in short supply a few cases received sulphapyridine or sulphadiazine. Oral administration of the drug was employed except in a few patients who were desperately ill on admission, when the first dose was given intravenously (sodium sulphathiazole 2 gm. in 20 cc. sterile water). A

full discussion of dosage and results of treatment will be given in the chapter on "Sulphonamides and Resolution".

The importance of an adequate fluid intake was stressed. While on the drug, the patient had to drink at least six pints of fluid during the twenty-four hours, and the condition of the tongue was a valuable indication of the efficacy of such treatment, for, as the patient's condition improved the tongue lost its dry, coated appearance and became moist and clean.

A regular evacuation of the bowels was ensured. Thus, if the patient was constipated on admission, a soap and water enema was administered. If necessary, this was repeated every night during the febrile period.

(3) Subsequent investigation.

An X-ray of the chest was taken either on the day of admission or on the following day. Thereafter, radiographs were taken at varying intervals - the period between successive exposures not exceeding seven days.

Twenty-four hours after admission another specimen of blood was withdrawn (about 6 cc.). Of this, 2 cc. were used for an estimation of the blood sedimentation rate which was thereafter repeated at weekly intervals. The remainder of the blood was put into a heparinized container, and used for a further estimation of the sulphonamide blood concentration, giving the level of drug in the blood at the end of twenty-four hours' treatment.

Total leucocyte counts and differential white cell counts were performed every third day after admission during the acute illness.

The progress of physical signs in the lungs was closely followed. Clinical notes were made daily during the acute stage, and, thereafter, during the period of convalescence, any change in physical signs was noted. In order to facilitate an analysis of the series, the chief findings in each case were summarized on a special card. A completed specimen illustrating both sides of this card is attached below.

CORPORATION OF GLASGOW—PUBLIC HEALTH DEPARTMENT

HOSPITAL CASE No. 627

PNEUMONIA CARD

Investigator C. Ross **Serial Number**

Age 61 **Sex** Male **Date of Admission** 1. 5. 44

Duration, in days, ill prior to Admission 3

Bacteriology :

Sputum : Type II Method and Result of Typing Neufeld. Mouse Inoculation.

Bacteræmia : On Admission + Colony Count on Admission 0 Repeated Blood Culture? Repeated Colony Count?

If pneumococci were obtained from more than one source, were results obtained in agreement ? Yes.

Complications :

Empyema ? Meningitis ? Sterile Effusion ? Delayed Resolution ?

Other ? (Specify)

Result : Recovery/Death. Days in hospital at death

Duration of Stay in Hospital (Days) 45

Mode of Onset : Sudden ? Rigor ? Pain ? Vomiting ? Prelim. " Cold " ?

Admission Record : T.° 101^{4} P 108 R 32 B.P. 130/70.

Lobar ? Atypical ? Consolidation : L1 L2 R1 R2 R3. Density "III"

Associated Diseases Auricular Fibrillation on admission - gone in 2 days (Digitalis)

W7880

Temperature Record : Duration Primary Pyrexia (Days) 7

	1	2	3	4	5	6	7	8	9	10	
Highest Temperature (Day in Hospital)	102	100	98 (8)	100	99 (4)	99 (4)	99				

White Blood Record :

	1	2	3	4	5	6	7	8	9	10	
(a) Daily Count ($\times 10^3$) (Day in Hospital)	2.0 1st	14.8 4th	19.6 7th	14.2 10th	8.6 13th					Day of illness	B.S.R. in mms.
(b) Differential (Day in Hospital) My 1	11	0	1	0	0					4	50 : 80
B 2	34	18	12	11	6					11	56 : 86
P2 3	25 (72)	47 (87)	34 (72)	34 (77)	36 (56)					18	30 : 70
P3 4	2	22	32	32	12					25	20 : 50
L1	0	5	9	9	20					32	12 : 32
Ls 5	18	6	6	6	8						
Mon. 6	10	2	8	8	16						

Admission Plasma Proteins

Total . 6.0 gm.%
Albumen 3.2 gm.%
Globulin 2.15 gm.%
Fibrinogen 0.65 gm.%

~~**Record of Bacteræmia**~~ **Day:**

	1	2	3	4	5	6	7	8	9	10	
Sputum (oz.) ~~Daily Blood Culture (Day in Hospital)~~	-	1	2	1	0	2	0				

Method of Treatment Sulphathiazole

(a) Doseage : 1st 24 hours 12 gm. Total Dose 54 gm. Days Administered 8

(b) Routine Sodium Bicarbonate ? Nicotinic Acid ?

	1	2	3	4	5	6	7	8	9	10	
(c) Blood Levels mg.% (Day in Hospital)	1.9	4.0									

(d) Toxic Effects Nil.

My = Myelocytes
B = Band cells
P2 = Bilobed polymorphs
P3 = Trilobed Polymorphs
Ll = Large lymphocytes
Ls = Small lymphocytes
Mon = Monocytes

SECTION (ii)

Description of Methods Employed

(1) Identification of the Pneumococcus.

(a) Typing of Pneumococci. If the sputum was rusty in colour, that is, typical of a case of lobar pneumonia, it would be likely to contain abundant pneumococci. In such a sputum, the "direct" method of typing was employed. Various flecks of the sputum were taken up with a sterile wire loop and deposited on a clean microscope slide. One drop of Lederle's type-antiserum was added - a different type-antiserum to each portion. A drop of methylene blue was mixed with each, and a No.1 cover slip placed on top. Each was then examined under the microscope with an oil immersion lens. If pneumococci were present, enlargement of the capsules occurred within a few minutes in presence of the appropriate antiserum (Neufeld reaction).

Where pneumococci could not be detected by the direct method, or where the sputum was not rusty, mouse inoculation was performed. About 2 cc. of the sputum was made into a suitable consistency with a little broth and injected into the animal's peritoneal cavity. If pneumococci were present the mouse usually died within 24 hours. The peritoneal cavity was then opened and gently washed out with broth. A search for pneumococci was carried out as described above. If it revealed a very mixed growth, a portion of brain or a sample of heart blood was put into broth under aseptic conditions. This was left overnight in the incubator to

obtain a pure culture, and the Neufeld reaction then employed.

(b) Blood culture. All-glass "Vim" syringes, which had been previously sterilized in the hot-air oven, were used for this purpose. The blood culture bottle employed was of six-ounce capacity and was fitted with a screw cap. It contained 100 cc. of sterile Hartley's digest broth.

The skin in the antecubital fossa was sterilized by "Cetavilon" and dried thoroughly. Blood was withdrawn by venipuncture. The bottle of broth was unstoppered, and 5 cc. of blood added, the blood and broth being thoroughly mixed by rotation. The bottle was placed in the incubator at 37°C., for 18 to 24 hours. Films were then made from the blood-broth mixture and stained by Gram's method. Pneumococci, if present, showed up as Gram-positive, lanceolate or oval cocci occurring in pairs with the rounded ends together. If organisms were noted, they were then typed. If none was observed, sub-inoculations were made from the blood-broth mixture on a plate of blood agar by the successive stroke method. Subcultures were incubated, and any organisms developing were identified by their microscopic characteristics and colony appearances. If these preliminary examinations gave no result, before stating the blood culture to be negative, the blood-broth was incubated continuously for four days, and films and sub-inoculations were made each day.

The method of making the admission pour plate for an estimation of the degree of bacteriaemia was as follows:- 5 cc. agar-broth medium was melted and cooled down to a temperature between 40°C. and 50°C. (52°C. being the thermal death point of the pneumococcus). Under aseptic conditions 2 cc. of blood were then added to the agar, the blood-agar mixture poured into a petri dish, covered, and placed in the incubator for 24 hours. Pneumococci came up as small semi-transparent colonies. The number of colonies per cubic centimetre of blood was then readily estimated.

(2) Sulphonamide blood concentration

The method employed was a modification of that described by Bratton and Marshall (1939) for the estimation of free sulphanilamide in the blood.

Reagents used:-

Hydrochloric acid 4 N.
Trichloracetic acid 12 per cent.
Freshly-prepared sodium nitrite 0.3 per cent.(1.5 gm. per 500 cc.)
Ammonium sulphamate 0.5 per cent. (2.5 gm. per 500 cc.)
N-I-nephthyl-ethylene-diamine-dihydrochloride 0.1 per cent. (coupling reagent).

Preparation of the blood. Two cubic centimetres of the heparinized blood were injected into a 100 cc. conical flask containing 30 cc. of 4 N hydrochloric acid. The flask was shaken to ensure that lysis was complete; 8 cc. of 12 per cent. trichloracetic acid were then added, and the flask again shaken to cause complete precipitation of the plasma proteins. After two minutes, the contents of the

flask were filtered into a clean bottle and the filtrate obtained was then ready for subsequent examination. Ten cubic centimetres of this filtrate were measured into a large pyrex test-tube.

Diazotisation and coupling of the solutions. To the test-tube containing the blood filtrate 0.1 cc. of 0.3 per cent. sodium nitrite was added, and the test-tube was shaken. After two minutes 0.1 cc. of 0.5 per cent. ammonium sulphamate was added, and the test-tube again shaken. After a further two minutes 0.1 cc. of coupling reagent was added. A purple colouration developed in the presence of sulphanilamide. The test-tube was allowed to stand for ten minutes by which time the colour had reached its maximum intensity.

A Lovibond's Comparator with a sulphanilamide disc, was used for the estimation. The unknown blood filtrate was placed in the right hand compartment. A "blank" solution, substituting distilled water for the blood, was placed in the left hand compartment. The Comparator was held facing a uniform source of white light, and the disc rotated until the colour of the test solution was matched by one of the glass standards. The value, expressed as mgs. per 100 cc. blood, was read from the indicator window. This reading was in terms of sulphanilamide, and, to make it applicable for sulphathiazole, it had to be multiplied by the correction factor of 1.5. (M.R.C. War Memorandum No.10). "Free" sulphonamide only was estimated and no attempt was

made to measure the conjugated drug which is usually considered inert.

(3) Estimation of plasma proteins.

I did not myself perform the actual estimations. These were carried out in the Biochemistry Laboratory at Stobhill Hospital. The methods employed were as follows:-

(a) Total plasma proteins. This estimation was carried out by means of the dipping refractometer which measures the refractive index of a liquid. The refractometer dips into a bath of water kept at 17°C. A very thin film of plasma is smeared on the special prism, and, by the aid of a lamp, the point on the graduated scale at which a dividing line appears is duly noted. This reading gives the refractive index and, from this, by consulting a book of tables, the percentage of total proteins is obtained.

Several observers, for example Salvesen (1926-27) and Kumpf (1931), are quoted by Rennie (1935) as having observed that the refractometric technique tends to give a higher result than the micro-Kjeldahl. Linder (1924) found the total protein of the serum to be 1.59 gm. per cent. higher than by the Kjeldahl method. This discrepancy is in the main due to the presence of fat. Robertson (1915), however, showed that, although in nephritic patients refractometry gives too high results, yet in normal individuals there is a fair correlation with the values

obtained by the Kjeldahl method.

(b) Plasma albumen. This was estimated by the Lovibond Comparator. The principle employed is that of the biuret method. The globulins are first precipitated by half-saturation with ammonium sulphate. Trichloracetic acid is added to the filtrate to precipitate the albumen. The precipitate of albumen is then dissolved in caustic soda solution and copper sulphate is added. The resulting purple solution is centrifuged to throw down the suspended copper hydroxide after which it is matched against the glass standards, and the result noted.

(c) Plasma fibrinogen. The Lovibond Comparator was again used for this estimation. To isolate the fibrin, however, a gel is first formed by adding sodium chloride and a small quantity of calcium chloride solution to the plasma. This is incubated overnight. The gel so formed is whipped with a glass rod and the fibrin contracts down and becomes attached to the rod. It is dried thoroughly and thereafter boiled with caustic soda to dissolve the fibrin, cooled, and copper sulphate solution added. The supernatant fluid is then matched against the standards in the Comparator.

(d) Plasma globulin. This was obtained by subtracting the combined readings for albumin and fibrinogen from the total plasma protein reading.

The results obtained for the individual fractions by

the Lovibond Comparator are less accurate, when compared with the Kjeldahl technique, than the results obtained by the refractometric technique for estimating the total plasma proteins.

(4) Blood sedimentation rate.

The method used was that of Westergren. Into a small test tube containing 0.5 cc. of 3.8 per cent. sodium citrate solution, 2.0 cc. of blood was placed. The test tube was inverted two or three times, and the blood drawn up the long Westergren tube to the mark "0 m.m.". The tube was then placed in the stand. The distance of sedimentation of the red cell column was read at the end of the first hour, and again at the end of the second hour. (In normal individuals the first reading varies from 2 m.m. to 5 m.m., and the second reading varies up to 20 m.m.).

(5) Differential white cell count.

Thin, even, blood films were made on microscopic slides and allowed to dry. These were then stained by Leishman's stain. The best results were obtained by covering the film with the stain and leaving for a half-minute, then diluting with an equal quantity of water and allowing to act for a further four minutes. The film was washed under a gentle stream of water and allowed to dry. The count was performed under an oil immersion lens and the slide was moved in various directions longitudinally and

vertically to obtain as fair an average distribution as possible. Only 100 cells were counted.

The method employed for differentiating the various kinds of polymorphonuclear leucocytes was that described by Arneth (quoted from Whitby and Britton) who classified them according to their number of lobes. (At an earlier stage of development the nucleus, of the granular white cell, is round and not yet segmented - this cell is called a myelocyte. A band cell is an intermediate stage between a myelocyte and a bilobed polymorph - the nucleus is elongated but unsegmented.) Cooke (1927), in a modification of the Arneth count, grouped myelocytes and band cells together and called them "Group I" cells. As I shall show in a subsequent chapter, I found that the estimation of "Group I" cells was of some value in the prognosis of pneumonia.

The non-granular white cells were classified as monocytes, large lymphocytes or small lymphocytes.

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CHAPTER II

A DESCRIPTION OF THE CASES COMPRISING THE STUDY

The observations in the following chapters are based on 225 consecutive cases of lobar pneumonia admitted to Knightswood Fever Hospital over the period January, 1943, to July, 1944. The cases were all males over fifteen years of age in whom the clinical diagnosis of pneumonia was confirmed both by radiographic and bacteriological examination.

(1) Fatality rate

The fatality rate for the series was 5.7 per cent. This is a low figure when it is compared with the figures given by other observers for sulphonamide-treated pneumonia. The fatality rate found by Anderson and others (1938 - 1942) in a series of 2,000 cases, was 10.9 per cent. However, in any comparison of fatality rates in lobar pneumonia, the severity of the infection is of prime importance, for a likely explanation of the low figure found in the present series might be that I was treating a milder form of the disease. Now, in respect of the severity of the disease, the Glasgow report has shown that this depends on several factors, namely the type of the infecting organism, the age of the patient, and the presence or absence of bacteriaemia. In the report it was demonstrated that Type II and Type III infections were associated with a more severe illness and a higher fatality rate than Type I or "Group IV" infections.

In respect of age, the number of deaths in those over forty years old was more than six times the number under this age. Finally, cases with a positive blood culture showed a much higher proportion of deaths than non-bacteriaemic cases. It is thus obvious that the present series must be analysed in respect of these three factors.

(2) Type of infecting organism

Table I shows the distribution of cases according to the type of pneumococcus isolated. Type I, II and III were the commonest types and were responsible for 61.7 per cent. of the total series of 225 cases. A notable feature was the high prevalence of Type II infections which comprised 41.3 per cent. of the total cases. The Glasgow report (1938-42) showed that there had been a consistently high incidence of Type II infections in the City over that period of time comprising 36.9 per cent. of the cases. The present series shows that this state of affairs still continues.

TABLE I

The Type Distribution of 225 Cases of Pneumonia

Type	Total Cases	Deaths	Type	Total Cases	Deaths	Type	Total Cases	Deaths
I	32 (14.2)	1	IX	3	-	XVIII	4	-
II	93 (41.3)	7	X	1	-	XXI	1	-
III	14 (6.2)	2	XI	2	-	XXII	3	-
IV	3	-	XII	1	-	XXIV	2	1
V	3	-	XIII	1	-	XXVII	2	-
VI	3	-	XV	2	-	B.Fried.	3	-
VII	7	-	XVI	1	-	Str.virid.	7	-
VIII	9	-	XVII	3	-	Untypable	25	3

(The figures in brackets represent percentages of the total.)

B.Fried. = B.Friedländer
Str.virid. = S. viridans.

(3) Age distribution

Age distribution?

In the series, the proportion of cases over forty years of age was 58.4 per cent. This differs little from 60.2 per cent. - the figure given in the Glasgow report for that age group. Further, Anderson and others demonstrated that the proportion of pneumonia cases over forty years of age had steadily risen during the preceding twelve years. In McGregor's series (1930-32) only 17 per cent. of the cases were over 40 years of age. Anderson attributed the change in age incidence to a falling birth rate, and also perhaps to the fact that conscription had removed a large portion of the younger age group from the civilian population.

(4) Bacteriaemia

Table 2 depicts the incidence of bacteriaemia in the series in relation to the age of the patient, the type of the infecting organism, and the fatality rate. The Glasgow report showed that the risk of occurrence of bacteriaemia was greater in the older age group, and my findings are in agreement with this. Of the 91 cases under forty years of age, ten were bacteriaemic (10.6 per cent.) whereas, in those over that age, 131 cases produced 28 with bacteriaemia (21.3 per cent.). Again, Anderson and others demonstrated that the bacteriaemic rates varied in the different type infections: the order for males from highest to lowest was

Type II, Type III, Type I and "Group IV". Although the total number of bacteriaemic cases in the present series was small, the Type bacteriaemic findings were ranged in a similar order, except that Type III infections, by a very small majority, occupied first place.

TABLE 2

The Incidence of Bacteriaemia in respect of Age, Type of Pneumococcus and Outcome

Age Group (years)	Type I				Type II				Type III				Total Series					
	Bacteriaemic		Non-Bacteriaemic		Bacteriaemic		Non-Bacteriaemic		Bacteriaemic		Non-Bacteriaemic		Bacteriaemic		Non-Bacteriaemic		Combined	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
-40yrs.	2	-	13	-	8	1	34	1	-	-	3	-	10	1	84	1	94	2
40+yrs.	3	1	14	-	17	3	34	2	4	2	7	-	28	6	103	5	131	11
Total	5 (15.6%)	1	27	-	25 (26.8%)	4	68	3	4 (28.0%)	2	10	-	38	7	187	6	225	13

(The figures in brackets are rates per cent. of the type total.) C = Cases; D = Deaths.

That the presence of bacteriaemia has a marked influence on the outcome can be seen from the fact that, in my series, the fatality rate for those whose blood was sterile was only 3.2 per cent., whereas, in those with a positive blood culture at the commencement of treatment, the rate was 18.4 per cent. Now, it is seen from Table 2 that only 38 of the total cases (16.8 per cent.) had positive blood cultures whereas the corresponding figure in the Glasgow Report was

32.8 per cent. It is, therefore, more than likely that the small number of bacteriaemic cases found in the present series is sufficient to explain the low fatality rate.

(5) Complications

Some of the main complications are shown in Table 3. They are arranged in relation to the type of infecting organism. (Henceforth, the term "Group IV" will be used to describe infections caused by pneumococci other than the first three types).

TABLE 3

Main Complications

Type of Organism	Empyema	Sterile Effusion	*Cross Infection	Meningitis	Delayed Resolution
I	2	3	-	-	5
II	2	3	-	1	27
III	3	-	-	-	6
"Group IV"	-	5	2	-	15
Totals ..	7	11	2	1	53

The complication of prime importance was clearly delayed resolution which occurred in 53 of the 225 cases, i.e. 23.5 per cent. of the series.

* By the term "cross-infection" is meant an illness acquired while in hospital, and caused by a different type of organism from that responsible for the original infection. The following notes on the two cases of cross-infection which occurred in the present series present several interesting features.

Case 1. The initial infection was mild: Type XVI pneumococcus isolated from the sputum. Sulphathiazole was only administered for three days. Cross-infection

occurred six days after the drug was stopped: Type II pneumococcus was isolated from the sputum. Patient became sharply ill. Sulphathiazole was recommenced but there was no response to therapy and patient died three days later.

Case 2. The initial infection was severe: "Group IV" pneumococci isolated from the sputum. A full course of sulphathiazole was given (eight days). Cross-infection occurred six days after the drug was stopped: Type II pneumococcus isolated from the sputum. Patient again sharply ill. Sulphathiazole was recommenced. Response to therapy was very good - at the end of twenty-four hours general condition much improved and temperature back to normal. The patient made a good recovery.

It is interesting to note that, in both cases, a "Group IV" pneumococcus was responsible for the initial infection, and, in both cases, subsequent infection was caused by a Type II pneumococcus which was the most prevalent organism amongst the other patients in the ward. Further, it seems reasonable to suggest that the small initial course of sulphathiazole administered in Case 1 created a state of sensitivity to the drug which became apparent when the same treatment was recommenced. Thus, no matter how mild the infection, every subsequent case of pneumonia received a full initial course of sulphonamide, so that, if cross-infection should occur, sulphonamide could be re-administered with less fear of producing sensitization phenomena.

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CHAPTER III

PATHOLOGY AND RESOLUTION

Section (i)

(a) Process of infection.

(b) Spread of pneumonic process.

(c) Evolution of pneumonic process.

(d) Impairment of pulmonary circulation.

Section (ii)

(a) Resolution and delayed resolution.

(b) Termination in fibrosis.

The prevailing theories on the pathology of pneumococcus lobar pneumonia have been very fully revised by Heffron (1939). The following chapter is based on Heffron's work. Section (i) will summarize briefly the most important views on the initiation, spread and evolution of the pneumonic process. In Section (ii) a synopsis of the process of resolution will be given. From this study I shall concentrate on certain factors which seem relevant to the progress of resolution, and they will form a nucleus for my subsequent investigations.

SECTION (i)

(a) Process of infection

For the development of pneumococcus lobar pneumonia a certain combination of circumstances must be present. It seems that (a) pneumococci of some virulence must have reached the lower respiratory tract, that (b) some unfavourable condition must be present which allows infection to gain a foothold, and that (c) the body reacts to the infection.

The pneumococcus comprises a number of serological types. It is known that the higher types of pneumococci may be normally present in the upper respiratory tract of healthy individuals. Type I and Type II organisms, however, are rarely normal commensals, and, if found in the sputum, are generally considered pathogenic.

These two types are associated with the most typical clinical picture. A Type III infection varies in pathogenicity with the age and resistance of the host. It carries a high mortality in older individuals who tend to have a lower resistance to infection and the pneumonic consolidation is frequently patchy in distribution. In younger individuals, on the other hand, the resistance to infection is greater and, in such, a Type III illness is relatively benign.

The second condition is intimately bound up with the first. As may be inferred from the preceding paragraph, an organism which may be non-virulent when the host's resistance is high may attain virulence when the resistance to infection is lowered. It is well known that minor respiratory infections often predispose to pneumonia, and a history of precedent chill is frequently obtained. The mechanism by which these favour infection is, however, obscure.

Finally, the reaction of the host to the assault of the pneumococcus is generally characteristic. The most apparent pathological manifestation of this reaction is the pneumonic consolidation, but other less obvious changes are apparent elsewhere in the body.

(b) Spread of pneumonia

There are two views on the mechanism of spread of lobar pneumonia, the chief exponents being Lauche (1927)

and Loeschcke (1931). The former considered that pneumococci after gaining entrance to the lymphatics in the region of the hilum set up an inflammatory action there which resulted in blocking of the lymph channels. Thereafter infection spread throughout the entire lobe in the reverse flow of lymph. Loeschcke, however, disagreed with this, and claimed that air-borne organisms reach the alveoli of the lung, and in a sensitized individual, cause an out-pouring of oedematous fluid in which bacteria multiply. The fluid then spreads quickly throughout the whole lobe, passing through the alveoli by means of the alveolar pores of Cohn, the process being aided by the negative pressure within the lung.

Various radiographic studies have been carried out to determine the location of the initial process. There is general agreement that, in adults at least, the process spreads from the hilum towards the periphery. Two groups of observers (Davies, Hodgson and Whitby (1935) and Graeser, Wu and Robertson (1934)) have, however, demonstrated that, in occasional cases, the pneumonic process may spread from the periphery towards the hilum.

(c) Evolution of the pneumonic process

The classical description falls into three stages - engorgement, red hepatization and gray hepatization. These terms refer to the various pathological changes seen, and it is rare to find the entire pneumonic lesion at any single stage. The portion initially involved may be at a

later stage than an area more recently involved or than an area which has developed more slowly.

Laennec first described these changes more than a century ago. In the first stage there is great engorgement of the capillaries of the alveolar walls with swelling of the alveolar epithelium. This stage probably lasts only a few hours, and, due to the rapid outpouring of exudate, soon assumes the features of the second stage.

The stage of red hepatization is the earliest one commonly seen. The lung is no longer crepitant and resembles liver. The surface is dark red, or reddish-brown, Microscopically, the lumen of the alveoli are filled with a coarse network of fibres along with serum, red blood corpuscles, organisms, polymorphonuclear and some mononuclear leucocytes, and desquamated epithelial cells. The most distinctive thing about the exudate at this stage is the fresh appearance of the cells.

In the stage of gray hepatization the lung is gray or grayish-white, dense, heavy and friable. The alveoli are densely packed with cellular exudate consisting chiefly of leucocytes especially polymorphonuclears. The cells show considerable degeneration and the leucocytes frequently contain ingested organisms. The capillaries in the alveolar walls appear compressed and are no longer distended with blood.

In 1931, this conception was challenged by Loeschcke. He correlated the clinical and pathological features in

fifty cases of lobar pneumonia, and his observations on the evolution of the pneumonic process may be briefly summarized as follows:-

Firstly, in response to the presence of pneumococci, there is a great outpouring of oedematous fluid into the alveoli. In the neighbourhood of this exudate there is always congestion of capillaries with emigration of leucocytes and a few red blood cells. Thereafter, the alveoli and passages become packed with leucocytes, a few erythrocytes, alveolar lining cells, and a fine fibrin network. The alveoli become distended with consequent compression of the alveolar capillaries. A local ischaemia results. This ischaemia, plus the white blood cells present in the alveoli, produces the appearance of gray hepatization. In the next stage, shrinkage of fibrin occurs which causes relaxation of the alveoli and a refilling of the capillaries. As a consequence, haemorrhages occur between the alveolar walls and the fibrin masses. This accounts for the appearance of numerous red lines which are seen in the septa at this stage and give the appearance of red hepatization.

When Loeschcke correlated the pathological findings with clinical data, he found that the time required to reach the stage of gray hepatization, with complete precipitation of fibrin in the alveoli, was only about forty-eight hours. Evidence of fibrin shrinkage was found from the fifth to

the twenty-second day.

It is evident that Loeschcke's conception does not differ appreciably from the classical description. In each, the stage of gray hepatization occupies the forefront. The chief difference is that Loeschcke scarcely recognised a stage of red hepatization prior to the gray one. Indeed, he claimed that the true stage of red hepatization really occurred after gray hepatization.

(d) Impairment of pulmonary circulation

No matter what theory is upheld, it is evident that there is an impairment of circulation in the pneumonic lung during the stage of gray hepatization. This ischaemia is chiefly due to compression of the alveolar capillaries, although a widespread distribution of fibrin thrombi in the capillaries may be a contributory factor. Several observers have studied the subject: Wang and van Allen (1933) injected Congo red into the bronchus of the affected lobe at varying intervals after infection and determined the time required for the dye to appear in the blood. A much longer interval was required in dogs injected late and in which the consolidation was advanced than in others injected only a few hours after the onset of their consolidation. It would thus appear, both from experimental and pathological findings, that there is a progressive impairment of the pulmonic circulation during the evolution of the pneumonic process.

Section (ii)

(a) Resolution and delayed resolution

Several days after the development of the pneumonic lesion the process of resolution begins - the degeneration of cells and fibrin which began in gray hepatization is now marked and a general liquefaction of the exudate occurs.

During resolution, the removal of exudate from the pulmonary alveoli may be accomplished in two ways:- (a) expectoration, and (b) absorption. Now, if expectoration performed an important role in the process, then in any patient showing scanty sputum one would expect to find inhibition of resolution. This, however, does not occur*(vide footnote). Thus, the chief method for the removal of the exudate must be by absorption into the circulation via the subdivisions of the pulmonary blood vessels and lymph channels.

Before absorption can begin the exudate must first be prepared by autolysis, the exact process of which is imperfectly understood. The various factors which are said to be involved in the process are as follows:-

1. Autolysis of the exudate by enzymes produced by the polymorphonuclear leucocytes was claimed by Opie in 1905. He also studied the enzymes and anti-enzymes found in inflammatory exudates and showed that the blood serum contained an anti-enzyme which inhibited the action of the enzyme produced by the leucocytes.
2. It has been asserted by other observers that there is a local increase in the acidity, and that biochemical changes are the basis of the process of resolution.
3. The importance of the large mononuclear cells has been stressed. Robertson, Coggeshall and Terrell (1933)

showed that these cells were present in the exudate during resolution and were derived from the cells of the alveolar walls. They claimed that they acted as phagocytes, replacing the polymorphonuclear leucocytes, and that areas early in resolution showed few of these cells while areas in later stages showed increasing numbers. This was termed the "macrophage reaction".

From the above observations it has been suggested that delay in resolution would occur if there were a deficiency of leucocytes in the consolidated area, as insufficient enzyme would be present to cause rapid autolysis. Further, it would appear that the macrophage reaction is an important factor. Now, any study of the polymorphonuclear leucocytes and macrophage cells present in the pneumonic exudate in respect of resolution would involve intricate investigations. Further, in an ill patient, the interference required for such a study would prove very exhausting. However, it may be that the cellular changes occurring in the pulmonic exudate are reflected in the cellular content of the blood. It thus seems reasonable to study the leucocytes and monocytes of the blood in relation to the progress of resolution.

Again, it would appear that if there is excess of anti-enzyme (present in serum) the same slowing of resolution should result. This would be difficult to prove. Kline (1917) by the intrabronchial injection of normal dog serum into dogs with pneumonia was able to maintain an excess of serum in the consolidated areas, and he showed that, in most instances, resolution was inhibited. Now, from a practical viewpoint, it might be argued that excess of serum in the pulmonary alveoli is equivalent to a very dense

consolidation. Thus, the relation of the density of the consolidation to the progress of resolution requires investigation.

(b) Termination in Fibrosis

In most instances although resolution may be gradual yet it is generally complete. In some cases, however, granulation tissue from the alveolar walls invades the exudate, the area becomes an airless mass of scar tissue and the function of the lung is much impaired.

*(Daily estimations of the quantity of sputum expectorated were performed in 57 cases of my series. The total quantity of sputum over the first seven days of the illness was correlated in each case against the progress of resolution. As shown in Table 5, "normal" resolution displayed a greater number of cases with scanty sputum (below 5 oz.) than "fair" or "delayed" resolution.

TABLE 5

Resolution in respect of the Quantity of Sputum

Resolution	Total quantity of sputum (ounces in first 7 days)			Total Cases
	5 or less	6 to 20	20 and over	
Normal ..	11	16	2	29
Fair ...	2	7	2	11
Delayed ..	1	12	4	17

If expectoration were an important method of removal of the exudate, one would expect just the opposite state of affairs. It seems, therefore, reasonable to conclude that expectoration plays only a very minor role in resolution. It might also be argued from this experiment that cases with delayed resolution had more sputum because absorption of the exudate was deficient, but the number of cases in the series is too

small to make such a statement.)

(Note:- The terms "normal", "fair", "delayed", as applied to resolution, will be fully explained in a subsequent chapter.)

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CHAPTER IV

The Progress of Resolution in Pneumonia under Chemotherapy - a Radiological Study

Introduction.

Section (i) : Radiographic Characteristics.
- (a) Evaluation of intensity of opacity.
- (b) The effect of sulphonamides on the density of the opacity.
- (c) Commencement of resolution.

Section (ii) : Types of Resolution.
- (a) Rapid resolution.
- (b) Fair resolution.
- (c) Delayed resolution.

Section (iii) : Some Factors known to influence the Progress of Resolution.

Section (iv) : Relation of Radiographic Appearances to Resolution.
- (a) Density of opacity and resolution.
- (b) Lobar involvement and resolution.

Appendix : Examples of Delayed Resolution.

Introduction

Several observers have shown that radiography is of more value than physical signs in detecting the early stages of pneumonic consolidation. Graeser, Wu and Robertson (1934) took daily radiograms of 40 cases of pneumonia during the febrile period and found that X-ray films showed a density within 24 to 48 hours from the commencement of the illness. Often in such cases no physical signs of consolidation could be detected. Furthermore, long after the ordinary physical signs of consolidation have disappeared radiographs frequently reveal considerable opacities.

Thus, in evaluating the progress of resolution, I will concentrate in the following chapter on the radiographic findings as the most reliable index of the progress of resolution.

Methods employed. The present study is based on the radiological examination of 148 cases of lobar pneumonia. Radiographs were taken in the ward by means of a mobile apparatus, the one using being a Philips mobile "D" X-ray apparatus. The tube-film distance was adjusted to 3' 4", and the exposures varied from .15 seconds for a very thin adult to .25 seconds for a stout adult. The average exposure was .2 seconds, at which there was an output of 36 milliamperes at 69 kilovolts. Radiographs were taken on the day of admission to hospital, except when the patient was admitted after 1 p.m., when an X-ray was not taken till the

following day. The patient was usually placed in the prone position, but, if he were too ill to be turned, the supine position was adopted. Thereafter, X-rays were repeated at variable intervals depending on the clinical condition of the patient, the maximum number of days between successive radiographs rarely exceeding seven. If radiographs did not show complete clearance of the consolidation by the time the patient was discharged from hospital, he returned for X-ray and clinical examination at four-weekly intervals thereafter, until resolution was complete.

Section (i)

Radiographic Characteristics

(a) Evaluation of intensity of opacity

Generally speaking, radiographs which show dense consolidations are associated with severe constitutional symptoms, while hazy opacities are associated with milder forms of pneumonia. I have arbitrarily divided the density of consolidation as revealed by radiographs into three broad categories.

The first group consists of radiographs showing a uniform intense opacity through which no lung markings can be seen. It will hence-forth be called a "III" opacity.

The second group comprises films which reveal a hazy opacity through which lung markings are evident. It will be called a "II" opacity.

In the last group, the radiographs merely show a faint grayness obscuring a portion of lung. This will be equivalent to an opacity of density "I".

Plates VIIIa, VIIIb and VIIIc are illustrative examples of these categories and demonstrate grades "III", "II" and "I" respectively. Now, patients who, during the acute stage of their illness showed only a "I" opacity had mild constitutional symptoms. There were 58 cases in this group, none of which died. Further, resolution of such a consolidation was rapid: the lung cleared up completely in a week or so and none of the cases developed delayed resolution. For this reason, cases which showed a maximum opacity of density "I" throughout their illness have been excluded from the present study. Cases which developed empyema or sterile effusions have also been omitted, as these complications obscure and prolong the process of resolution both from the clinical and radiographic aspects.

Thus, of the total series of 225 cases, 148 cases of uncomplicated lobar pneumonia showed radiological evidence of an opacity of density "III" or "II" on admission to hospital.

In respect of the initial radiograph, it might, of course, be reasonably argued that the density of the opacity would depend on how long the patient had been ill prior to admission. The consolidation might take several days to reach a maximum, and photographs at different times during this period would reveal opacities of varying intensity. Now,

prior to the introduction of sulphonamides, the progress of the pneumonic consolidation was studied radiologically by two groups of observers - Graeser, Wu and Robertson (1934) and Davies, Hodgson and Whitby (1935). They showed that the opacity did not usually reach its maximum intensity till between the fourth and seventh day. Table 6 depicts, in relation to the day of illness, the number of cases in the present series who showed their maximum opacity (density "III") on admission. (As the majority of patients were admitted to hospital in the afternoon or evening, a radiograph was not performed till the following day, so that day of illness when the initial radiograph was taken is usually one day more than "days ill prior to admission".) It is seen that, of the 41 cases X-rayed before their fourth day of illness, 26, (i.e. 63 per cent.) showed an opacity of density "III". Of the 94 cases in which the initial radiograph was not taken till between their fourth and eighth day of illness, 47 cases (i.e. only 50 per cent.) revealed an opacity of density "III". Thus, in the series, the maximum intensity of the consolidation seemed to occur earlier in the course of the illness than the time given by the two groups of observers quoted above.

TABLE 6

Distribution of Cases in respect of Initial Radiograph and Density of Opacity

Days of illness when initial radiograph taken	Number of Cases		Density "III" (Number of cases)	
1	2		2	
2	16	41	11	26
3	23		13	
4	23		11	
5	27		11	
6	14	94	10	47
7	15		9	
8	15		6	
8 +	13		5	

(b) The effect of sulphonamides on the density of the opacity

To demonstrate the effect of sulphonamides on the density of the pneumonic lesion, it would be necessary to receive patients early in the course of their illness and to X-ray them at frequent intervals. This was not done in my series of cases. However, in Knightswood Hospital, during 1942, daily radiographs were taken during the acute stage of the illness in a series of 29 cases of lobar pneumonia. The initial radiographs varied between the second to fifth day of illness. From this small series it was possible to study the effect of sulphonamides in respect of the day of illness when treatment was commenced. For this purpose I divided these cases into two groups. One group included

PLATES Ia TO Id.

COMMENCEMENT OF RESOLUTION IN A CASE ADMITTED AND TREATED 'EARLY' IN THE COURSE OF THE ILLNESS.

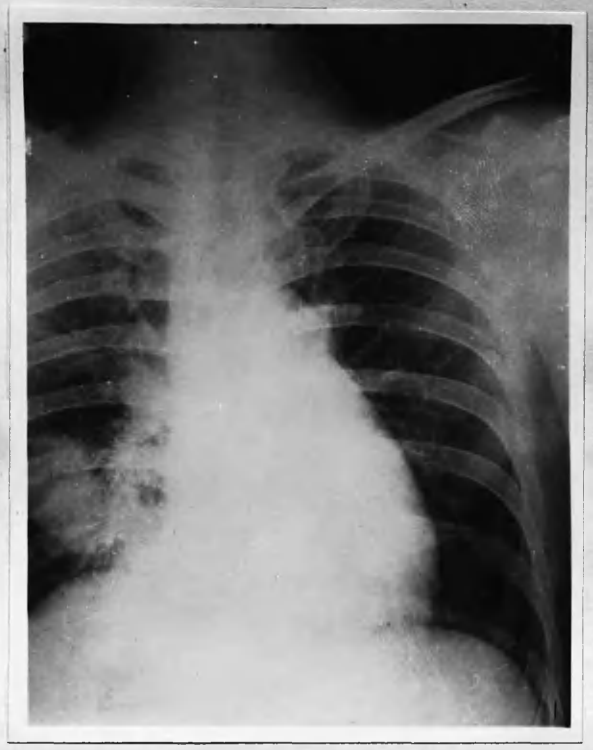


PLATE Ia. 3RD DAY OF ILLNESS
CONSOLIDATION R. LOWER LOBE ~ DENSITY II

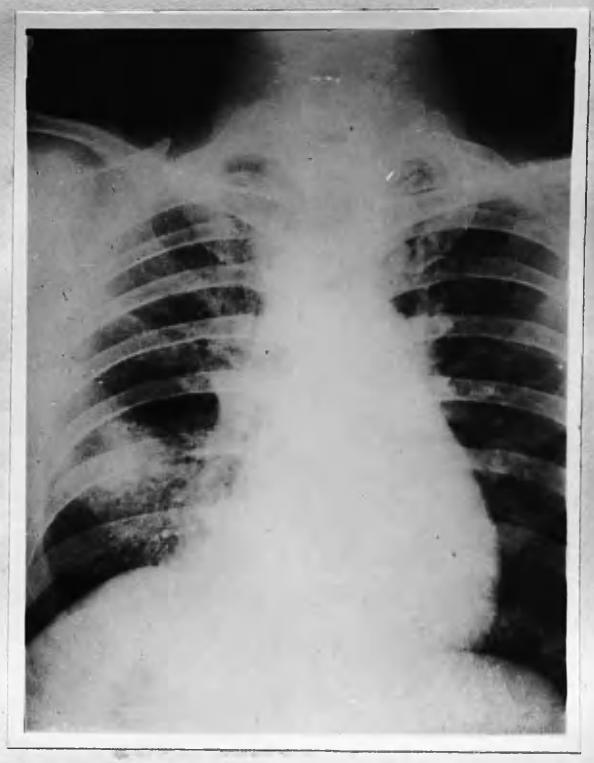


PLATE Ib. 4TH DAY OF ILLNESS
RESOLUTION HAS ALREADY COMMENCED.

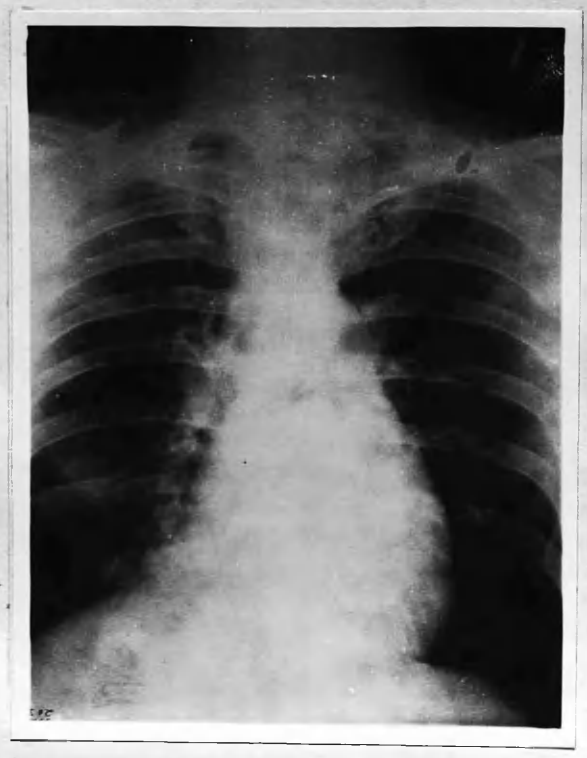


PLATE Ic 5TH DAY OF ILLNESS
ALMOST CLEAR.

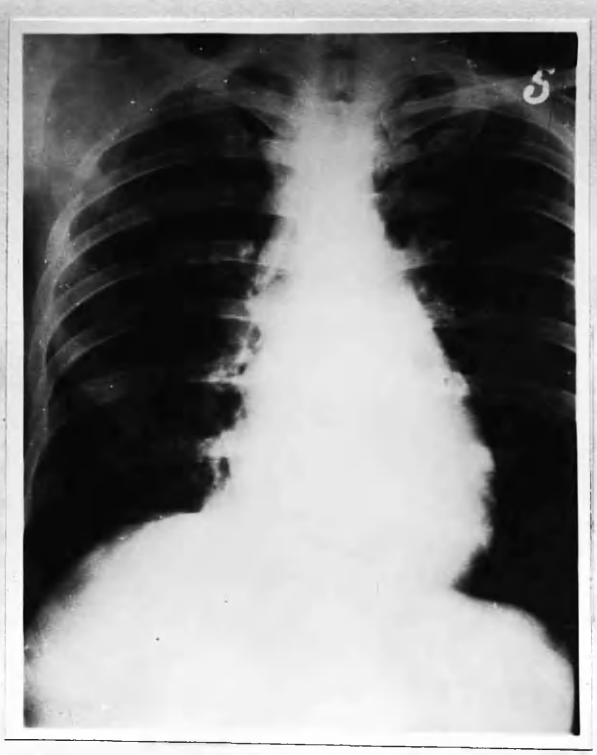


PLATE Id. 6TH DAY OF ILLNESS.
RESOLUTION COMPLETE.

cases admitted "early" in the course of their illness, in which the initial radiograph was taken on the second or third day. In the other group, the cases were not admitted till "late" in the course of the illness, and films were not taken till the fourth or fifth day. Each group was studied in respect of the time required to attain maximum consolidation.

TABLE 7

Attainment of Maximum Consolidation in Cases admitted "early"

Day of initial X-ray	Total number of cases	Day of maximum consolidation			
		2nd	3rd	4th	5th
2nd	9	5	3	-	1*
3rd	8	-	7	1	-
Totals .	17	5	10	1	1

(*vide footnote at end of Section)

From Table 7 it is seen that of the 17 cases X-rayed on the second or third day of their illness, 15 had attained maximum consolidation by the third day.

The radiographs Ia to Id illustrate one example. In this case, films were commenced on the third day and radiographs were taken on subsequent days thereafter. It is seen that the consolidation was only of density "II" on the first film, but it was then at its maximum. On the fourth day, resolution had already commenced. By the fifth day, the consolidation had practically disappeared and, by the sixth day, no trace of the lesion could be detected in the film.

PLATES IIa TO IId.

COMMENCEMENT OF RESOLUTION IN A CASE ADMITTED AND TREATED 'LATE' IN THE COURSE OF THE ILLNESS.

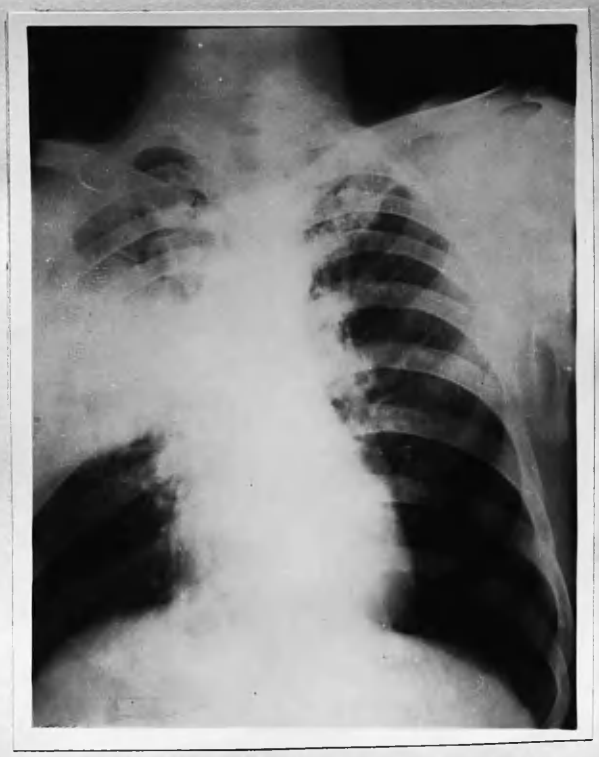


PLATE IIa 5TH DAY OF ILLNESS.
CONSOLIDATION R. UPPER LOBE ~ DENSITY III

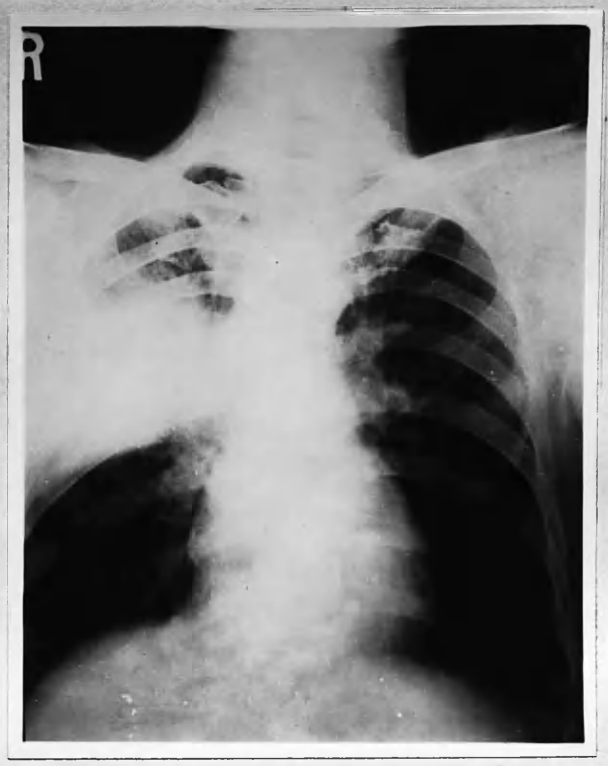


PLATE IIb. 6TH DAY OF ILLNESS.
INCREASE IN INTENSITY.

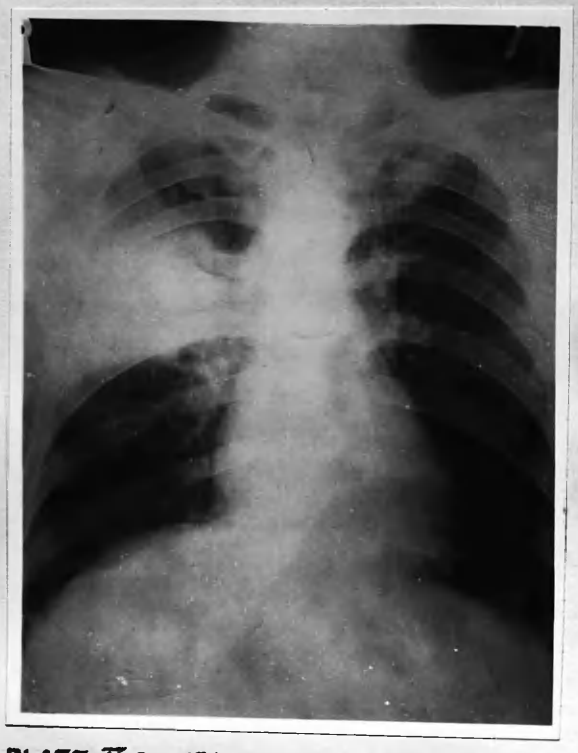


PLATE IIc 11TH DAY OF ILLNESS.
COMMENCEMENT OF RESOLUTION.

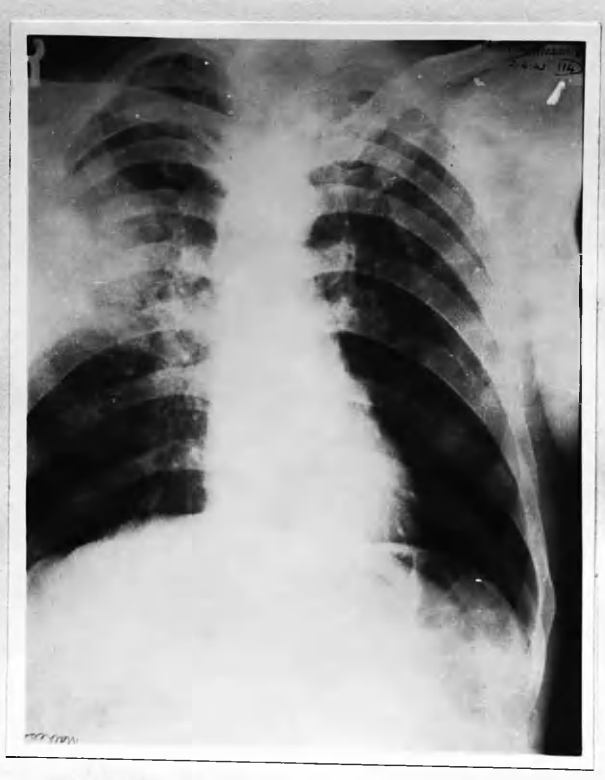


PLATE IId. 14TH DAY OF ILLNESS.
SLOW RESOLUTION.

TABLE 8

Attainment of Maximum Consolidation in Cases admitted "Late"

Day of initial X-ray	Total number of Cases	Day of maximum consolidation			
		4th	5th	6th	7th
4th	5	2	2	1	-
5th	7	-	5	1	1
Totals	12	2	7	2	1

From Table 8 it is seen that of the 12 cases X-rayed on the fourth or fifth day of their illness, 9 had attained maximum consolidation by the fifth day.

The radiographs IIa to IId illustrate one example. In this case, films were commenced on the fifth day. On the sixth day, the consolidation had increased in intensity. This, however, was the maximum intensity attained, as subsequent films up to the eleventh day gave practically identical pictures and so have not been included here. On the eleventh day, the radiographs showed commencement of resolution, but, even by the fourteenth day, there was still a considerable opacity.

From these findings it would appear that sulphonamides act rapidly and strike at the infection as it is, thus preventing further increase in the density of the consolidation. It is true that a few cases in the above two groups showed slight increase in density after treatment was begun, but it was noteworthy that the proportion of these was greater in the group admitted "late" in the course of the illness. This lends support to the findings of Anderson and others who have shown that sulphonamide chemotherapy is more effective when commenced early in the course of the illness.

(c) Commencement of resolution

Before proceeding to discuss the various types of resolution it is of interest to note the time at which resolution begins in pneumonia treated by chemotherapy. For this purpose I have again utilized the 17 cases admitted on their second or third day of illness, and which were discussed in the preceding section in relation to the day of maximum consolidation. I have not included the cases which were initially X-rayed on their fourth or fifth day of illness, as it could be argued that such consolidations might have already commenced to resolve by that time.

TABLE 9

Commencement of Resolution

Day of initial X-ray	Total Cases	Day resolution commenced						
		3rd	4th	5th	6th	7th	8th	8+
2nd	9	4	2	2	-	-	-	1*
3rd	8	-	4	1	1	-	-	2
Totals	17	4	6	3	1	-	-	3

(* vide footnote at end of Section)

In each of the seventeen cases, daily radiographs extended well past the time of commencing resolution. The arithmetic mean for the commencement of resolution in the whole series was 4.94 days, and, as seen from Table 9, ten cases already showed some clearing of the opacity by the fourth day. Now, Davies (1935) found that the commencement

of resolution lay between the fourth and seventh day. Thus, it would appear that sulphonamides exert no inhibitory effect so far as the commencement of resolution is concerned. Indeed, when chemotherapy is begun early in the course of the illness, the consolidation in the great majority of cases will show no further progression in intensity. Consequently, resolution will tend to begin earlier than in cases where treatment is commenced late in the course of the illness or than in untreated cases.

*(An incidental observation from this series was that consolidationswhich developed slowly were also slow in commencing to resolve. The case in Table 7, initially X-rayed on the second day of illness and not showing maximum consolidation till the fifth day of illness, did not begin to resolve till the twelfth day (see also Table 9).)

RAPID RESOLUTION.

MALE, AGED 16 YEARS.

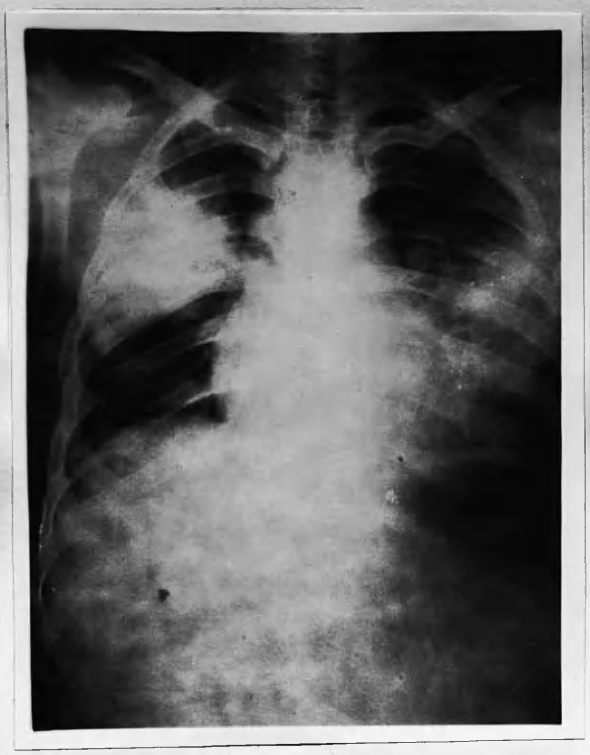


PLATE IIIa 7TH DAY OF ILLNESS.
BILATERAL CONSOLIDATION ~ DENSITY III.

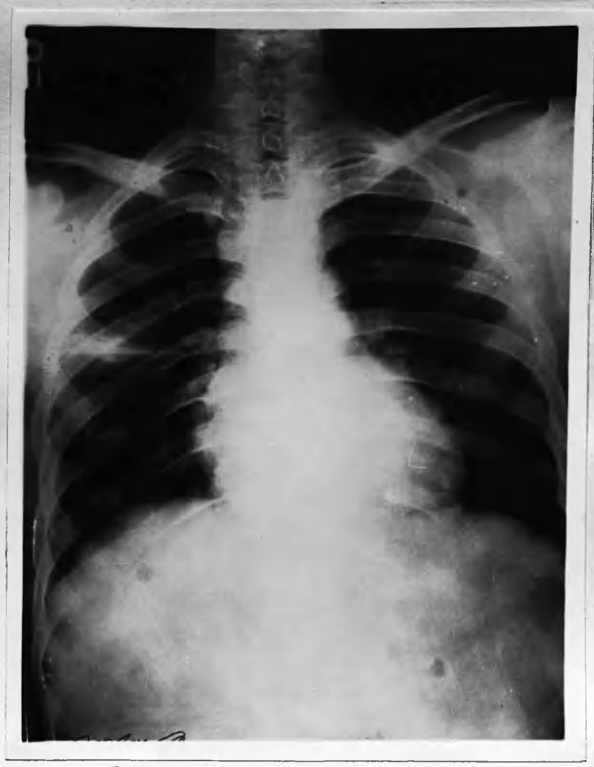


PLATE IIIb. 21ST DAY OF ILLNESS.
RESOLUTION COMPLETE APART FROM SLIGHT INTERLOBAR PLEURAL THICKENING.

MALE, AGED 24 YEARS.

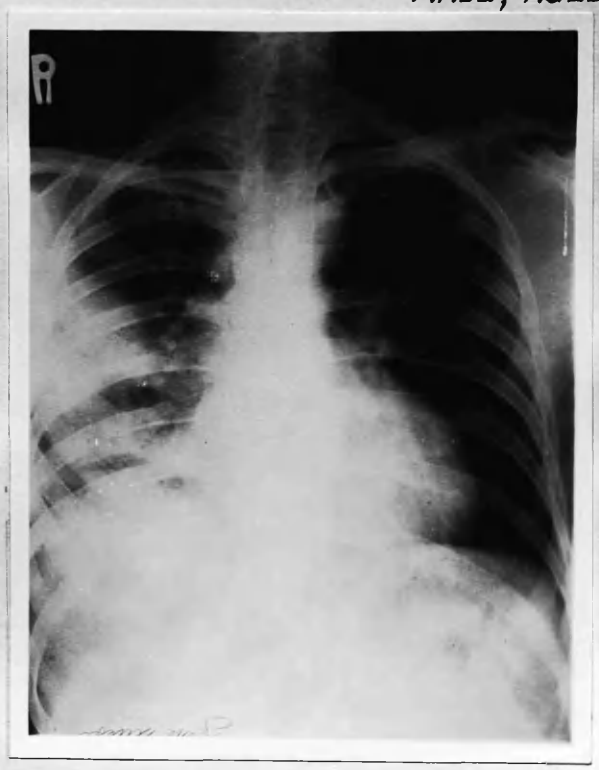


PLATE IVa 5TH DAY OF ILLNESS.
CONSOLIDATION R. LOWER LOBE ~ DENSITY II

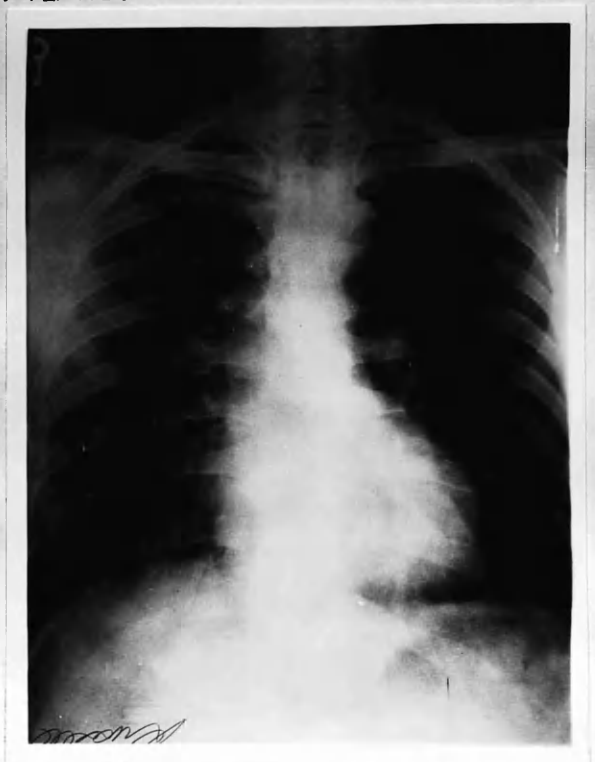


PLATE IVb. 14TH DAY OF ILLNESS.
RESOLUTION COMPLETE.

RAPID RESOLUTION.

MALE, AGED 32 YEARS.

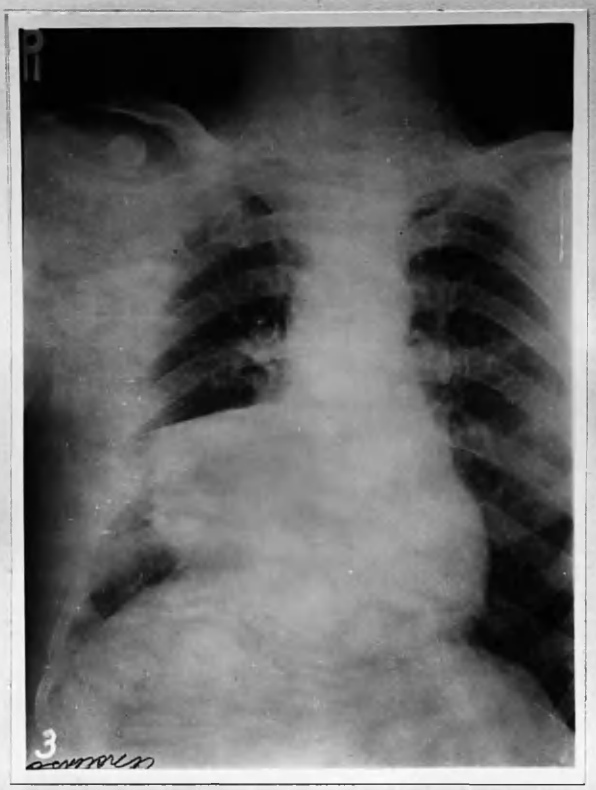


PLATE Va. 3RD DAY OF ILLNESS.
CONSOLIDATION R. MIDDLE LOBE ~ DENSITY III.

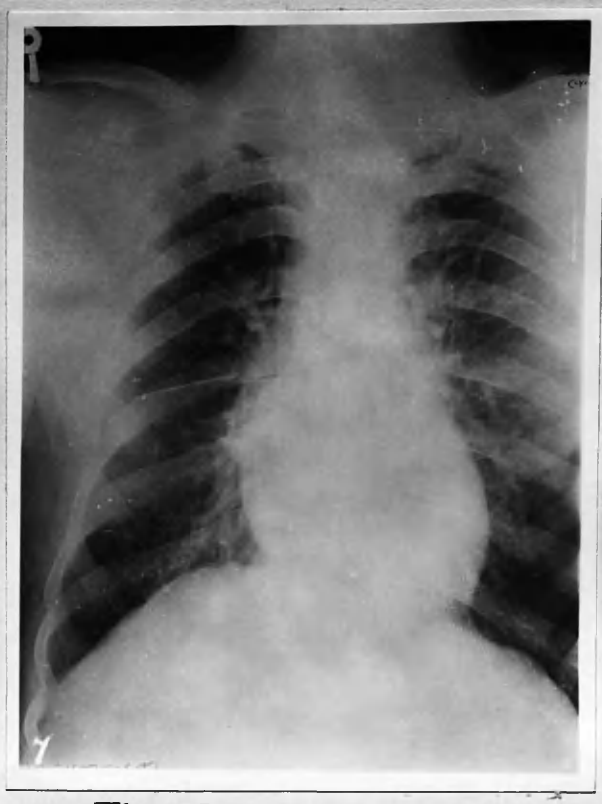


PLATE Vb. 17TH DAY OF ILLNESS.
RESOLUTION COMPLETE.

MALE, AGED 39 YEARS.

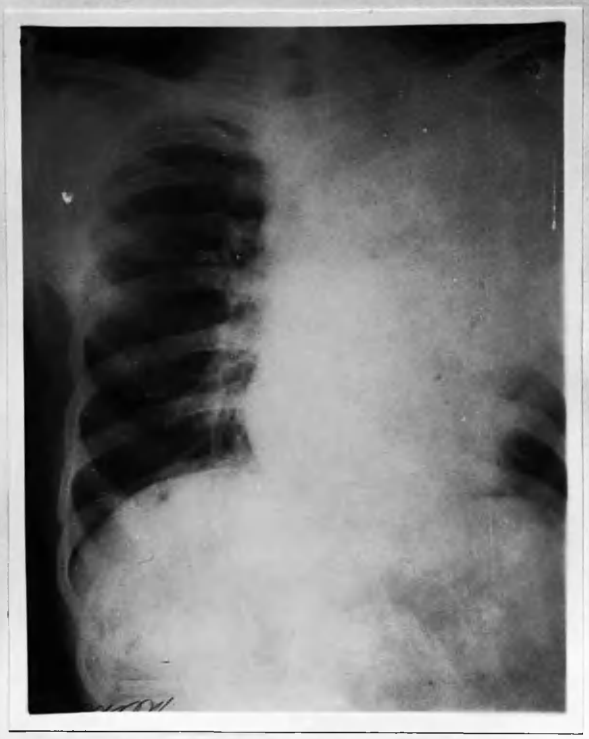


PLATE VIa. 4TH DAY OF ILLNESS
CONSOLIDATION L. LUNG ~ DENSITY III.

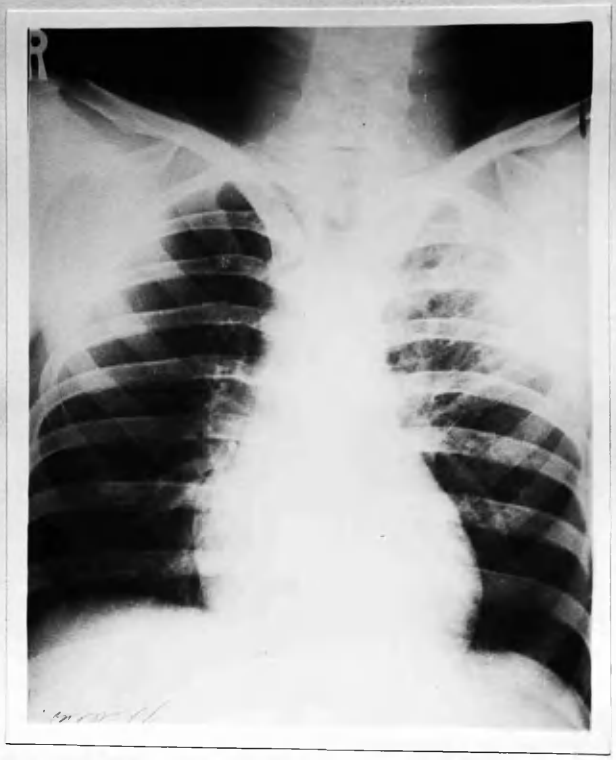


PLATE VIb. 14TH DAY OF ILLNESS.
RESOLUTION ALMOST COMPLETE.

RAPID RESOLUTION.

MALE, AGED 52 YEARS.

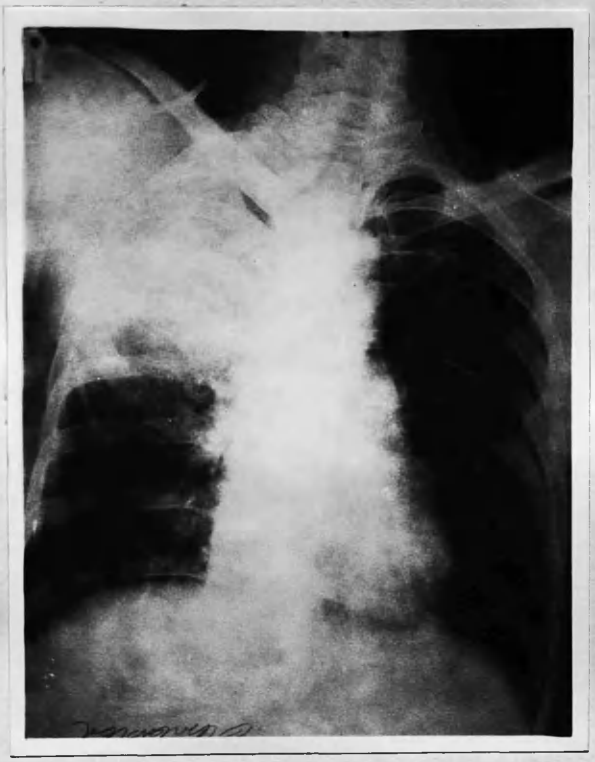


PLATE VIIa 6th DAY OF ILLNESS.
CONSOLIDATION R. UPPER LOBE ~ DENSITY III

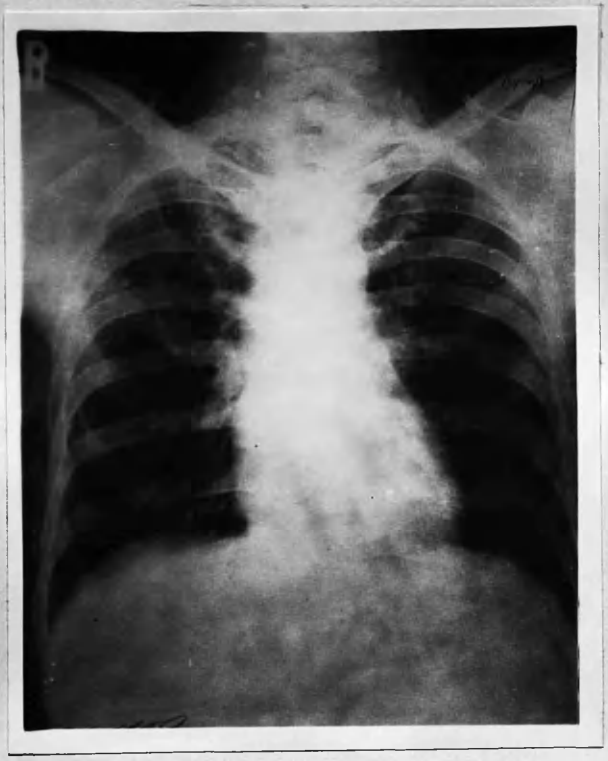


PLATE VIIb. 17th DAY OF ILLNESS.
RESOLUTION ALMOST COMPLETE.

SECTION (ii)

Types of Resolution

The progress of resolution in any case of pneumonia may be placed in one of three broad categories:-

Group (i) - Rapid resolution
Group (ii) - Fair resolution
Group (iii) - Delayed resolution

(a) Rapid resolution

This group comprises cases where the radiographs show complete clearing of the opacity by the twenty-first day. This type of resolution is typically seen in children and young, healthy adults, although it may occur at any age. Clinically, these patients may be sharply ill on admission to hospital, but, after commencement of chemotherapy, temperature and pulse fall rapidly by lysis, reaching normal at varying periods from two to five days. Physical signs of consolidation disappear in one to two weeks. The groups of radiographs III to VII illustrate examples of rapid resolution at various age groups.

(b) Fair resolution

In this group of cases, resolution of the consolidation is somewhat slower than in the first group and evidence of the lesion can be detected radiologically up till the fourth or fifth week. Plates VIIIa to VIIId illustrate an example.

FAIR RESOLUTION.

PLATES VIIIa TO VIIId.
MALE, AGED 32 YEARS.

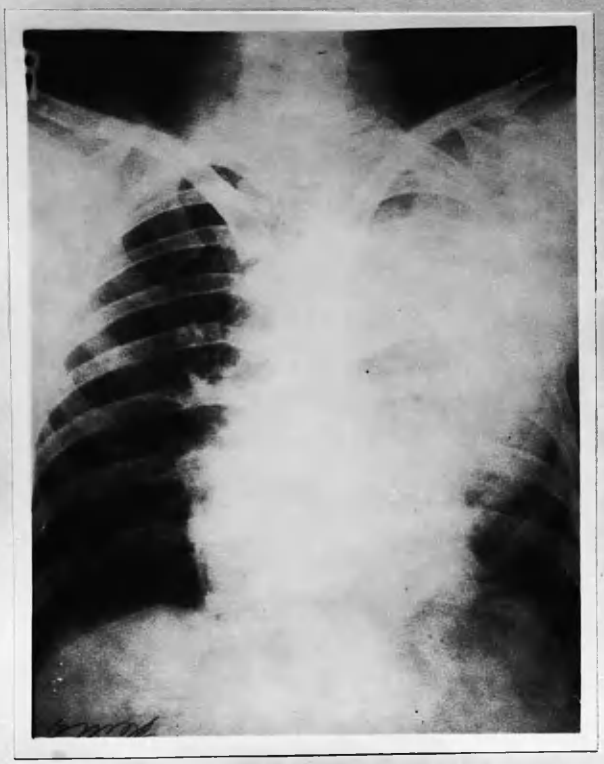


PLATE VIIIa 5TH DAY OF ILLNESS.
CONSOLIDATION L. LUNG ~ DENSITY III

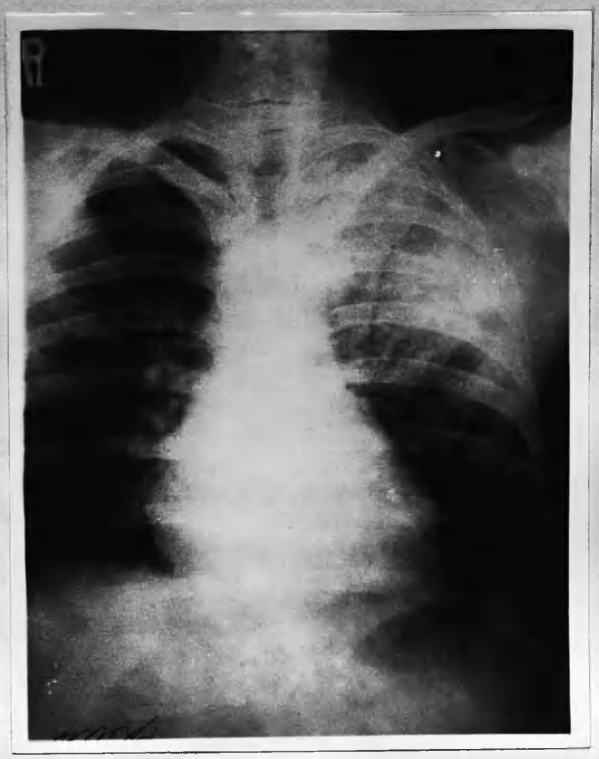


PLATE VIIIb. 14TH DAY OF ILLNESS.
CONSIDERABLE IMPROVEMENT.

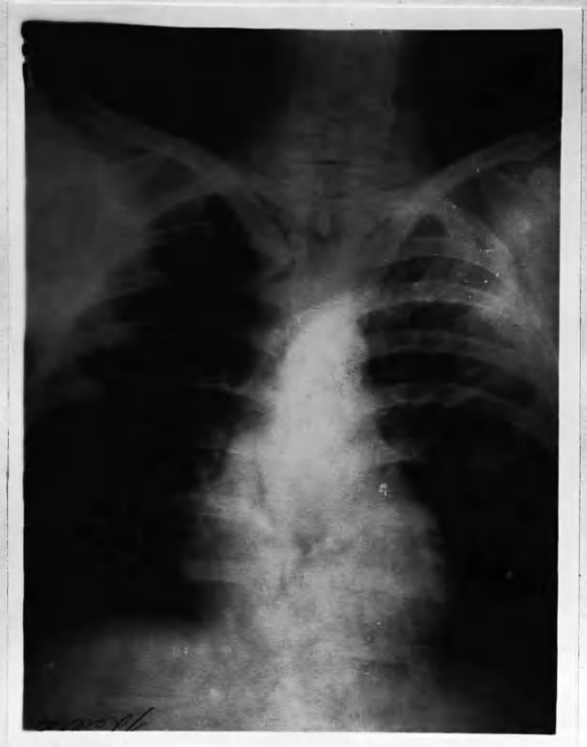


PLATE VIIIc 21ST DAY OF ILLNESS
RESOLUTION NOT YET COMPLETE.

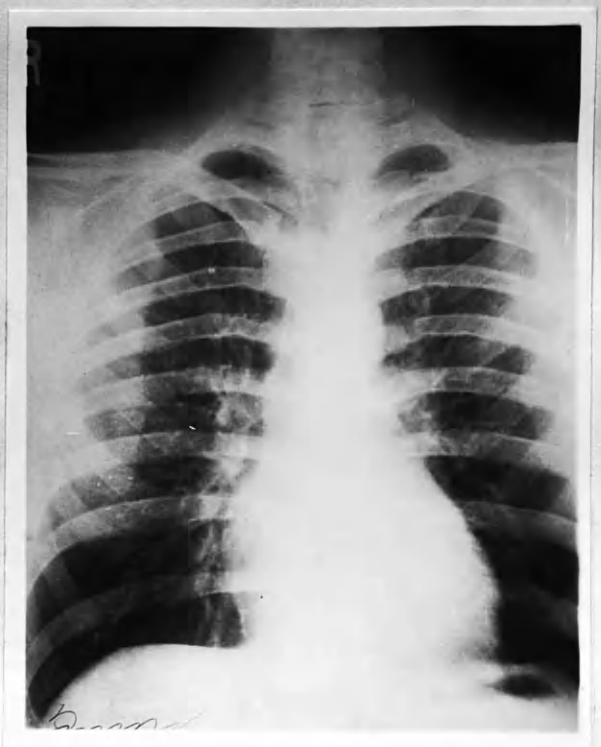


PLATE VIIId 65TH DAY OF ILLNESS.
RESOLUTION COMPLETE.

(c) Delayed resolution

In this group I have placed cases where the radiographs show opacities after the fifth week, i.e. after the 35th day. At that time, in many of these cases, the consolidation was still well marked, and often several months elapsed before the X-rays were clear. Indeed, in some cases, where delay was unduly prolonged, some degree of permanent fibrosis resulted. Clinically, physical signs of intense consolidation were also prolonged up to variable periods. In every case, however, radiographs showed opacities long after physical signs of consolidation had disappeared.

The X-ray findings in some typical cases of delayed resolution are illustrated in Plates IX to XIV.

At the end of this chapter, I have attached five charts from the series with accompanying case histories to illustrate the course of the illness in delayed resolution.

Spread of consolidation. Another type of case which often falls into the delayed resolution group is one which shows spread of the pneumonic consolidation even after the commencement of chemotherapy. Here, the consolidation does not confine itself to the lobe or part of lobe originally affected but spreads to involve a fresh part of the lung. Thus, while resolution may be well advanced in the lobe initially involved, the consolidation may not yet have reached its maximum intensity in the portion of lung more recently affected.

DELAYED RESOLUTION.

PLATES IXa TO IXc
MALE, AGED 44 YEARS.

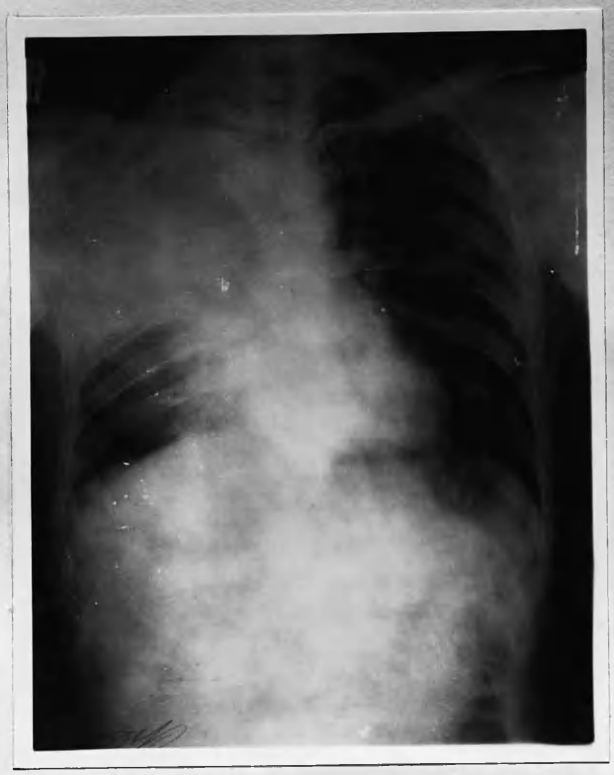


PLATE IXa. 9TH DAY OF ILLNESS.
CONSOLIDATION R. UPPER LOBE ~ DENSITY III

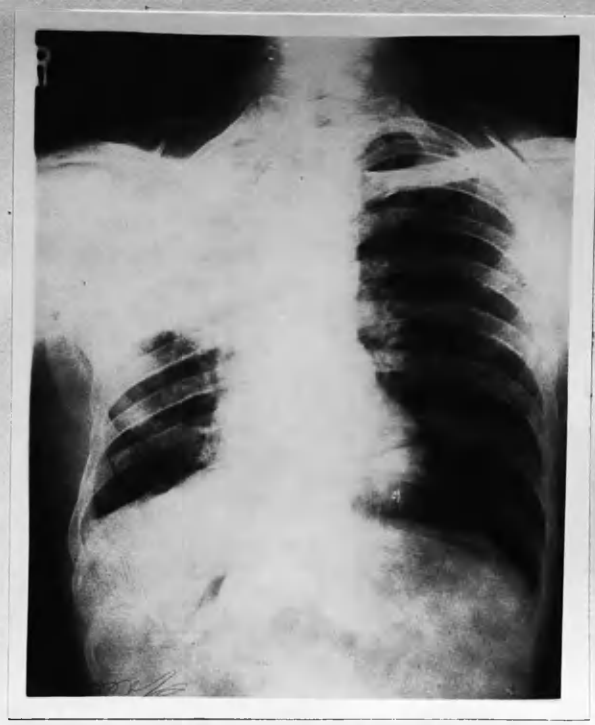


PLATE IXb. 21ST DAY OF ILLNESS.
NO IMPROVEMENT.

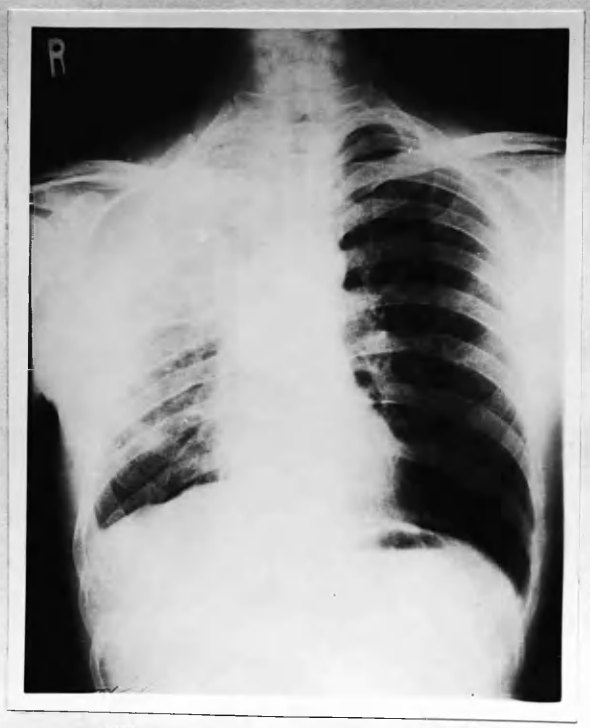


PLATE IXc 65TH DAY OF ILLNESS.
VERY LITTLE CHANGE.

DELAYED RESOLUTION.

PLATES Xa TO Xd.
MALE, AGED 28 YEARS.

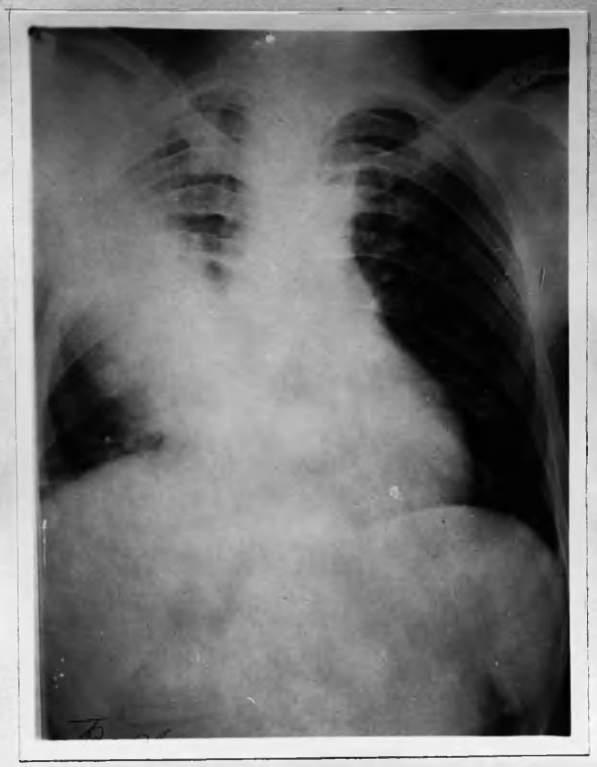


PLATE Xa. 3RD DAY OF ILLNESS.
ATYPICAL CONSOLIDATION R. LUNG ~ DENSITY III

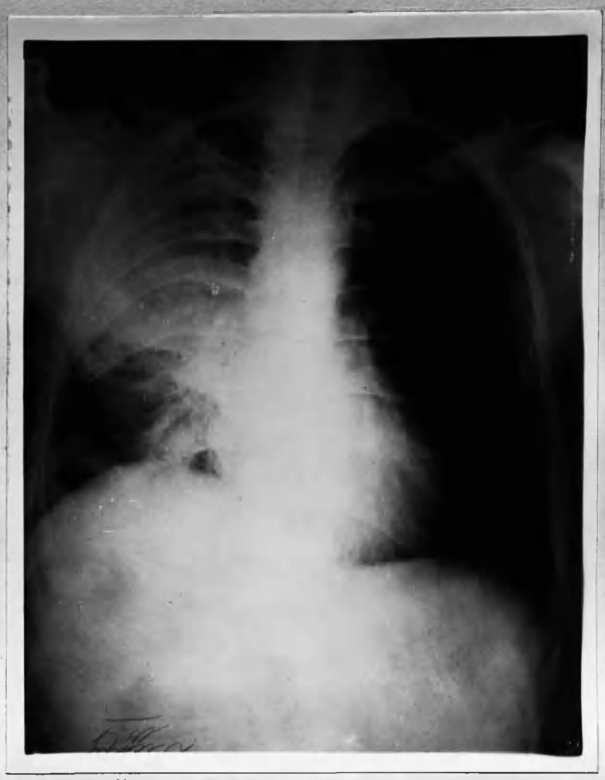


PLATE Xb. 12TH DAY OF ILLNESS.
RESOLUTION GOOD AT FIRST.

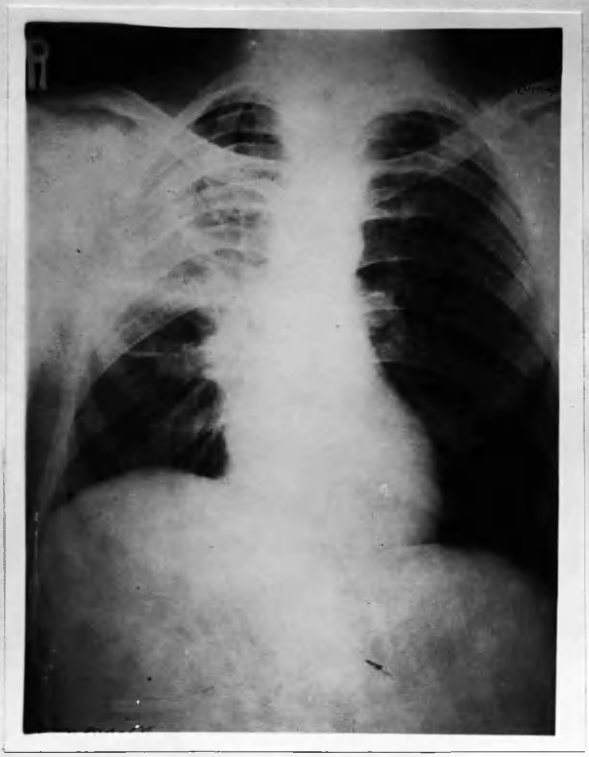


PLATE Xc. 35TH DAY OF ILLNESS.
RESOLUTION NOT YET COMPLETE

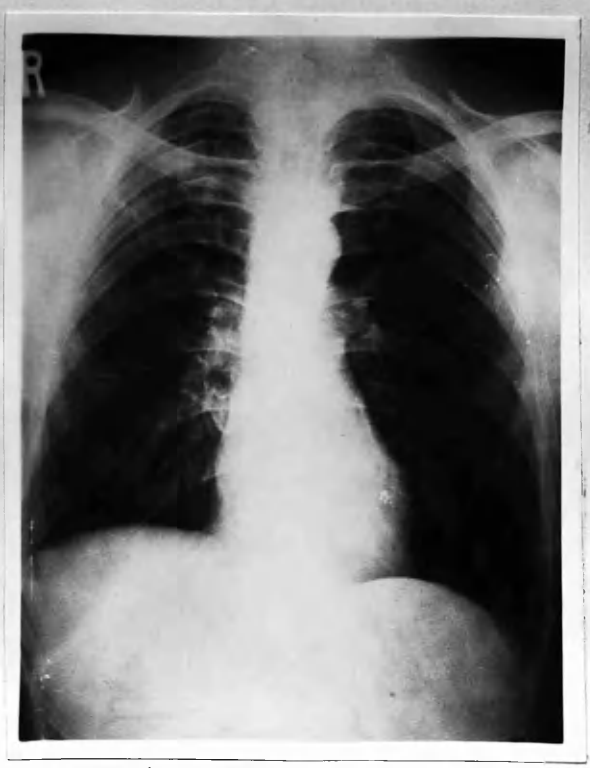


PLATE Xd. 130TH DAY OF ILLNESS.
RESOLUTION COMPLETE.

DELAYED RESOLUTION.

PLATES XIa. TO XId.
MALE, AGED 22 YEARS.

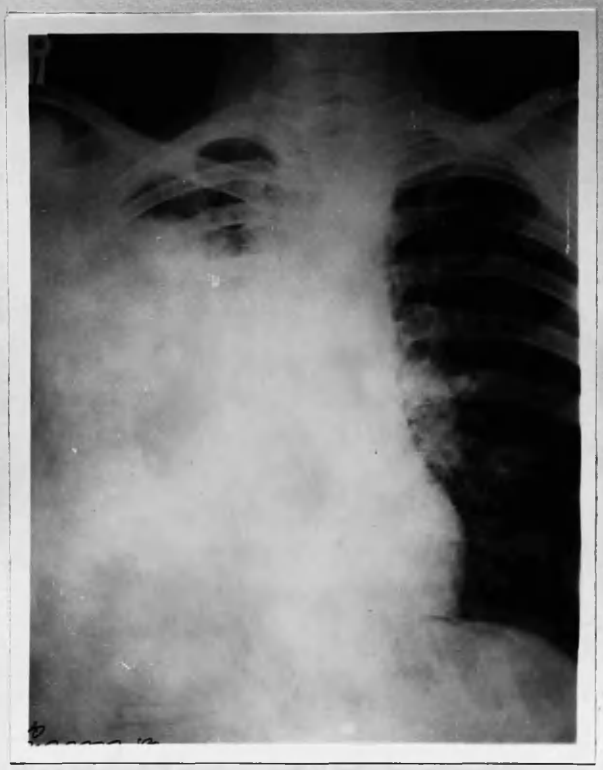


PLATE XIa. 5TH DAY OF ILLNESS.
CONSOLIDATION R. LUNG ~ DENSITY III

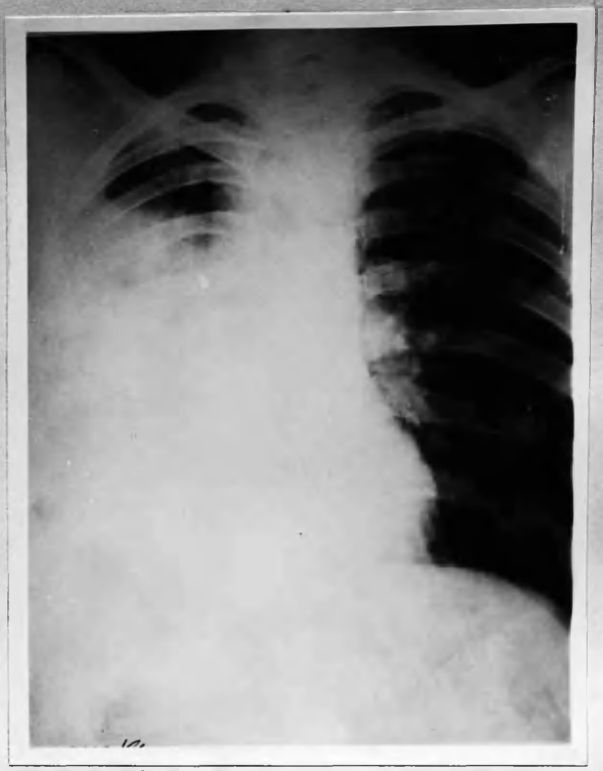


PLATE XIb. 19TH DAY OF ILLNESS.
NO IMPROVEMENT.

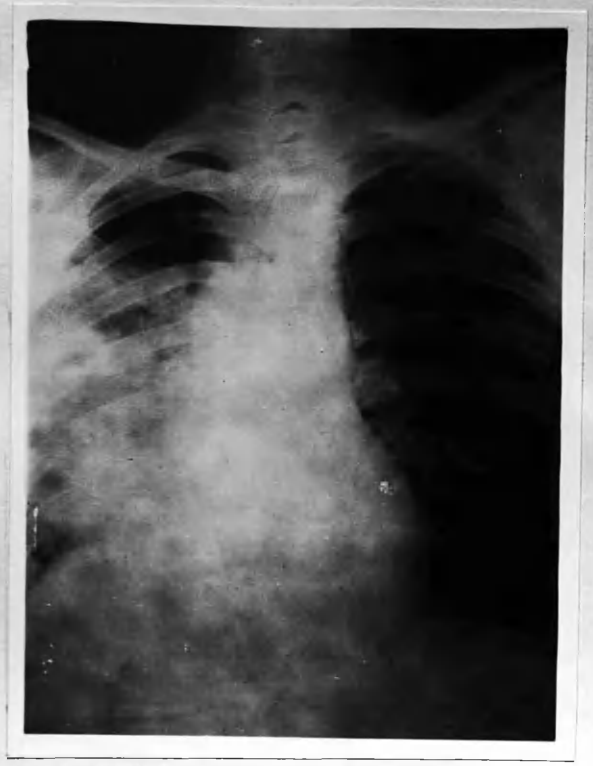


PLATE XIc. 61ST DAY OF ILLNESS.
VERY SLOW RESOLUTION.

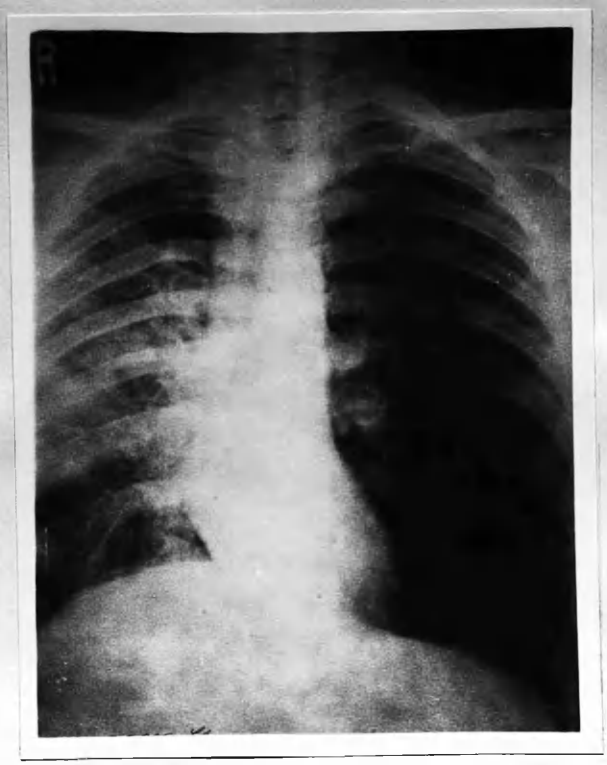


PLATE XId. 102ND DAY OF ILLNESS.
RESOLUTION NOT YET COMPLETE.

DELAYED RESOLUTION.

PLATES XIIa. TO XIIc.
MALE, AGED 41 YEARS.

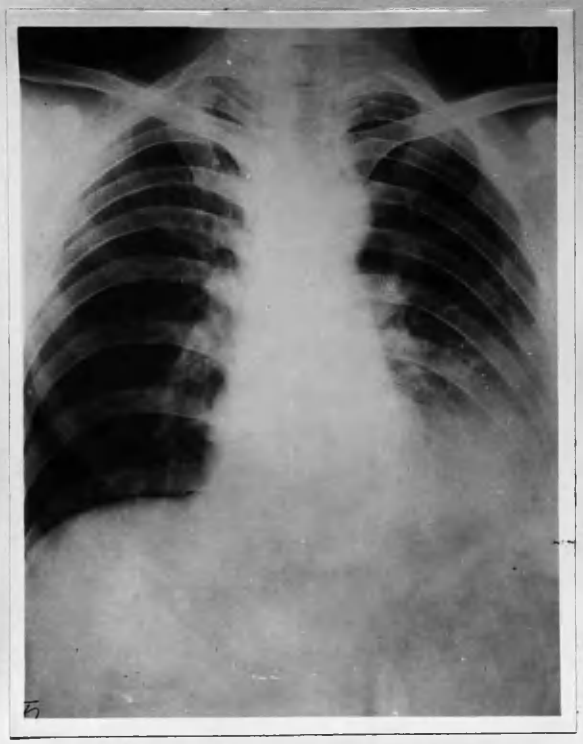


PLATE XIIa. 13TH DAY OF ILLNESS.
CONSOLIDATION L. BASE ~ DENSITY III

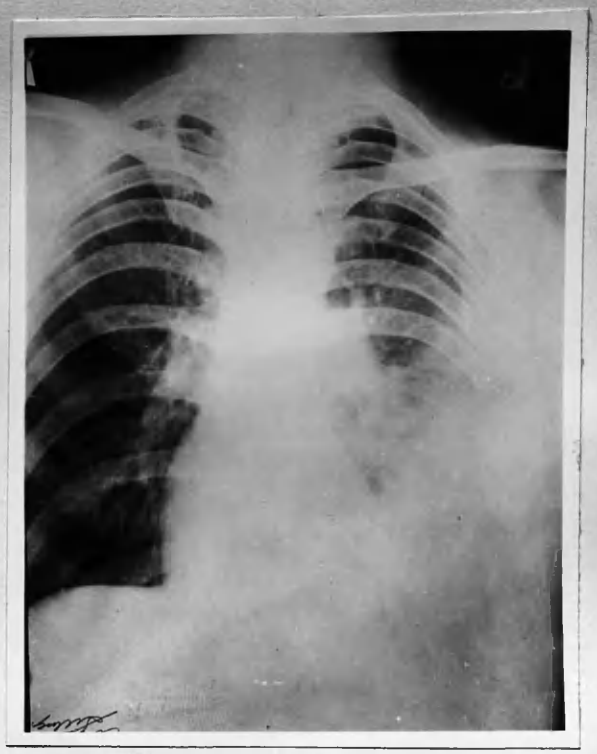


PLATE XIIb. 22ND DAY OF ILLNESS.
NO IMPROVEMENT. PLEURAL EFFUSION PRESENT.

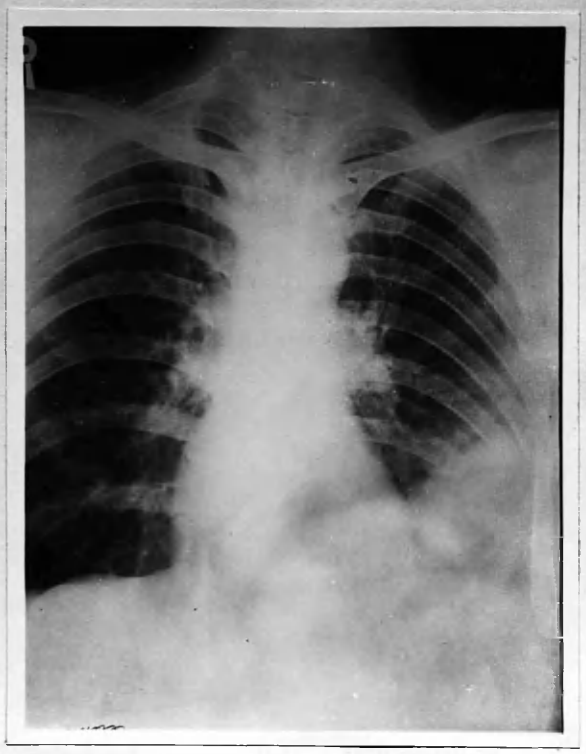


PLATE XIIc. 48TH DAY OF ILLNESS.
RESIDUAL OPACITY AT BASE ~ SIMULATES CARCINOMA.

Note: Plate XIIIb was taken with the patient in the supine position, as he was too ill to be turned into the prone position.

DELAYED RESOLUTION.

PLATES XIIIa TO XIIId.
MALE, AGED 64 YEARS.

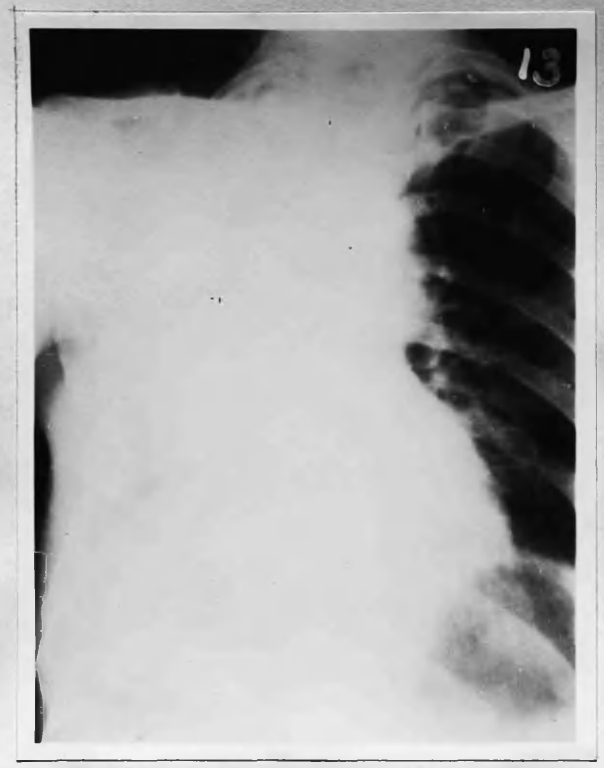


PLATE XIIIa. 6TH DAY OF ILLNESS.
INTENSE CONSOLIDATION R. LUNG ~ DENSITY III

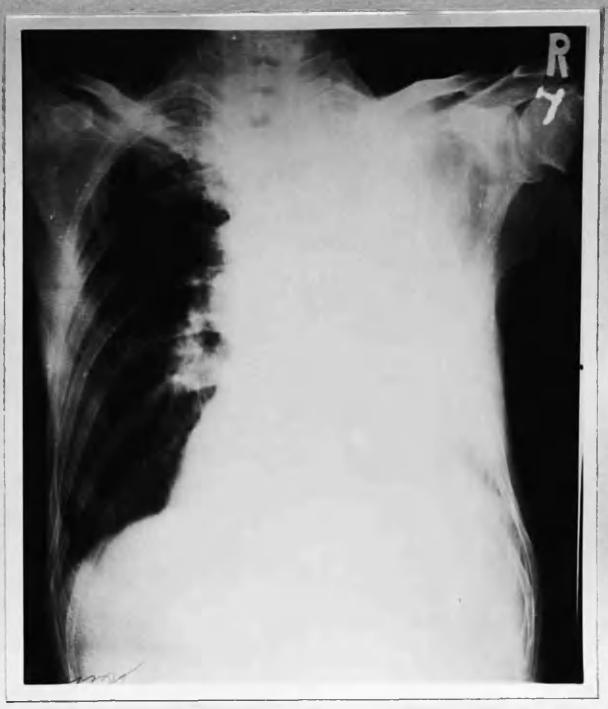


PLATE XIIIb. 26TH DAY OF ILLNESS.
NO IMPROVEMENT.

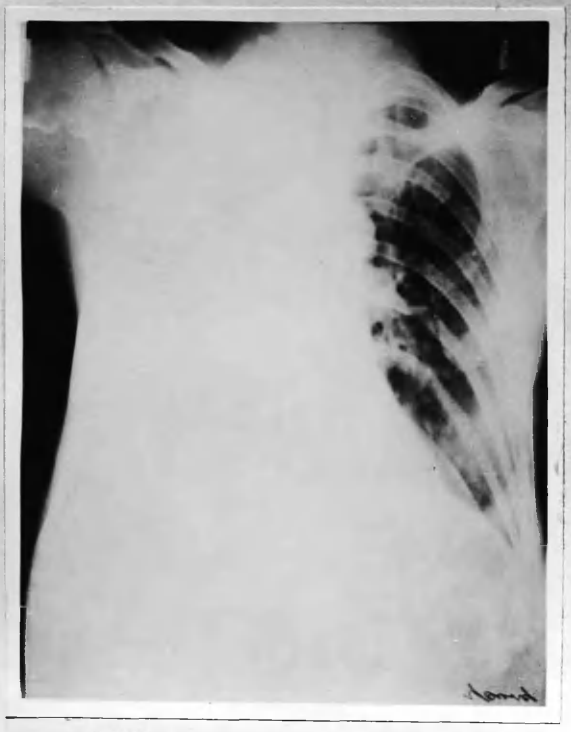


PLATE XIIIc. 64TH DAY OF ILLNESS.
STILL NO IMPROVEMENT: MASSIVE COLLAPSE.

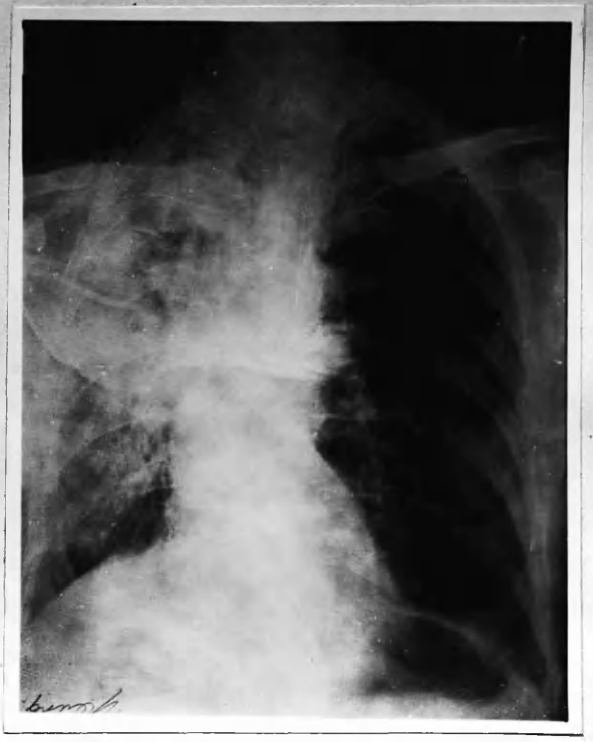


PLATE XIIId. 110TH DAY OF ILLNESS.
CONSIDERABLE IMPROVEMENT.

DELAYED RESOLUTION.

PLATES XIVa TO XIVb.

MALE, AGED 42 YEARS.

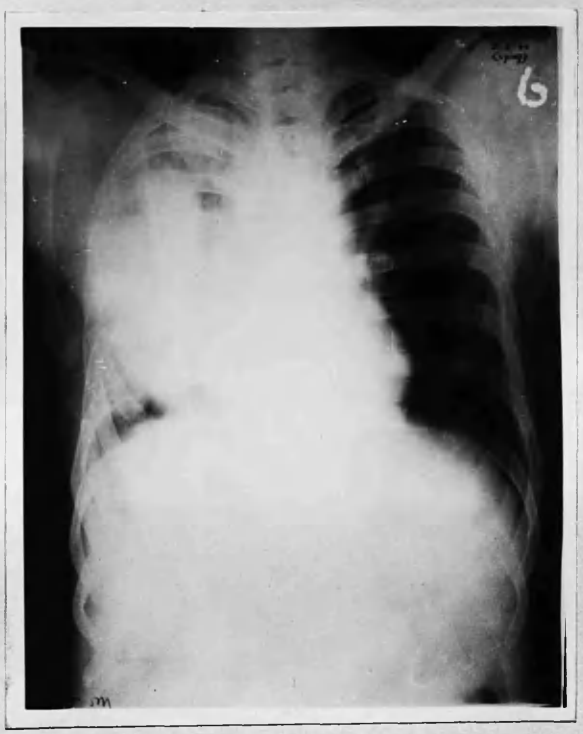


PLATE XIVa. 6TH DAY OF ILLNESS.
CONSOLIDATION R. LUNG ~ DENSITY III

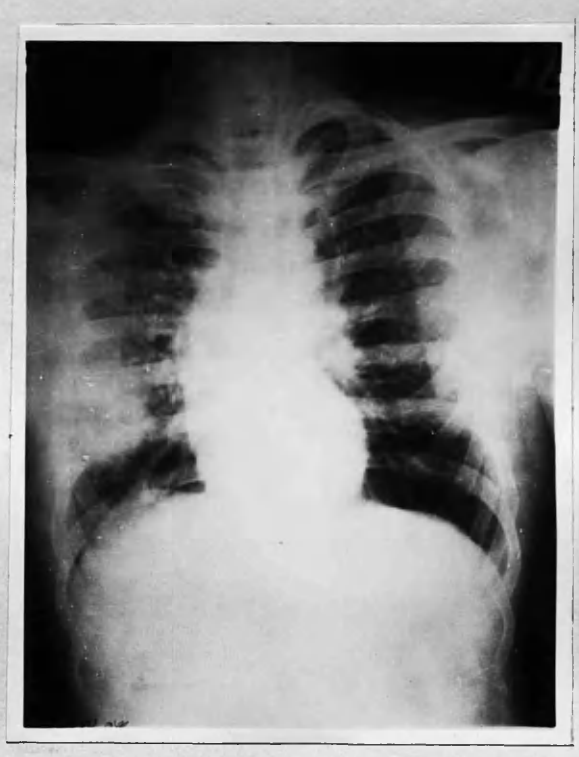


PLATE XIVb. 90TH DAY OF ILLNESS.
RESOLUTION NOT YET COMPLETE.

From Table 10, it is seen that no case, less than four days ill prior to admission, showed spread of the consolidation to involve a fresh lobe or an unaffected part of the same lobe. On the other hand, 11 cases, who had been ill 4 days and over prior to admission, showed spread of the consolidation in subsequent radiographs (Table 10). Plates XVa to XVd illustrate the X-ray findings in one of these cases.

TABLE 10

Spread of Consolidation in respect of Days Ill prior to Admission

Days ill prior to admission	1	2	3	4	5	6	7	7+
Cases showing spread of consolidation	-	-	-	4	1	2	1	3

This finding provides additional support to the conclusion reached in the previous section, namely that sulphonamides are more effective when commenced early in the course of the illness. Then, however, the assessment of such effectiveness was the speedy attainment of a maximum consolidation in the original opacity. Now we are concerned with the influence of the drug in preventing spread of the consolidation beyond the original area of lung affected. And it now appears that spread of the consolidation occurred only in cases where treatment was commenced late in the

SPREAD OF CONSOLIDATION.

PLATES XVa TO XVd.
MALE, AGED 47 YEARS.

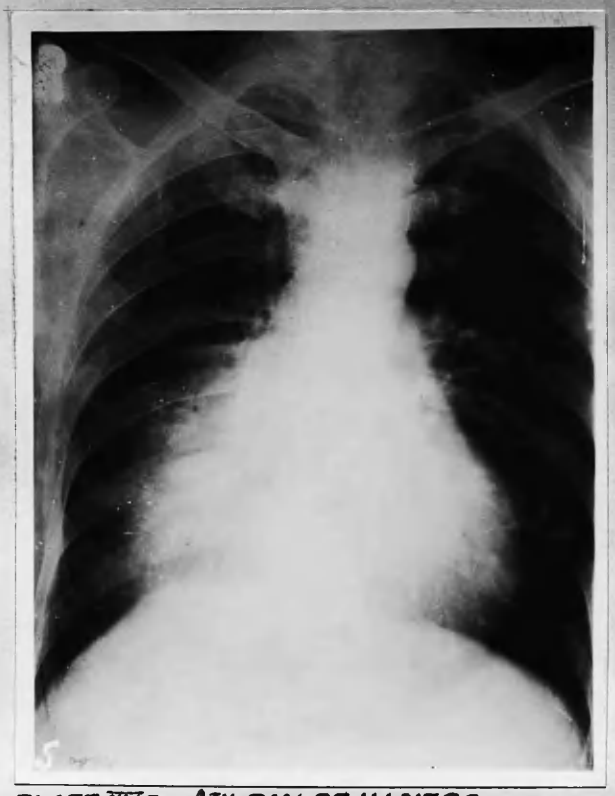


PLATE XVa. 4TH DAY OF ILLNESS.
HILAR CONSOLIDATION R. LOWER LOBE.

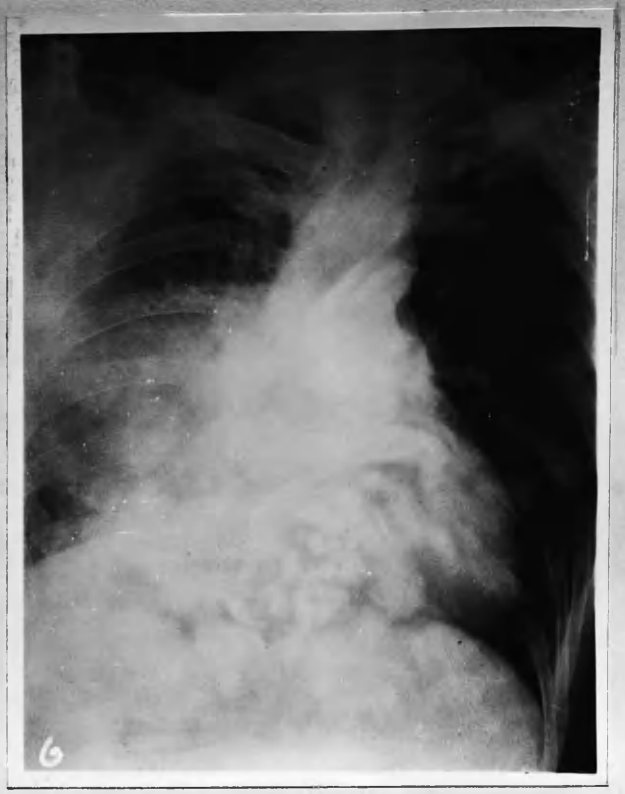


PLATE XVb. 8TH DAY OF ILLNESS.
SPREAD OF CONSOLIDATION TO PERIPHERY.

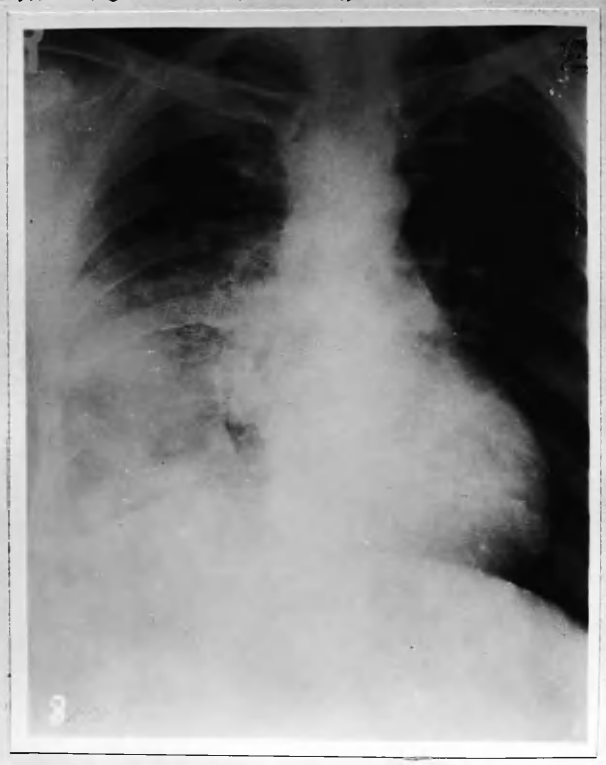


PLATE XVc. 16TH DAY OF ILLNESS.
NO IMPROVEMENT.

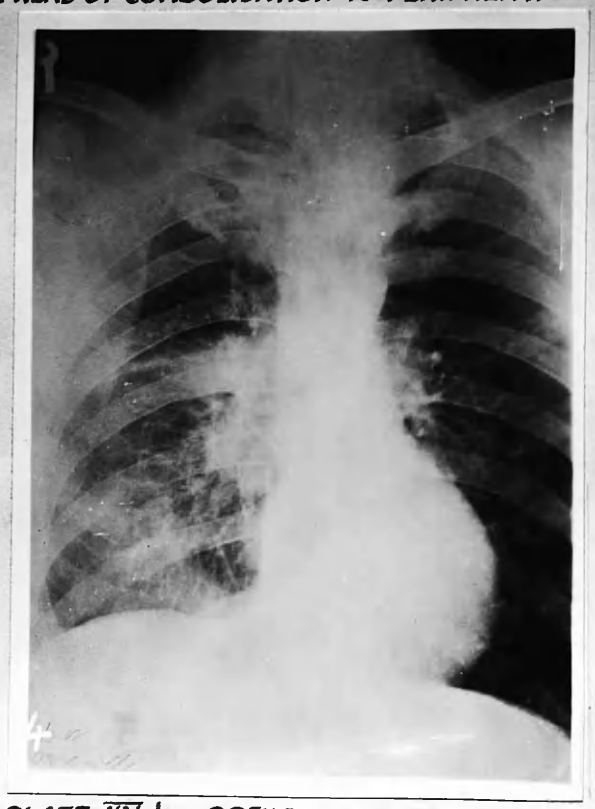


PLATE XVd. 29TH DAY OF ILLNESS.
RESOLUTION NOT YET COMPLETE.

course of the illness. This finding is rather curious as it might reasonably be expected that the longer the patient had been ill prior to admission to hospital and, therefore, to the start of chemotherapy, the greater his opportunity of developing antibodies, which would help in arresting the spread of the disease. In this connection the following two observations are of interest:-

(1) Anderson (personal communication) investigated the effects of a combination of chemotherapy with specific serotherapy in 33 cases of Type II pneumonia who were considered to be severely ill. He found that, in respect of the fatality rates (specific for age and the presence of bacteriaemia) the duration, in days, of primary pyrexia, and the occurrence of complications particularly as regards the high incidence of delayed resolution, the results of combined therapy showed no improvement over those obtained with sulphonamide alone.

(2) In the report on the treatment of meningococcal meningitis, 1944, Anderson and others found that combined treatment with sulphonamides and serum was less effective than treatment by sulphonamides alone.

The surprising conclusion from these findings would seem to be that sulphonamides and antibodies are antagonistic to one another.

Distribution of cases in relation to the type of resolution

The distribution of the cases in relation to the type

of resolution is depicted in Table 11. Before the introduction of chemotherapy the only comparable analysis, based on radiological evidence, was that of Davies, Hodgson and Whitby. Over their whole series of 119 cases, the average time required for complete resolution was 20 days, and the maximum figure was 50 days.

TABLE 11

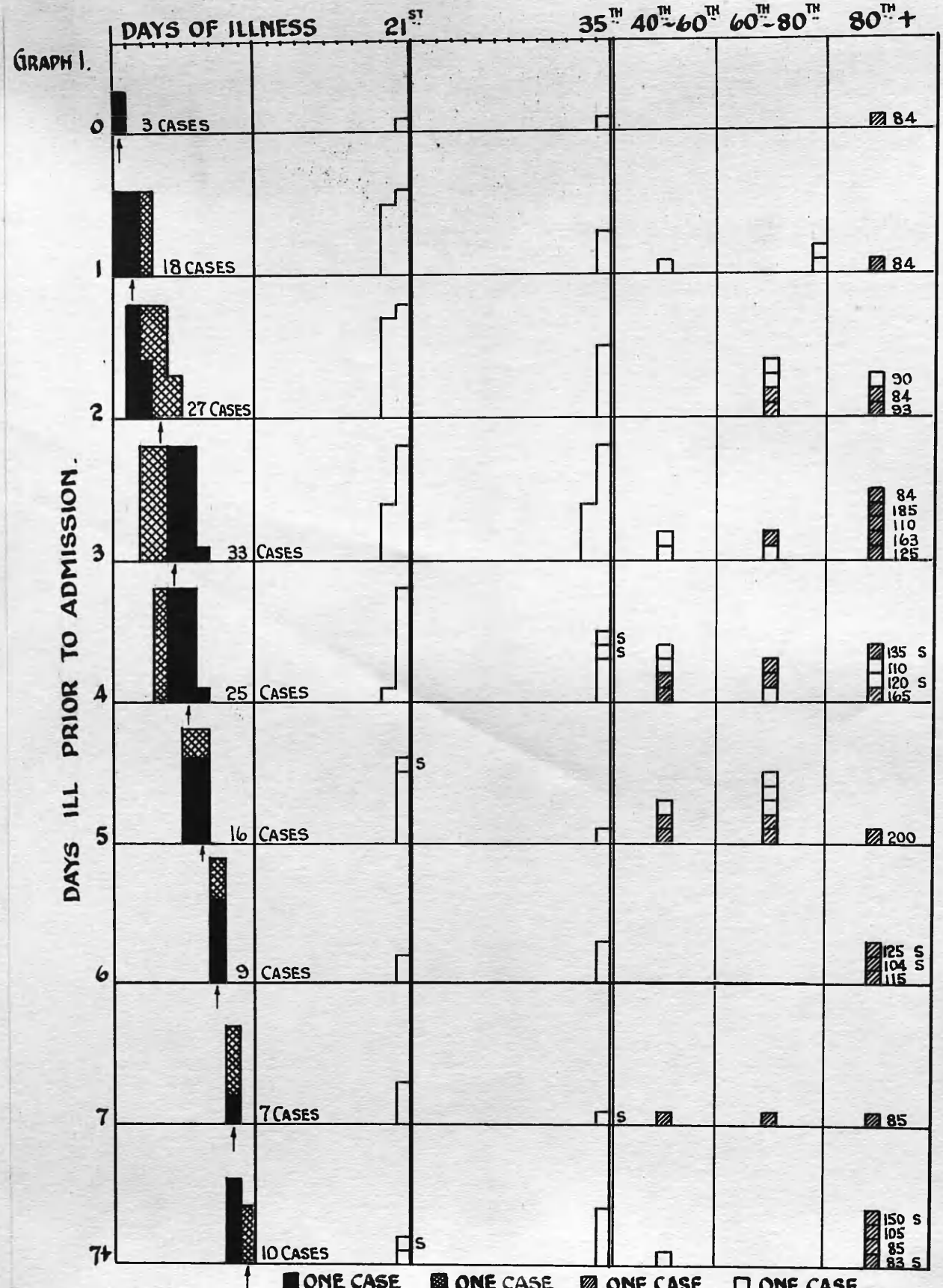
Distribution of Cases in respect of Progress of Resolution

Total cases	Resolution		
	Rapid	Fair	Delayed
148	61 (41.2)	34 (23.3)	53 (35.5)

(The figures in brackets are percentages of the group total)

In the present series it is seen that only 41.2 per cent. of the cases showed rapid resolution, that is, a complete clearing of the consolidation by the 21st day. Further, in respect of the maximum number of days required for complete resolution, Graph 1 depicts that of the 53 cases showing delayed resolution 40 still had opacities after the 60th day. In 20 cases there was still evidence of consolidation after the 80th day, and four cases still showed remains of the opacities by the 150th day.

PROGRESS OF RESOLUTION IN RELATION TO "DAYS ILL PRIOR TO ADMISSION."



It is thus evident from the above figures that the time required for complete resolution of pneumonia under sulphonamide chemotherapy is, in many instances, much longer than that required with other methods of treatment.

SECTION (iii)

Factors known to influence Resolution

In the Glasgow report on pneumococcal pneumonia (1938-42) the association of certain factors with the incidence of delayed resolution was studied, and Table 12 shows that the most important of these is the age of the patient, for the incidence in those over 40 years of age is almost twice that under this age. The figures given also show that bacteriaemia and the duration, in days, of illness prior to admission are important, for, both in bacteriaemic patients and in those who are more than three days ill prior to admission, delayed resolution is frequent.

TABLE 12
The Incidence of Delayed Resolution
(Glasgow Report)

	Age		Bacteri-aemia		Duration in days ill prior to admission		Types			
	-40 yrs.	40+ yrs.	Pos.	Neg.	-4	4+	1	2	3	"Gp. 4"
Total series	1,016	933	277	1,081	1,124	825	400	718	156	675
Cases showing delayed resol-ution	200 (19.8)	347 (37.1)	72 (26.1)	229 (21.3)	270 (24.0)	277 (33.6)	113 (28.2)	223 (31.0)	49 (30.8)	162 (24.0)

(The figures in brackets are percentages of the group total.)

Finally, infections caused by a Type II or Type III pneumococcus show a somewhat higher percentage of delayed resolution than those caused by Type I or "Group IV".

When the cases in the present series were analysed in respect of the above factors, the findings were as follows:-

Age. It is seen from Table 13 that the effect of age was even more striking than in the Glasgow report, for the percentage of cases showing delayed resolution in those over forty years of age was five times that under this age. It must be remembered, of course, that in a personal study of this nature more attention was paid to the occurrence of delayed resolution.

TABLE 13

Progress of Resolution in respect of Age

	Total cases	under 40 years	40 + years
Rapid ...	61	41	20 (32.7)
Fair ...	34	9	25 (73.5)
Delayed .	53	7 (13.2)	46 (86.8)
Totals .	148	57	91

(The figures in brackets are percentages of the group total)

Further, radiographs were employed throughout the illness in the present series and thus the condition was readily diagnosed, whereas, in the larger combined study, X-rays were not always available.

Bacteriaemia. The number of bacteriaemic cases was small in the present series. However, the increased percentage of delayed resolution in these cases as compared with the non-bacteriaemic cases is significant.

TABLE 14

The Progress of Resolution in respect of Bacteriaemia

	Total cases	Rapid Resolution	Fair Resolution	Delayed Resolution
Bacteri-aemic	20	5	4	11 (55)
Non-Bacteri-aemic	128	46	30	42 (33)

(The figures in brackets are percentages of the group total)

Duration in days ill prior to admission. Table 15 shows that in cases over three days ill prior to admission there was a much higher proportion of delayed resolution. Graph 1 (in the previous section) depicts, in greater detail, the influence of this factor on the course of resolution.

TABLE 15

Resolution in respect of the Duration in Days Ill prior to Admission

Duration in days ill prior to admission	Total Cases	Rapid Resolution	Fair Resolution	Delayed Resolution
- 4 days	81	39	19	23 (28.4)
4 + days	67	22	15	30 (43.6)

(The figures in brackets are percentages of the group total)

From the Graph, it is seen that the total number of days required for complete resolution tends to be higher in those admitted "late" in the course of their illness than in those admitted "early" in the course of their illness.

Type of infecting organism. Type III pneumonia showed the highest proportion of delayed resolution, but, as seen from Table 16, the total number of Type III cases was very small. The total numbers in each of the other three groups were large enough to give significant findings, and it is seen that Type II infections showed a higher percentage of delayed resolution than Type I or "Group IV" infections.

TABLE 16

The Progress of Resolution in respect of Type

Type	Total Cases	Rapid Resolution	Fair Resolution	Delayed Resolution
I	24	7	12	5 (28.3)
II	71	29	15	27 (38)
III	8	2	-	6 (75)
"Group IV"	45	23	7	15 (33.3)
Totals .	148	61	34	53

(The figures in brackets are percentages of the group total)

The above results in respect of age, bacteriaemia, duration in days ill prior to admission, and type of infecting organism correspond with the Glasgow report, and corroborate the finding that, of these, age is the most

important factor in the production of delayed resolution.

SECTION (iv)

The Relation of Radiographic Appearances to Resolution

The value of radiography in following up the progress of resolution in pneumonia has already been demonstrated. It would now be of interest to find out if the initial radiographic characteristics of the consolidation, before commencement of chemotherapy, have any value in prognosticating the subsequent course of resolution. In this respect, the density of the opacity seems of primary concern, for, when discussing the pathological process of resolution in Chapter III, it was suggested that the density of the initial pneumonic opacity might be one factor in the incidence of delayed resolution. Again, McCrae (1910) claimed that the situation of the pneumonic lesion was another radiographic characteristic of importance. He showed that the lower lobes were more frequently involved in delayed resolution than the upper lobes, and the right lower lobe in particular.

In this section, these two radiographic characteristics, namely, the density of the initial opacity, and the lobar involvement will be studied in relation to the progress of resolution.

(a) Density of opacity in relation to resolution

As shown from Table 17, 88 cases had opacities of density "III" at the commencement of their illness and 60

cases had opacities of density "II". Of the former group of cases, 38 (43.2 per cent.) developed delayed resolution compared with 15 cases (25 per cent.) in the group showing hazy opacities. The density of the initial lesion is thus an important factor in delayed resolution - intense consolidations showing a higher proportion of cases.

TABLE 17

Incidence of Delayed Resolution in respect of Initial Density

	Initial Density "III"	Initial Density "II"	Totals
Total cases ...	88	60	148
Cases showing delayed resolution	38 (43.2)	15 (25)	53 (35.5)

(The figures in brackets represent percentages of the group total)

Now, clinical observations indicate that a dense consolidation is associated with severe constitutional symptoms while a hazy opacity is associated with a milder form of pneumonia. In assessing the severity of any infection the temperature and pulse rate are probably the most valuable objective clinical signs. So to substantiate clinical impressions it is of interest to correlate the density of the opacity with these two signs.

(1) Temperature in relation to density. In Table 18 I have correlated dense consolidation with (i) the temperature

on admission to hospital, and (ii) the duration of primary pyrexia. It is seen that the actual height of the temperature on admission in relation to density was not statistically significant - the proportion of cases having readings below 101°F. and above 101°F. was approximately the same. On the other hand, when the duration of primary pyrexia is considered, it is seen that the vast majority of cases showing prolonged pyrexia occurred with intense consolidations.

TABLE 18

Temperature in respect of the Density of the Opacity

	Temperature on Admission		Duration of Primary Pyrexia		
	-101°F.	101°F.+	1-3 days	4-6 days	7+ days
Total series	78	70	78	41	29
Cases with opacity of Density "III"	45 (58)	43 (64)	39 (50)	26 (63)	23 (79)

(The figures in brackets represent percentages of the group total)

(2) Cardio-vascular system and density. It is well known that in severe cases of pneumonia the cardio-vascular system is often affected. In such cases physical signs of such involvement are frequently evident - tachycardia, heart sounds which are soft and of poor tone, low blood pressure, and, in a few cases, auricular fibrillation. In a subsequent chapter, I will deal more fully with the subject of the

subject of the cardio-vascular system in pneumonia. Here, in relation to density of opacity, I merely wish to show how frequently an intense consolidation was found in cases showing involvement of the cardio-vascular system. Table 19 demonstrates that a greater percentage of dense opacities are associated with a high pulse rate.

TABLE 19

Cardio-Vascular System in respect of the Density of the Opacity

	Highest Pulse Rate during first 24 hours		Myocarditis	Auricular Fibrillation	Low B.P. on Admission
	-110 beats per min.	110+ beats per min.			
Total series	72	76	13	3	12
Cases with opacity of density "III"	36 (50)	51 (67)	10	2	8

(The figures in brackets represent percentages of the group total)
B.P. = Blood pressure.

Other signs of cardio-vascular involvement occurred in 28 cases in the series - thirteen cases had extremely soft heart sounds, three developed auricular fibrillation, and twelve cases had low admission blood pressures (i.e. below 100 mm. Hg. systolic, or 50 mm. Hg. diastolic). As shown from Table 19, a high proportion of dense consolidations accompanied all these lesions.

The above findings thus confirm the association of an intense opacity with a severe infection. From this association it might well be argued that the severity of the initial infection would in itself explain the delay in resolution which occurs in dense consolidations. But, if the intensity of the consolidation is the basic cause behind delayed resolution, then the factors which influence the incidence of delayed resolution should likewise influence the incidence of intense consolidations. So it now remains to correlate the age of the patient, the presence of bacteriaemia, the duration, in days ill prior to admission, and the type of the infecting organism, with the density of the opacity.

TABLE 20

	Age		Bacteriaemia		Duration, in days, ill prior to admission		Types			
	-40 yrs.	40+ yrs.	Pos.	Neg.	-4	4+	I	II	III	"Group IV"
Total series	59	89	20	128	81	67	24	71	8	45
Cases with density "III" consolidation	34 (57.7)	54 (60.6)	15 (75)	73 (57.3)	45 (55.5)	43 (64.7)	15 (62.5)	43 (60.5)	4 (50.0)	26 (57.8)

(The figures in brackets are percentages of the group total)

From Table 20 it is seen that cases with a positive blood culture showed a slightly higher proportion of intense

consolidations than non-bacteriaemic cases. Again, in cases over four days ill prior to admission, the percentage of intense consolidations was greater than in cases under four days ill prior to admission. Thus, the influence of these two factors in the incidence of intense consolidations is similar to their influence in the incidence of delayed resolution. But this similarity does not extend to the other two factors, namely the age of the patient and the type of the infecting organism. In respect of the type of pneumococcus, the highest percentage of intense consolidations was associated with Type I infections, while Type III infections, which are radiologically associated with consolidations which are patchy and not typically lobar, showed the smallest number of dense opacities. These findings are entirely different from the influence of the type of the infecting organism in the incidence of delayed resolution.

But perhaps the most surprising observation is that the age of the patient seems of no importance in the incidence of dense consolidations. This is in marked contrast to the effect of age in delayed resolution where it is the most important factor.

From these findings it is apparent that the density of the opacity is not the ultimate cause of delayed resolution. What then is the exact relationship between the density of the opacity and delayed resolution? An answer to this question was forthcoming when I studied all the cases with

dense opacities, and compared the proportion of these in the older age group which developed delayed resolution with the corresponding figure in the younger age group. Of the 34 cases in the latter group only seven (20.6 per cent.) developed delayed resolution compared with 31 out of 54 cases (55.5 per cent.) in the older age group. It thus seems that a dense consolidation in a young individual has a good prognosis as regards resolution, but, in an older individual, resolution is very liable to be delayed.

(b) <u>The progress of resolution in relation to lobar involvement</u>

Before the progress of resolution in respect of lobar involvement is studied, it is of interest to consider first the frequency of involvement of the individual lobes in the pneumonic consolidation. From Table 21, it is seen that, in the present series, the right lower lobe was affected more frequently than any of the other lobes. This may possibly be explained from the anatomy of the respiratory tract, for the right bronchus arises from the trachea at a higher level than the left, and is wider, shorter and more vertical. Thus infecting organisms will tend to be directed down the right bronchus, and gravity will deposit the infection in the right lower lobe.

TABLE 21

The Progress of Resolution in respect of Lobar Involvement

	*Total times lobe involved	Normal Resolution	Fair Resolution	Delayed Resolution
R_1 ..	24	12	6	6 (25)
R_2 ..	34	12	7	15 (44)
R_3 ..	66	17	16	33 (50)
L_1 ..	16	8	1	7 (44)
L_2 ..	35	7	10	14 (40)

R_1 = right upper lobe
R_2 = right middle lobe
R_3 = right lower lobe
L_1 = left upper lobe
L_2 = left lower lobe

(The figures in brackets are percentages of the group total)

* A multilobar infection was placed in each of the lobes involved.

In respect of the progress of resolution in relation to lobar involvement, Table 21 shows that the incidence of delayed resolution was highest in the right lower lobe. This is similar to McCrae's earlier findings. When I considered why the right lower lobe should be so frequently involved in delayed resolution, I found that the local anatomy would afford two possible explanations:-

(a) The presence of the liver on the right side results in a

raising of the diaphragm. The respiratory excursion of the right lower lobe is thus more limited than any other part of the lungs. A pneumonic consolidation situated in this lobe will thus cause more marked compression of the alveolar capillaries, and the local ischaemia will be consequently more pronounced.

(b) The arterial supply of the lungs. The lungs receive blood from two sources, (1) the pulmonary artery and (2) the bronchial arteries. The former conveys venous blood to the lungs to be "arterialised", while the branches of the bronchial artery are responsible for the nutrition of the bronchi, vessels, interlobar connective tissue and bronchial lymph glands. Now, on the right side there is generally one bronchial artery which arises from the first aortic intercostal or from the upper left bronchial artery, whereas, on the left side, there are two bronchial arteries arising from the thoracic aorta. Thus, the left lung has a better blood supply than the right lung.

It may, therefore, be concluded that the greater frequency of delayed resolution in the right lower lobe, as compared with any other lobe, is partly due to its poorer blood supply, and partly due to the more limited respiratory excursion of this part of the lungs. Both these factors will aggravate the local ischaemia caused by the pneumonic consolidation. In consequence, the exudate from the right lower lobe will be more slowly absorbed into the circulation and resolution will tend to be prolonged.

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APPENDIX

Examples of Delayed Resolution

1. Case 1 - Delayed resolution in older age group.
2. Case 2 - Delayed resolution in younger age group.
3. Case 3 - Delayed resolution in an atypical consolidation simulating carcinoma.
4. Case 4 - Atelectasis complicating pneumonia - delayed resolution.
5. Case 5 - Lack of response to chemotherapy - delayed resolution.

Case 1. Example of delayed resolution in the older age group.

S. Duffield, aged 37 years (see Chart I).

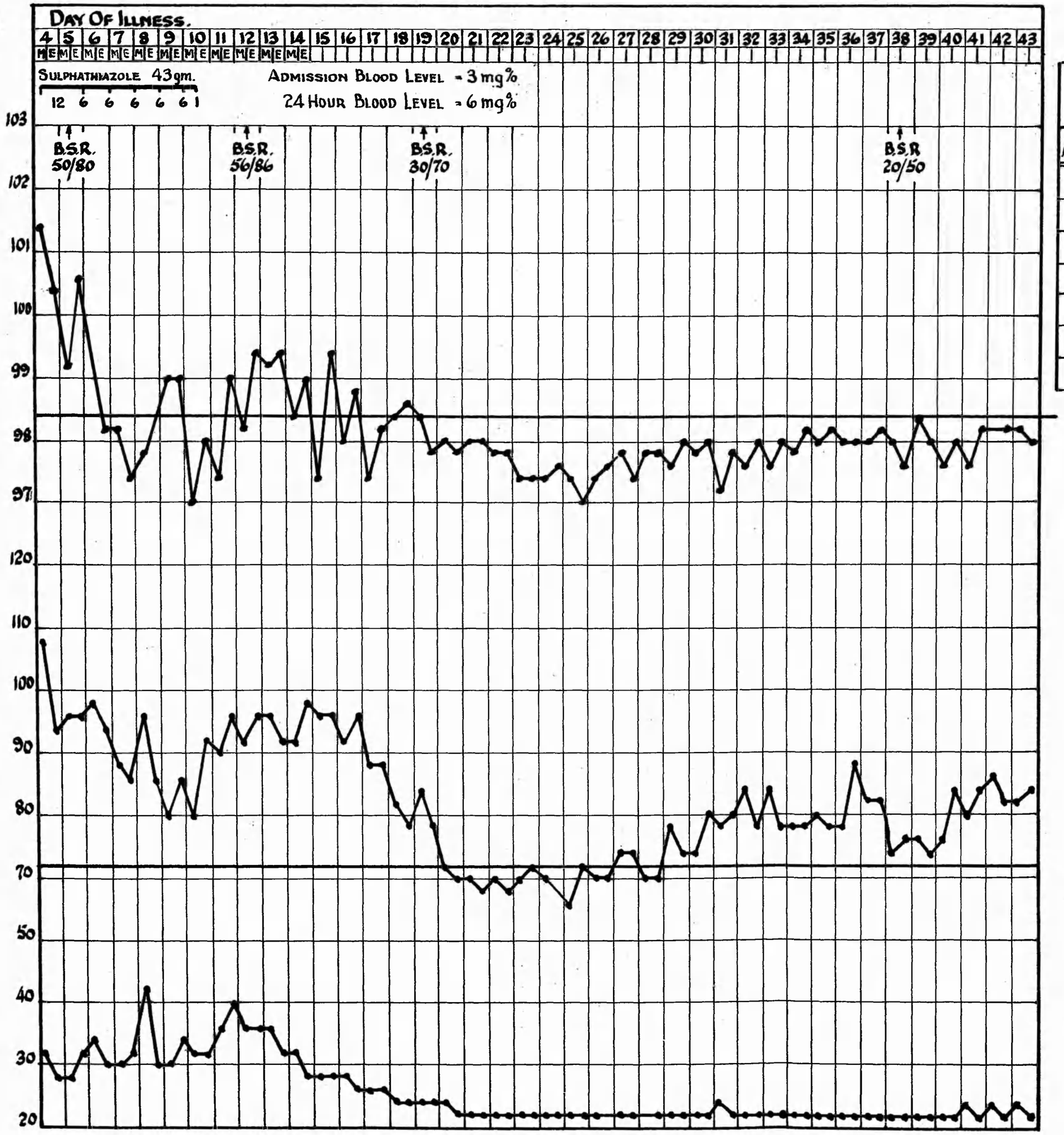
History: Admitted on the fourth day of illness; history of sudden onset with rigor, pain in right side of chest and vomiting. No previous illnesses.

Examination:

On admission, sharply ill, "gray" and toxic-looking, cyanosed. Intense pneumonic consolidation of right upper lung. Pulse irregular and heart fibrillating. B.P. 130/70. Type II pneumococci isolated from sputum. Blood culture negative. Total leucocyte count on admission was only 2,000 per c.mm., and "Group I" cells numbered 46 per cent. In spite of this low count, chemotherapy was commenced and subsequent counts showed a progressive rise in the total count and a fall in the percentage of "Group I" cells. Plasma proteins rather low: total plasma proteins 6.0 gm. per cent., albumen 3.2 gm.

Progress: The heart had regained normal rhythm by the sixth day (third day after admission). Temperature and pulse did not return to normal till two weeks after admission. Allowed up on 35th day of illness and discharged on 43rd day. B.S.R. on discharge was 20 m.m. at the end of the first hour.

CHART I.



S.D.
AGE 61
TYPE II

DAY	TOTAL W.B.C (THOUSANDS)	POLYS (%)	GROUP I CELLS (%)	MONOS (%)	PLASMA PROTEINS (gm %)			
					TOTAL	ALBUMIN	GLOBULIN	FIBRIN
ADMISSION.	2·0	72	46	10	6·0	3·2	2·15	0·65
4TH	14·8	87	18	2				
7TH	19·6	72	13	16				
9TH	14·2	77	11	8				
11TH	7·6	73	10	10				
15TH	8·6	56	6	16				
18TH	6·0	49	1	10				
22ND	5·6	54	2	7				

Case 2. Example of delayed resolution in the younger age group.

A. McAloon, aged 22 years (see Chart II and X-ray plates - figs. X1a to X1d).

History : Admitted on the fourth day of illness. History of sudden onset with rigor, pain in right side of chest, much cough, and abundant rusty sputum. Previous history of frequent attacks of bronchitis, and also of a recurrent sensitization dermatitis of arms and legs.

Examination : On admission sharply ill, dyspnoeic and cyanosed. Intense pneumonic consolidation of whole of right lung. B.P. 115/60.
Type II pneumococci isolated from sputum. Blood culture negative.
Total leucocyte count on admission was only 12,600 per c.mm. and "Group I" cells numbered 19 per cent.
Total plasma protein not unduly low; plasma albumen, however, was only 3.2 gm. per cent. (normal value is 4 gm. per cent.).

Progress : Recovery very slow. Pulse rate remained rapid throughout the illness. Allowed up on 48th day and discharged on 57th day. On discharge, pulse rate still rather rapid, and B.S.R. still high - 80 mm. at the end of the first hour; X-ray showed a considerable residual opacity.
One month after discharge the X-ray was much improved, although still far from clear; the plasma proteins had risen, the plasma albumen being 3.6 gm. per cent.

Note : The previous history of bronchitis, and of the allergic phenomena of asthma and dermatitis may have been factors in the extreme delay in resolution. The high pulse rate throughout the illness was a further notable feature.

CHART II

A. McA.
AGE 22.

DAY OF ILLNESS

4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53

M E M E M E M E M E M E M E M E M E M E M E M E M E M E

B.S.R 40/82

B.S.R 75/115

B.S.R. 100/105

B.S.R 80/113

SULPHATHIAZOLE 47gm.
12 6 6 6 6 6 5

ADMISSION BLOOD LEVEL = 0·0 mg %
24-HOUR BLOOD LEVEL = 4·5 mg %

DAY.	TOTAL W.B.C. (THOUS)	POLYS. (%)	GROUP I CELLS (%)	MONOS. (%)	PLASMA PROTEINS (gm %) TOTAL	ALBUMIN	GLOBULIN	FIBRIN.
ADMISSION.	12·6	86	19	3	6·12	3·2	2·4	0·5
4TH	12·3	74	16	8				
7TH	9·8	57	8	4				
10TH	10·6	66	9	3				
15TH	8·2	68	9	9				
28TH		70	10	5				

103 102 101 100 99 98 130 120 110 100 90 80 70 50 40 30 20

G.

Case 3. Example of delayed resolution in an atypical consolidation - simulating carcinoma.

D. Clark, aged 41 (see Chart III and X-ray plates : figs. XIIa to XIIc).

History : Admitted on the fourth day of illness. History of sudden onset with rigor, pain in left side of chest, cough and rusty sputum.

Examination: On admission, sharply ill, dyspnoeic, "gray" and toxic-looking. Consolidation of left lower lobe. Heart sounds of good quality. B.P. 120/60. Type XV pneumococci isolated from sputum. Blood culture negative. Total leucocyte count on admission was only 8,800 per c.mm., and "Group I" cells numbered 8 per cent. Plasma proteins rather low: total proteins 6.0 gm. per cent. Albumen 3.2 gm. per cent.

Progress : Four days after admission, the patient developed signs of fluid at his left base - a few cubic centimetres of clear sterile fluid were aspirated on three subsequent alternate days. The temperature continued to swing for many days and did not return to normal till after the 30th day, long after all signs of fluid had disappeared. A notable feature was that the patient complained of severe pain at his left base up to the 40th day. Allowed up on 52nd day, discharged on 60th day. B.S.R. on discharge still high - 30 mm. at the end of the first hour.

Note : The X-ray plates showed a rounded opacity at the left base which in the initial stages might well have been mistaken for a carcinoma. Subsequent plates, however, showed clearing and proved that the lesion was pneumonic.

CHART III

D. C.,
AGE 41
TYPE XV.

DAY OF ILLNESS

4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53

M E M E M E M E M E M E M E M E M E M E M E M E M E M E

B.S.R. 18/32

B.S.R 54/110

B.S.R 50/79

B.S.R 30/40.

SULPHATHIAZOLE 53 gm.

7 6 6 6 6 6 6 6 4

ADMISSION BLOOD LEVEL = 0·0 mg %

24 HOUR BLOOD LEVEL = 4·5 mg %

DAY.	TOTAL W.B.C. (THOUS.)	POLYS. (%)	GROUP I CELLS. (%)	MONOS (%)	PLASMA PROTEINS (gm %)			
					TOTAL	ALBUMIN	GLOBULIN	FIBRIN.
ADMISSION.	8·8	92	8	0	6·0	3·2	2·4	0·35
4TH	13·0	80	8	9				
7TH	11·2	83	5	5				
16TH	9·2	77	7	4				

104 103 102 101 100 99 98 130 120 110 100 90 80 70 50 40 30 20

G.

Case 4. Atelectasis complicating pneumonia and resulting in delayed resolution

W. Young, aged 64 (see Chart IV and X-ray plates : figs. XIIIa to XIIId).

History : Admitted on the fourth day of illness. History of sudden onset with rigor and pain in right side of chest. No previous illnesses.

Examination: On admission, sharply ill, "gray" and toxic looking. Intense consolidation of whole of right lung. Heart sounds soft at all areas and second pulmonic sound of poor tone. B.P. 120/60. Type II pneumococci isolated from sputum. Blood culture negative.
Total leucocyte count very low, 2,400 per c.mm. and "Group I" cells numbered 24 per cent.
Total plasma proteins 6.98 gm. per cent., plasma albumen 3.6 gm. per cent.

Progress : On 7th day after admission, while patient still receiving sulphathiazole, temperature rose again, and drug was stopped on the assumption that it might be drug fever. However, it continued to swing, and on the 24th day, patient had a rigor. Re-infection was diagnosed. Sulphathiazole was recommenced, temperature dropped abruptly and drug was stopped.
On 32nd day, patient developed a fibrinous pericarditis accompanied by haematuria. Very ill and collapsed. By this time marked shrinkage of whole of right chest had developed with massive collapse of right lung. Haematuria lasted two days, pericardial friction persisted for 10 days.
Recovery very slow. Discharged after 88 days in hospital and right lung still showed much collapse. B.S.R. on discharge 25 mm. (first hour reading). One month after discharge

CHART IV

DAY OF ILLNESS.

4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63

M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E

B.S.R. 40/70

B.S.R. 85/110

B.S.R. 20/66

B.S.R. 25/40

SULPHATHIAZOLE 50 gm.
12 6 6 6 6 6 6 2

ADMISSION BLOOD LEVEL = 0·0 mg%
24 HOUR BLOOD LEVEL = 6·0 mg%

SULPHATHIAZOLE 8 gm.

DAY	TOTAL W.B.C. (THOUS.)	POLYS. (%)	GROUP I CELLS. (%)	MONOS (%)
ADMISSION.	2·4	79	24	6
4TH	7·6	96	52	0
7TH	10·6	92	14	7
10TH	14·2	91	9	2
16TH	9·2	68	20	9
20TH	8·0	83	18	6
22ND	18·2	74	14	11
29TH	25·0	76	4	10
35TH	11·0	83	15	4

PLASMA PROTEINS (gm%)			
TOTAL	ALBUMIN	GLOBULIN	FIBRIN.
6·98	3·6	2·48	0·9

104 103 102 101 100 99 98 130 120 110 100 90 80 70 50 40 30 20.

W.Y.
AGE 64
TYPE II

G.

the X-ray showed considerable improvement; plasma proteins had risen - total plasma protein 8.0 gm. per cent., albumen 5.2 gm. per cent. B.S.R. had fallen to 10 mm.

Note : Massive collapse in this case undoubtedly prolonged resolution.

Case 5. Example of lack of response to chemotherapy - delayed resolution

J. McCoo, aged 42 (see Chart V and X-ray plates: figs. XlVa and XlVb).

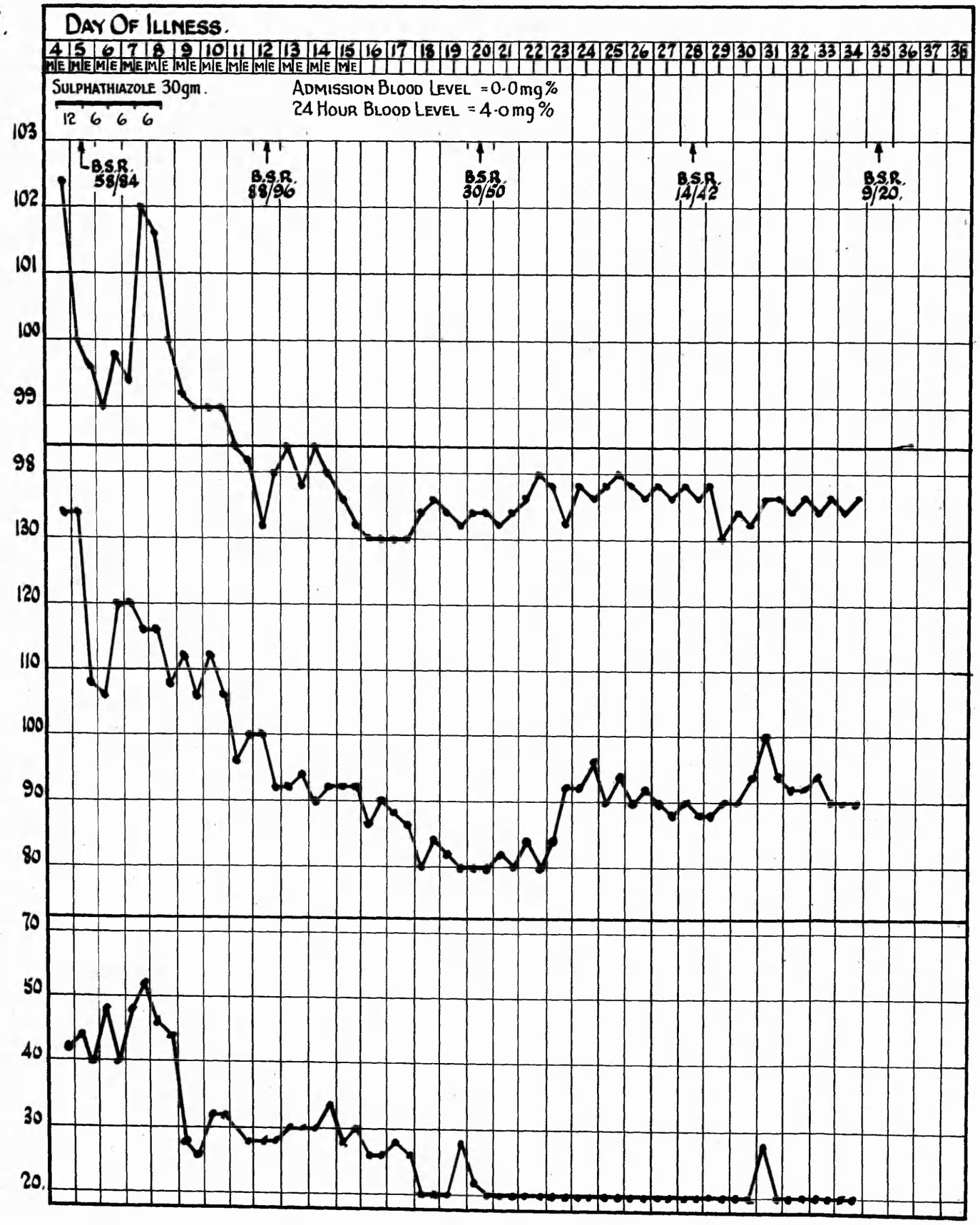
History : Admitted on the fourth day of illness. History of sudden onset with rigor and pain in right side of chest. No previous illnesses.

Examination : On admission sharply ill, very dyspnoeic. First heart sound at apex soft and second pulmonic of poor quality. B.P. 130/90. Type II pneumococcus isolated from the sputum. Blood culture negative. Total leucocyte count on admission only 10,100 per c.mm. and "Group I" cells numbered 51 per cent. Total plasma proteins 5.9 gm. per cent., albumen 3.2 gm. per cent.

Progress : On the seventh day, temperature rose again, and, as patient was not responding to sulphathiazole, this was discontinued. Thereafter, temperature, pulse and respirations rapidly returned to normal. Allowed up on 21st day; discharged on 34th day. B.S.R. on discharge 14 mm. (first hour reading).

Note : This case illustrates the occasional difficulty in diagnosing drug fever from the natural course of the disease.

CHART V.



J. MC. C.
AGE 42
TYPE II

DAY.	TOTAL W.B.C. (THOUSANDS)	POLYS (%)	GROUP I CELLS (%)	MONOS (%)	PLASMA PROTEINS (gm%)			
					TOTAL	ALBUMIN	GLOBULIN	FIBRIN.
ADMISSION.	10·0	99	51	0	5·9	3·2	1·9	0·8
4TH	17·2	82	11	5				
7TH	14·4	88	14	6				

CHAPTER V

THE BLOOD SEDIMENTATION RATE AND RESOLUTION

The erythrocyte sedimentation rate is an important index in assessing the activity of certain infections, e.g. rheumatic fever and tuberculosis, as it is well known that the figures remain high so long as the disease process remains active. My purpose in the present chapter is to investigate the course of the blood sedimentation rate (B.S.R.) in relation to the progress of resolution.

The B.S.R. was estimated in 55 of my cases - on admission, and every seventh day thereafter. The method employed was that of Westergren, and is described in Chapter I. The limits of normal were taken as a fall by the red cell column of up to 10 mm. by the end of the first hour, and up to 30 mm. at the end of two hours. These were the maximum outside limits accepted. (Average normal figures in healthy males vary from 2 to 5 mm. at the end of the first hour, and up to 20 mm. by the end of the second hour.)

In the series of cases, I found that there was an increase in the sedimentation rate of the erythrocytes during the acute illness, and, as the patient recovered, the reading gradually fell. It was observed that the figures reached normal at a variable period, and so it seemed reasonable to study not only the actual height of the B.S.R. in relation to the type of resolution, but

also the period of time required for the reading to return to normal.

(a) Time required for the B.S.R. to return to normal

This is depicted in Table 22 in relation to the progress of resolution. In 82 per cent. of the cases showing rapid resolution, the B.S.R. had returned to normal by the 21st day.

TABLE 22

Time required for B.S.R. to return to normal in respect of Resolution

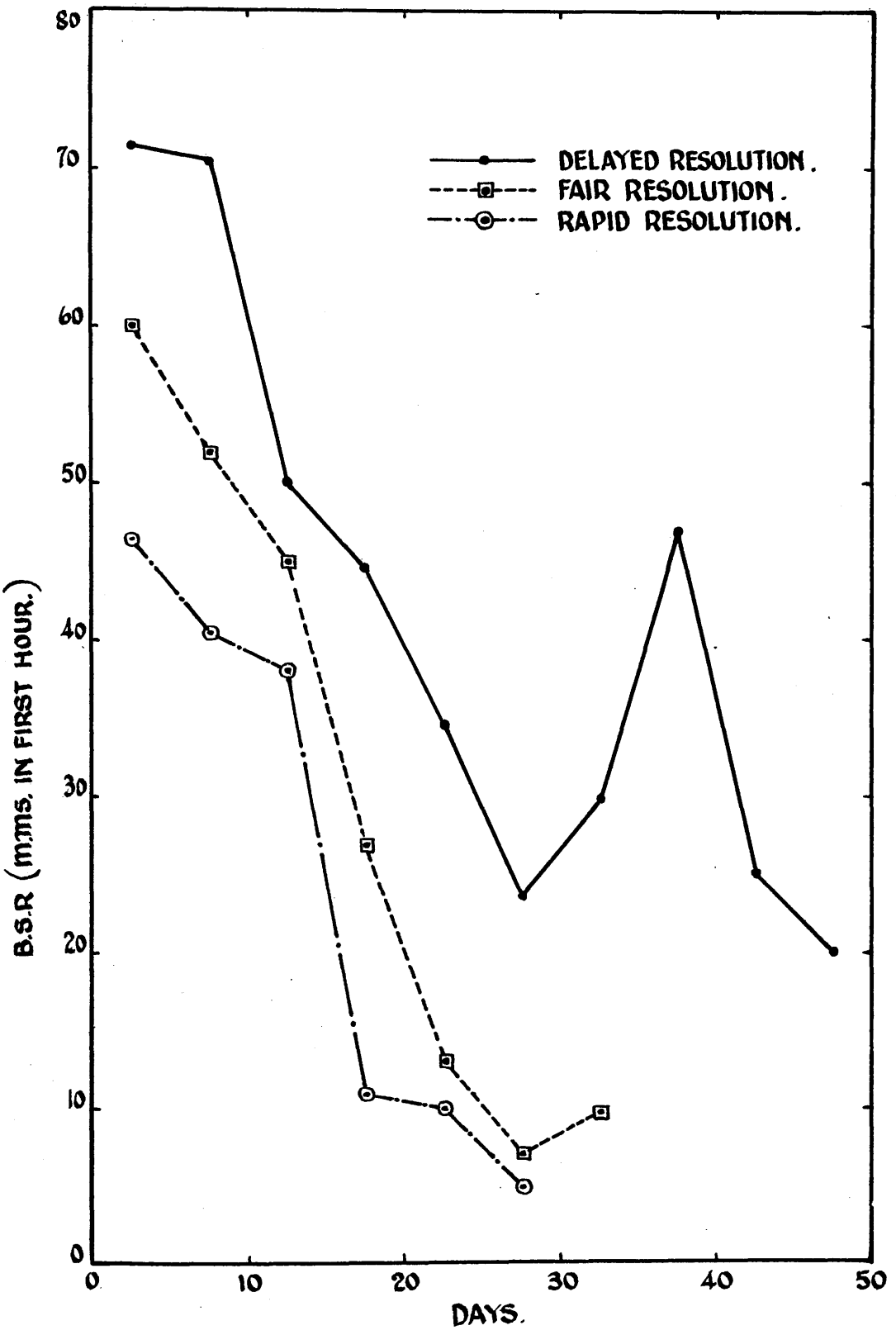
Time till B.S.R. back to normal (Days)	Resolution		
	Rapid	Fair	Delayed
- 21st day ..	18 (82)	3	-
21st - 35th ..	4	9	5
35 days and over	-	1	15 (75)
Totals ...	22	13	20

(The figures in brackets represent percentages of the group totals)

In fair resolution, the majority of cases required from 21 to 35 days to return to normal. In cases showing delayed resolution, the time required was longest: 75 per cent. of the cases in this group required more than 35 days before the sedimentation rate was normal.

GRAPH II

THE BLOOD SEDIMENTATION RATE AND RESOLUTION.



(b) The height of the B.S.R. on admission in respect of resolution

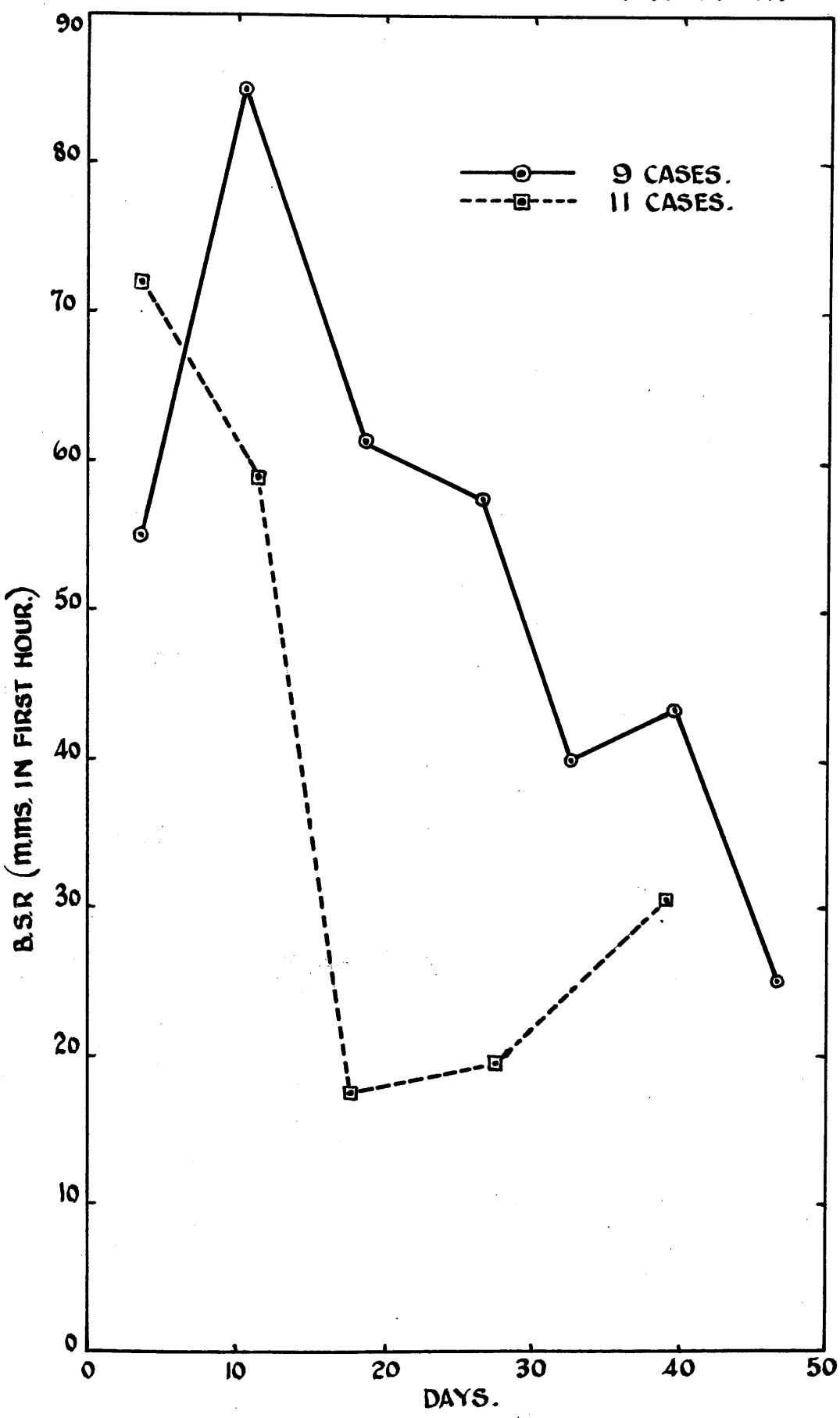
Graph II depicts the B.S.R. curves for cases of normal, fair, and delayed resolution, obtained by plotting the arithmetic mean of the B.S.R. reading at the end of the first hour against the day of illness. (The appendix to this chapter shows the individual B.S.R. levels.) It is seen that the curve for delayed resolution lies well to the right of the curves for rapid and fair resolution. Even at the 45th to 50th day, the reading in delayed resolution is still well above normal. Very few estimations were performed beyond the 50th day as, by that time, the patient was usually fit enough clinically for discharge from hospital, although radiographs frequently revealed considerable residual opacities. From Graph II, it would seem that the higher the initial reading the greater the likelihood of a slow recovery. Could then one single B.S.R. estimation on admission prognosticate the course of resolution? When I analysed the curve for delayed resolution more particularly, I found that it comprised two different curves which are depicted in Graph III.

(1) Curve "A" (9 cases). Here, the second reading plotted which is the average mean of the B.S.R.'s in the second week (8th to 14th days) was much higher than the first reading.

(2) Curve "B" (11 cases). The second reading was lower than the first, and the whole curve itself was below curve "A".

I found that the explanation of this seemed to lie in

GRAPH III


TWO TYPICAL CURVES IN DELAYED RESOLUTION.
9 CASES.
11 CASES.
B.S.R (MMS. IN FIRST HOUR.)
DAYS.
0
10
20
30
40
50
60
70
80
90

the fact that the cases in curve "A" had pyrexia lasting over seven days, while, in the cases comprising curve "B", the temperature had completely settled by the seventh day. Now, Table 23 shows that the initial B.S.R. bore no relation to the actual height of the temperature on admission. By estimating the B.S.R. daily during the acute illness in a few cases, I did find, however, that there was a progressive rise in the readings during the period of pyrexia.

TABLE 23

The B.S.R. in relation to temperature on admission

	Temperature on admission (degrees F.)					
	98-99	99-100	100-101	101-102	102-103	103-104
Number of cases	27	8	9	2	11	3
Average admission B.S.R.	60.2	81.2	59.4	70	18.6	75

Now in 1941, Fetter and Schnabel studied the effect of pyrexia on the B.S.R. They performed estimations in 41 patients receiving physically-induced fever in the hypertherm before, during and immediately after therapy. No significant variation was found between any of these readings and they concluded that physically-induced fever had no effect on the B.S.R. Again, in recent investigation on infective

hepatitis, Wood (1945) found no increase in the B.S.R. in this disease during the first 10 days, even although fever was present.

Pyrexia in itself, therefore, would appear to have little effect on the blood sedimentation rate. It must be remembered, however, that one of the main factors in producing an increase in sedimentation rate is the extensive destruction of body cells which occurs in infections and in toxic conditions, of which pyrexia is just a manifestation. While, therefore, the pneumonic process remains active, the B.S.R. will remain high, and a single estimation during the acute illness can be of little value.

B.S.R. and plasma proteins. Observers such as Hunt (1929) and Gram (1921) have claimed that the plasma contains a substance responsible for increased sedimentation rate, and it is generally accepted that fibrinogen is the fraction most concerned. Hunt, H.F. made fibrin determinations in 47 cases and correlated them with the B.S.R. He found a parallelism between increase in fibrin and increase in B.S.R. Gilligan (1934) however, claimed that there was more to this relationship than the fibrinogen content of the plasma and he explained it on the physico-chemical properties of plasma fibrinogen in respect of the effect on red cell aggregation.

In my series, I have been unable to find any

relationship between increase in fibrinogen and increase in B.S.R.

Clinical value of B.S.R. in pneumonia. I have shown that the time required for the B.S.R. to return to normal varies with the progress of resolution. I found that the most valuable B.S.R. reading was that taken on the 21st day. If, by that time, the reading were still above normal, then a certain degree of delayed resolution resulted. The clinical value of this lies in the fact that often, by the end of the third week, physical signs of consolidation have disappeared completely, although radiographs may still reveal considerable underlying opacity. X-ray facilities are not always immediately available, and, in their absence, a B.S.R. estimation is an excellent guide to the progress of resolution.

Moreover, I found, as shown from Table 24, that the height of the reading on the 21st day would prognosticate the degree of delay in resolution to be expected. Thus, if the reading lay between 10 mm. and 30 mm. at that time, a

TABLE 24

The B.S.R. at the end of the Third Week

	Total Cases	Limits of readings (mm. 1st hour)	Average reading (mm. 1st hour)
Rapid resolution .	22	5 - 10	7
Fair resolution ..	13	10 - 26	17
Delayed resolution	20	28 - 120	50

moderate delay in resolution resulted, but if the reading were

over 30 mm., then the delay was marked. Four of the cases with readings of over 100 mm. (1st hour) at the end of the third week showed a very marked delay in resolution, and, 4 to 5 months after admission to hospital, radiological examination still revealed opacities of varying intensity.

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APPENDIX

Individual B.S.R. Levels (in Millimetres)

Patient	Time of Estimation (in weeks)																Resolution
	1st		2nd		3rd		4th		5th		6th		7th		8th		8 +		
	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	
T.McQ.	50	70	1	4															RAPID
W.E.	57	90	2	10															
J.C.	85	115	15	30	8	24													
A.M.	66	104	2	6															
D.K.	11	27	6	14															
D.K.	38	68	3	15															
W.McC.	63	94	20	40	6	18													
J.S.	60	90	12	20	10	16													
W.K.	110	117	80	104	15	20													
E.W.	62	108	6	20															
J.L.	93	108	28	48	16	40													
J.L.	60	104	3	15															
R.T.	8	25	5	10															
D.K.	63	96	78	106	40	64	16	45											
R.T.	40	62	94	110	12	21													
W.T.	33	70	0	2															
F.L.	36	70	0	5															
A.Mc.	33	65	6	17															
D.E.	92	104	35	64	10	18													
J.D.	40	60	20	50	1	1													
C.McG.	80	100	8	23															
F.D.	75	90	92	103	28	44													
R.H.	110	120	36	104	13	28													FAIR
A.C.	35	50	28	54	11	30													
A.M.	20	45	10	42	6	20													
W.S.	50	76	60	95	55	84	20	34	5	10									
J.Mc.	76	98	18	38	14	34	8	36											
W.M.	85	100	50	64	22	36	12	28	11	18									
J.C.	60	68	24	42	10	35	9	20											
J.Y.	40	72	30	60	33	66	0	12											
W.S.	80	95	40	54	7	28													
J.M.	78	105			18	50	5	10											
R.T.	115	118			18	30	4	11											
S.C.	60	86			21	46	10	30											
A.C.	107	123			73	110	38	46	8	16									

APPENDIX (Contd.)

Patient	Time of Estimations (in weeks)																Resolution
	1st		2nd		3rd		4th		5th		6th		7th		8th		8+		
	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	
D.C.	18	32	34	62	54	110			50	79	30	40							DE-LAYED
W.Y.	80	100	105	116	40	70	85	110			20	66	25	40			10	28	
A.M.	40	82			75	115			100	100			80	113	75	106			
S.D.	50	80	56	86	30	70			28	58	20	50							
JMcC.	58	84	88	96	30	50	14	42	9	28									
J.C.	120	126	121	131	125	132	121	134	109	124	98	102							
J.C.	110	120	30	50	26	41	14	32											
D.K.	109	129			17	49	16	48											
F.O.	92	125	42	81	18	45	8	22											
R.W.	84	105	26	40	15	34	28	46	9	22									
H.C.	96	129	74	104			109	126	80	100	65	84							
M.K.	90	104	25	30			30	40			40	92			20	50			
R.C.	45	68					41	72	34	52	30	42							
A.M.	38	75			26	53	62	87	16	40	25	55							
M.C.	40	52	10	19	100	124					47	60							
J.C.	90	112	30	86	4	7			11	32									
J.D.	64	93			16	24	30	48	33	75	28	65	15	30					
D.G.	50	78							15	37	12	28	8	18					
W.C.	80	94	30	48	60	93			28	43									
T.W.	70	100	19	51	30	69			12	32									

CHAPTER VI

LEUCOCYTES AND RESOLUTION

Section (i) : Total Leucocyte Count.

Section (ii) : Differential Count.

Several observers have shown that leucocytes are actively phagocytic in pneumonia, and that they are intimately concerned with the destruction of the invading organisms. Further, as already stated, Opie has suggested that the autolysis of the alveolar exudate is accomplished by enzymes liberated from the leucocytes of the exudate. It thus seems of importance to study the leucocyte response in relation to the progress of resolution.

Total white cell counts and differential counts were performed, on admission to hospital, in 101 cases of my series. The methods employed are described in Chapter I. Subsequent total white cell counts and differential counts were performed every third day thereafter during the acute illness. In the great majority of cases, this comprised three estimations, namely, on the first day, the fourth day and the seventh day. In cases where pyrexia persisted after the seventh day, counts were continued until the temperature had returned to normal.

SECTION (i)

Total Leucocyte Count

Pneumococcal lobar pneumonia is typically associated with a leucocytosis, generally between 10,000 and 40,000 cells per c.mm. Cole (quoted by Heffron) in a series of 463 cases, found only 6 per cent. with a white cell count below 10,000, and only 8 per cent. with a count over 40,000. In my series, Table 25 shows that leucocytosis (a total white cell count over 10,000 per c.mm.) was present in 75 per cent. of the cases on admission, before commencement of chemotherapy.

TABLE 25

The Admission Leucocyte Count in respect of the Progress of Resolution

	Under 10,000 cells per c.mm.	10,000-20,000 cells per c.mm.	20,000-30,000 cells per c.mm.	30,000-40,000 cells per c.mm.	40,000-50,000 cells per c.mm.	Totals
Total cases	25	48	20	7	1	101
Rapid resolution	11	17	10	4	1	43
Fair resolution	3	14	6	-	-	23
Delayed resolution	11 (44)	17 (35.4)	4 (20)	3 (43)	-	35

(The figures in brackets represent percentages of the group total.)

Table 25 depicts the relation of the admission total white cell count to the progress of resolution. It is

seen that cases with counts between 20,000 and 30,000 cells per c.mm. showed the smallest percentage of delayed resolution. Of the 25 cases in my series with counts below 10,000 cells per c.mm., 44 per cent. developed delayed resolution. Now it has long been recognised that leucopenia is of serious prognostic significance as regards the fatality rate. In addition, Chatard (1910) has observed that in patients over thirty years of age and, especially in those over fifty, the leucocyte response may be less vigorous. Three of my cases had counts on admission below 5,000 cells per c.mm. and it is noteworthy that all three were over 40 years of age and subsequently showed very marked delay in resolution. In spite of the leucopenia they received chemotherapy and successive counts showed a progressive increase in the leucocytes. In no case did agranulocytosis develop.

Fleming, J. (1936) in a series of cases studied at the Royal Infirmary, Glasgow, has shown that the type of the infecting organism has an influence on the leucocyte count in lobar pneumonia. He demonstrated that a count of over 20,000 cells per c.mm., during the first three days of the illness, was characteristic of most cases of Type I or "Group IV" lobar pneumonia. In Type II and Type III infections, on the other hand, the leucocyte count was usually below this figure. Table 26 demonstrates that my results were very much in keeping with his findings.

TABLE 26

Admission Leucocyte Count in respect of Type of Infecting Organism

Type	Leucocytes (thousands) per c.mm.				
	-10	10-20	20-30	30-40	40-50
I	-	5	5	1	-
II	18	28	7	5	-
III	-	3	-	-	1
IV	7	12	8	1	-
Total Cases	25	48	20	7	1

Now, it has already been shown that Type II and Type III infections are responsible for the majority of cases of delayed resolution. Thus, these infections are associated both with low leucocyte counts and delay in resolution.

Another interesting observation from Table 25 is that three of the eight cases which had leucocyte counts of over 30,000 cells per c.mm. developed delayed resolution. This would seem to indicate that an unduly high leucocytosis may also be unfavourable in respect of the subsequent course of resolution. The explanation of this apparent paradox may be that overstimulation of the leucopoetic mechanism and leucopenia are possibly both manifestations of a poor defensive response. In one individual, lack of resistance will result in an overabundance of immature polymorphonuclear cells in the circulation, while, in another individual,

leucopenia may ensue.

SECTION (ii)

Differential Count

(a) Polymorphonuclear neutrophile count

During the acute illness there is an absolute and relative increase in the neutrophile polymorphonuclear cells. Table 27 shows the average absolute polymorphonuclear count, on admission to hospital, in relation to the progress of resolution. The average figure found in rapid resolution is only slightly above that for fair resolution, and the latter is also not significantly greater than the average figure in cases showing delayed resolution.

TABLE 27

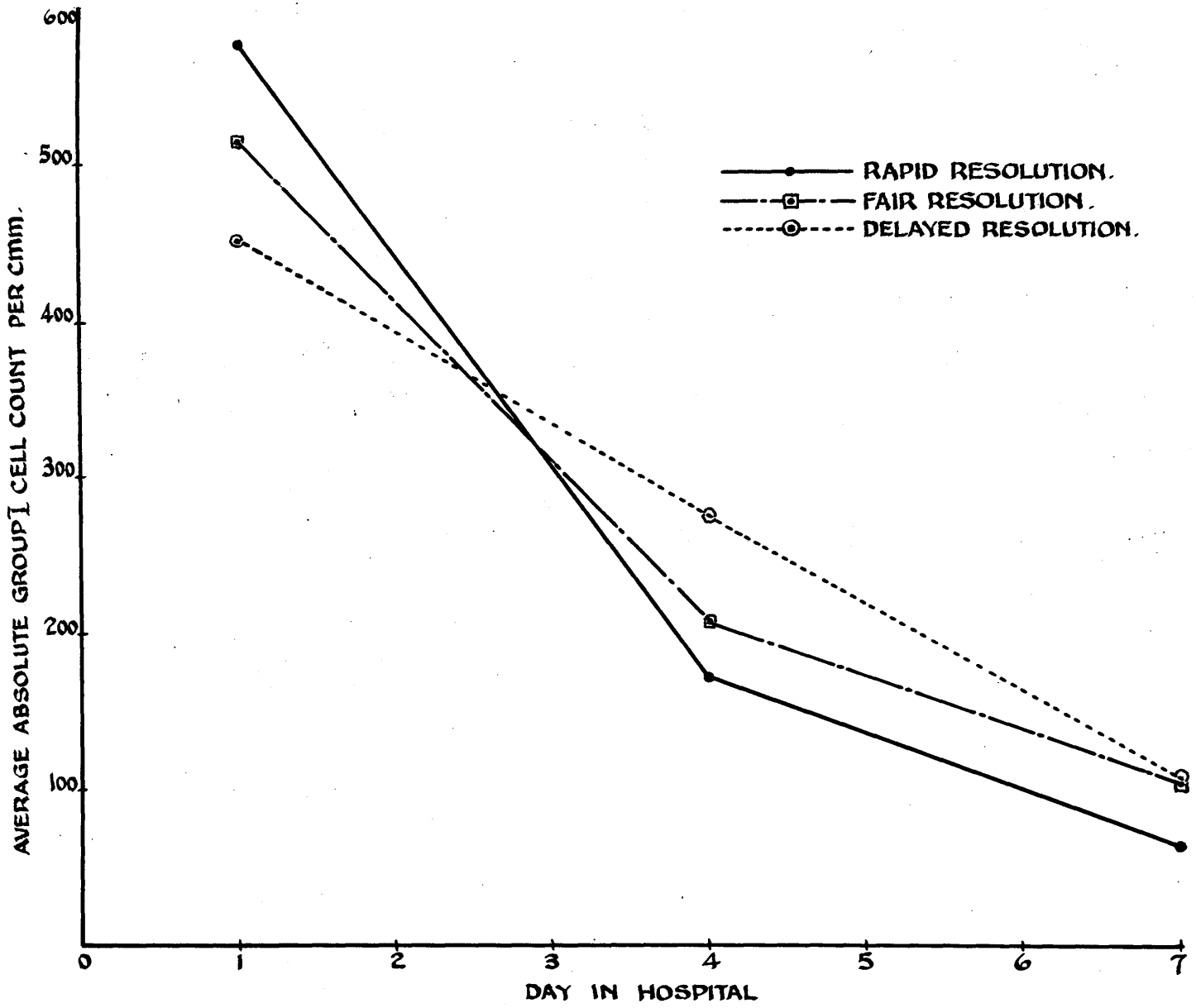
Admission Polymorphonuclear Count in respect of Resolution

	Rapid Resolution	Fair Resolution	Delayed Resolution
Total cases ..	43	23	35
Average absolute admission Polys. (per c.mm.)	15,918	13,873	12,408

Thus, there does not seem to be any significant relationship between the height of the polymorph count on admission and the progress of resolution.

FIG. 28.

ABSOLUTE "GROUP I" CELL COUNT IN RESPECT OF RESOLUTION.



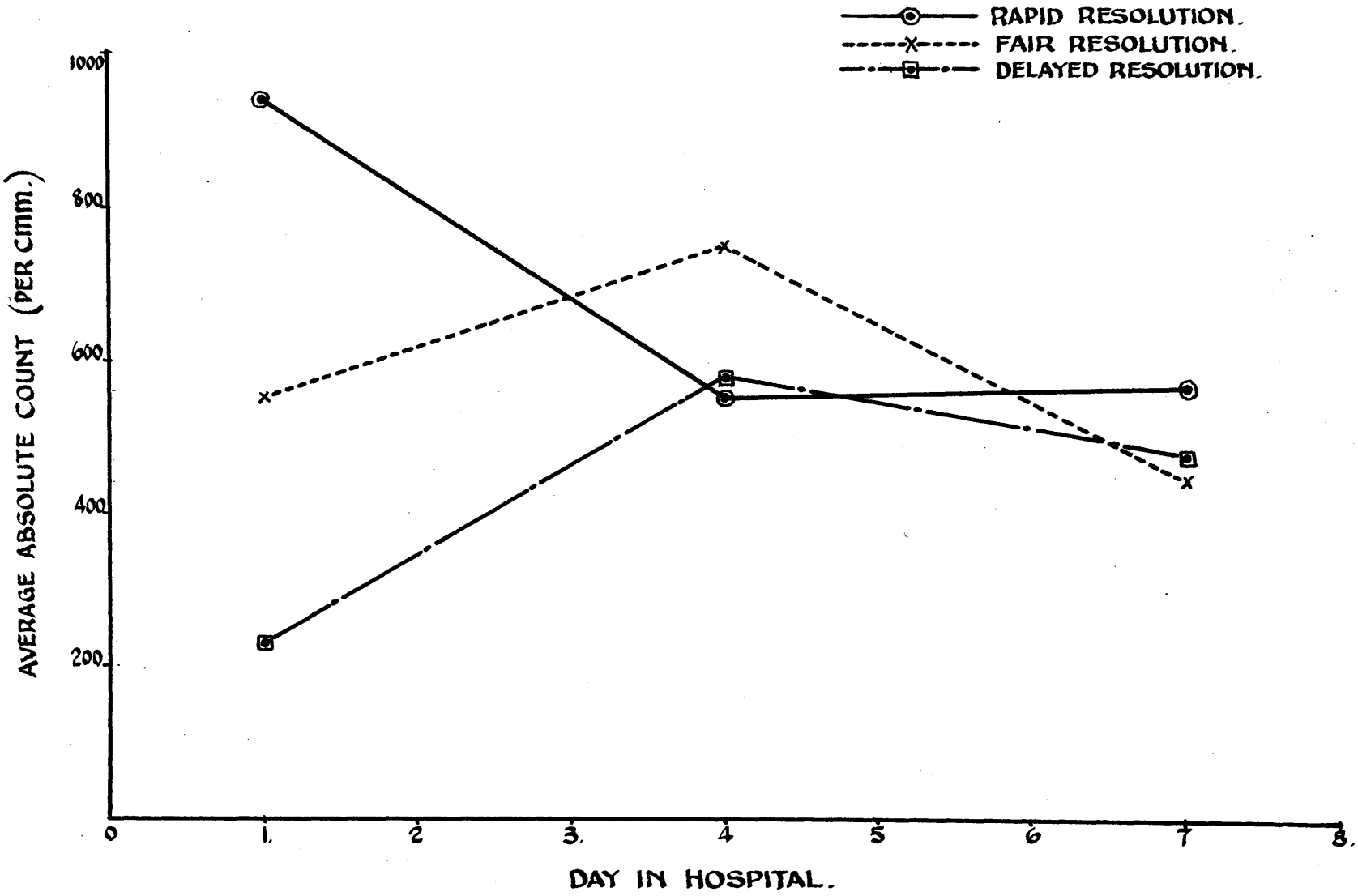
The presence of young forms of leucocytes is the rule in the acute stage of pneumonia. Myelocytes and band cells are the youngest forms of polymorphs, and Cooke, in a modification of the Arneth count, has grouped them together as "Group I" cells. From Fig.28 it is seen that the absolute "Group I" cell count on admission is highest in rapid resolution, but that it falls more quickly to normal levels than in fair or delayed resolution. From this it would appear that a high proportion of immature polymorphs is a normal phenomenon at the commencement of the illness. An explanation of the somewhat slower return of these cells to normal figures where resolution is delayed, may be that the infection is still latent and continues to provide a stimulus to the leucopoetic mechanism. It is interesting to note that I have only seen two cases (not included in this series) in which the absolute "Group I" cell percentage rose after the commencement of treatment - and both cases died. Here once again, therefore, overstimulation of the leucopoetic mechanism seems an unfavourable sign.

(b) Monocyte count.

Robertson and Uhley (1936) found that, in pneumonia during the process of resolution, a large number of mononuclear cells appeared in the alveolar exudate. They studied the post-mortem findings in forty cases and claimed that these cells were derived from the cells of the alveolar walls. They found as resolution progressed they

FIG. 29

ABSOLUTE MONOCYTE COUNT IN RESPECT OF RESOLUTION



increased, and gradually replaced the polymorphonuclear cells. Wherever a good macrophage reaction was present, pneumococci were few. Hickling (1927) has studied the relation of monocytes in the peripheral blood to pneumonia. He demonstrated that a monocytosis occurred which was greatest at the time of the crisis.

In the present series the relationship of the absolute blood monocyte count to the progress of resolution is depicted in Fig. 29. It is seen that in rapid resolution the initial count is high, and the figure falls in subsequent counts. In fair resolution, the absolute figures are fairly constant throughout. In delayed resolution the admission monocyte count is low, and the figure rises in subsequent counts.

From the above findings it would appear that a low initial monocyte count is associated with inhibition of resolution.

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CHAPTER VII

THE PLASMA PROTEINS AND RESOLUTION

Introduction.

Section (i) : Relation of total plasma proteins and individual fractions to the progress of resolution.

Section (ii) : Influence of certain factors on the plasma proteins.

Section (iii) : Cause of low plasma proteins in delayed resolution.

INTRODUCTION

In recent months there has been considerable investigation on the subject of shock and hypoproteinaemia. It has been found that low plasma proteins are a common finding in such conditions as burns, crush injuries, and injuries involving the soft tissues. Now, as the pneumonic process involves a great outpouring of plasma into the pulmonary alveoli, it seems relevant to study the relation of the blood plasma proteins to the progress of resolution.

I will first summarize some details about the plasma proteins. There are three main fractions - albumin, globulin and fibrinogen, all forming part of a single loosely-bound proteins system. It is generally accepted that the liver is the main site of origin of the plasma proteins. Plasma albumin and plasma fibrinogen seem to be formed exclusively in the liver: plasma globulin is formed mainly in the liver but also in the reticulo-endothelial system. The liver, as well as being the centre of production of the plasma proteins, is also the main storage depot, although many other tissues to a lesser extent hold reserves.

The normal albumin-globulin ratio is 1.6 to 1, and the normal limits of variation of the plasma proteins can be taken as:- total plasma proteins, 6.0 to 8.0 gm. per cent.;

albumin, 4.0 to 5.5 gm. per cent.; globulin, 1.6 to 3.0 gm. per cent.; fibrinogen, 0.2 to 0.4 gm. per cent. The plasma proteins have three chief functions :-

(1) They exert an osmotic pressure and thus control the interchange of fluid between blood and tissues.

(2) They play a part in regulating the acid-base equilibrium.

(3) The fibrinogen is necessary for the clotting of the blood.

Plasma protein estimations were performed in 53 of the cases of pneumonia on admission to hospital. As controls, the values of the plasma proteins were estimated in 33 healthy individuals who were obtained partly from the hospital staff, partly from pneumonia ex-patients and partly from blood donors. The methods employed are described in Chapter I - the refractometric technique for the total plasma proteins, and the biuret method for the individual fractions.

SECTION (i)

Relation of Total Plasma Proteins and Individual Fractions to the Progress of Resolution

(1) Total plasma proteins

Of the 25 cases showing rapid resolution, only three cases (12 per cent.) had total plasma proteins below 6.0 gm., whereas, of the 20 cases developing delayed resolution, 50 per cent. had values below 6.0 gm. Table 30 gives a broad distribution of the cases into two groups (values above 6.0 gm. were considered normal) and Table 30a shows a more detailed distribution. The individual plasma protein levels are given in Appendix A at the end of this chapter.

TABLE 30

Admission Total Plasma Proteins in respect of Resolution

	Total Cases	Total plasma proteins	
		Under 6.0 gm. per cent.	6.0 gm. per cent. and over
Controls	33	-	33
Rapid resolution	25	3	22
Fair resolution	8	6	2
Delayed resolution	20	10	10
TOTALS	53	19	34

Note:- "Totals" in Tables 30 to 33 exclude controls.

GRAPH IV.

FREQUENCY CURVE OF TOTAL PLASMA PROTEINS.

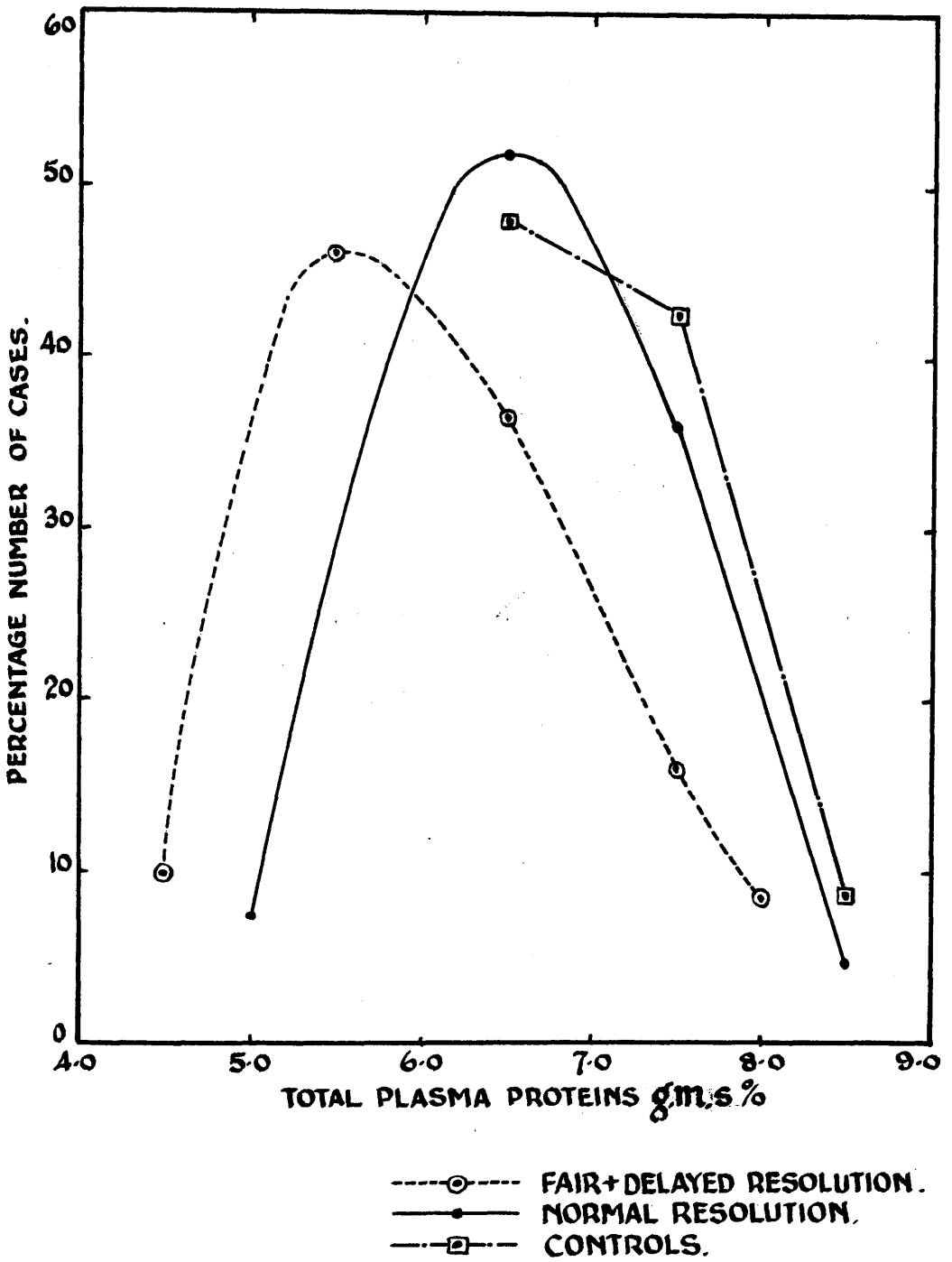

TABLE 30 a

Admission Total Plasma Proteins in respect of Resolution

	Total Cases	Total plasma proteins (grammes per cent.)				
		4.0-4.9	5.0-5.9	6.0-6.9	7.0-7.9	8.0-8.9
Controls ..	33	-	-	16	14	3
Rapid resolution	25	1	2	13	8	1
Fair resolution	8	-	6	1	-	1
Delayed resolution	20	2	8	9	1	-
Totals ..	53	3	16	23	9	2

Graph IV depicts the percentage frequency distribution of the total plasma proteins. As the cases of fair resolution were too few in number to be considered separately, they have been grouped with those showing delayed resolution in one curve. It is seen that this curve lies to the left of the curve for normal resolution and the curve for the control cases.

The arithmetic mean figures for the total plasma proteins in the various types of resolution and in the control cases were as follows:-

Control cases : 7.3 gm. per cent.
Rapid resolution : 6.7 gm. per cent.
Fair resolution : 6.0 gm. per cent.
Delayed resolution: 5.9 gm. per cent.

(2) Plasma albumen

Table 31 shows that only 28 per cent. of the cases

showing rapid resolution had plasma albumen levels below 4.0 gm., whereas 85 per cent. of the cases showing delayed resolution had values below this figure.

TABLE 31

Admission Plasma Albumen in respect of Resolution

	Total Cases	Plasma Albumen	
		- 4.0 gm. per cent.	4.0 + gm. per cent.
Controls	33	1	32
Rapid resolution.	25	7 (28)	18
Fair resolution .	8	5	3
Delayed resolution	20	17 (85)	3
TOTALS ...	53	29	24

(The figures in brackets represent percentages of the group totals).

The arithmetic mean figures for plasma albumen in the various types of resolution and in the control cases were as follows:-

Control cases : 4.85 gm. per cent.
Rapid resolution : 4.3 gm. per cent.
Fair resolution : 3.75 gm. per cent.
Delayed resolution: 3.45 gm. per cent.

(3) Plasma globulin

TABLE 32

Admission Plasma Globulin in respect of Resolution

	Total Cases	Plasma globulin		
		-1.6 gm. per cent.	1.6 - 3.0 gm. per cent.	3.0 + gm. per cent.
Controls ..	33	5	26	-
Rapid resolution .	25	6 (24)	15 (60)	4
Fair resolution .	8	3	5	-
Delayed resolution	20	4 (20)	12 (60)	4
TOTALS .	53	13	32	8

(The figures in brackets represent percentages of the group totals.)

It is seen that, for plasma globulin, the percentage of cases showing low values (below 1.6 gm.) shows no statistically significant difference between rapid and delayed resolution. Eight cases had values above normal, but again these cases were distributed evenly between delayed and rapid resolution.

(4) Plasma fibrinogen

The figures for plasma fibrinogen were above normal (that is, 0.5 gm.) in 62 per cent. of the total series of cases.

TABLE 33

Admission Plasma Fibrinogen in respect of Resolution

	Total Cases	Plasma fibrinogen	
		- 0.5 gm. per cent.	0.5 + gm. per cent.
Controls	33	33	-
Rapid resolution	25	9	16 (64)
Fair resolution .	8	3	5
Delayed resolution	20	8	12 (60)
TOTALS	53	20	33 (62)

(The figures in brackets represent percentages of the group totals.)

There was, however, no significant difference between this increase in delayed and normal resolution. The values for the controls all lay below 0.5 gm. per cent. The increase in fibrinogen had, therefore, no effect on the course of resolution. Now, in diseases accompanied by a leucocytosis, Pfeiffer (quoted by Hunt) found an increase in fibrin. In the present series, however, I was unable to find any correlation between the degree of leucocytosis and the plasma fibrinogen values.

Discussion

In 1931, Kumpf performed plasma protein estimations in 13 cases of lobar pneumonia, using both the refractometric method and the micro-Kjeldhal method. He found that in

all but one case the total plasma proteins were lowered, and the values given by refractometry tended to be higher than the micro-Kjeldhal. Further, he found that when the plasma albumen alone was studied this reduction was more striking. The plasma globulin showed a decided increase in most of the cases.

My findings in the present larger series are in agreement with those of Kumpf. In respect of the progress of resolution, it is seen that in cases showing rapid resolution, the fall in both total plasma proteins and in plasma albumen does not generally drop below the limits of normal variation. In cases developing delayed resolution, however, a considerable proportion have values below normal.

It now remains to discover in what way low plasma proteins are related to delay in resolution. In the next section, therefore, I shall correlate hypoproteinaemia with the factors already shown to be intimately concerned with the incidence of delayed resolution. Further, the question arises as to why the decrease in plasma proteins should be due to a fall in the albumen fraction? In answering this question I shall try to find an explanation for low plasma albumen which will at the same time explain the accompanying delay in resolution.

SECTION (ii)

The Influence of Certain Factors on the Plasma Protein Level

In Table 34 I have correlated low plasma proteins with the factors which were found to be concerned in the incidence of delayed resolution.

TABLE 34

The Incidence of Low Plasma Proteins in Pneumonia

	Age		Density of Consolidation		Bacteriaemia		Duration in days ill prior to admission		Type of infecting organism			
	- 40 yrs.	40 + yrs.	"III"	"II"	Pos.	Neg.	- 4	4+	I	II	III	"Gp. IV"
Total series	20	33	31	22	3	50	32	32	4	30	2	17
Total plasma proteins -6 gm. per cent	5 (25)	14 (42.4)	14 (45)	5 (22.7)	-	19	11 (34.3)	8 (38)	2	12 (40)	-	5 (29)

(The figures in brackets are percentages of the group totals.)

An analysis of the figures in Table 34 suggests the following conclusions.

(a) Age. The importance of the age of the patient is manifest, as the incidence of hypoproteinaemia in those over 40 years is almost double that under this age.

From this we may conclude either (1) that older people do have lower plasma proteins physiologically or (2) that pneumonia as an infection causes greater depletion of the plasma proteins in older people.

Now, several investigators have studied the relation of age to plasma proteins (Trevorrow and others, 1941) and have shown that age has no effect on the plasma protein level. Hence, it may be concluded that pneumonia, itself, causes greater depletion of plasma proteins in older people.

(b) Density of consolidation. The more dense the consolidation the greater the percentage of cases with hypoproteinaemia. This will be discussed more fully in relation to cause of low plasma proteins.

(c) Bacteriaemia. The number of bacteriaemic cases was too small to be significant, but it is curious that none of the cases with positive blood cultures had hypoproteinaemia.

(d) Days ill prior to admission. Of the cases under four days ill prior to admission, 34.3 per cent. had low plasma proteins, whereas of the cases over four days ill prior to admission, 38 per cent. had low plasma proteins. There is no significant difference between these figures.

(e) Type of infecting organism. Here again, the numbers are small. We can say, however, that Type II infections show a higher percentage of low plasma proteins than "Group IV". The finding of normal plasma proteins in the two cases of Type III infection may be explained by the fact that both these cases

occurred in patients under 45 years of age, and both showed rapid resolution. It is known that when Type III is the infecting organism in younger individuals, the illness is usually mild in contrast to the severe illness which a Type III organism produces in the older individual.

Once again then the importance of the age of the patient is evident. In addition, the density of the consolidation is of considerable moment in the incidence of hypoproteinaemia. It is to be remembered that these same two factors, namely, the age of the patient and the density of the consolidation were also the most important factors in the occurrence of delayed resolution. It seems reasonable, therefore, to conclude that low admission plasma proteins are in some way intimately concerned with delayed resolution.

SECTION (iii)

What is the cause of the low plasma proteins? Here, I wish to discuss four possible explanations.

(1) Loss of plasma in the exudate

It is reasonable to assume that the more dense the pneumonic opacity, the greater will be the outpouring of serum into the alveoli with a corresponding withdrawal of plasma from the blood stream. And indeed, the findings in Table 35 show that intense consolidations are associated with a high proportion of low plasma proteins.

TABLE 35

Admission Plasma Proteins in respect of Density of Opacity

	Total plasma proteins		Plasma albumen		Plasma Globulin		Plasma Fibrinogen	
	-6.0 gm. per cent.	6.0+ gm. per cent.	-4.0 gm. per cent.	4.0+ gm. per cent.	-1.6 gm. per cent.	1.6+ gm. per cent.	-0.5 gm. per cent.	0.5 + gm. per cent.
Total series ..	19	34	32	21	13	40	23	30
Cases with opacity of Density "III" ..	14 (74)	17 (50)	22 (66.6)	9 (43)	10 (77)	20 (50)	11 (48)	18 (60)

(The figures in brackets are percentages of the group totals.)

In the first three columns, namely total plasma proteins, plasma albumen, and plasma globulin, there are a greater percentage of cases showing an opacity of density

"III" where the values are below the normal limits. Now, I have already shown that the density of the consolidation is one factor in the incidence of delayed resolution. However, merely to attribute the low plasma proteins found in delayed resolution to outpouring of exudate into the alveoli would fail to explain why it is the albumen fraction which is reduced in delayed resolution, as the various fractions should be affected to an equal extent. In addition it would also fail to explain why age, which is intimately related to hyprproteinaemia and delayed resolution, bears no relation to the density of the opacity.

(2) Nutrition

Much work has been done recently on the relation of diet to the plasma protein level and it has been shown that an adequate intake of animal protein is essential for their maintenance. Figures from the Ministry of Labour survey show that the average consumption of animal protein in working-class families had fallen from 40 gm. daily per head in 1937-38, to 29 gm. in 1941, and 33 gm. in 1943. Attempts have also been made recently to determine the effects of single amino-acid deficiencies, and it has been shown by Harris, Neuberger and Sanger (1943) that lysine, which is mainly derived from animal protein, is essential for the maintenance of serum proteins.

It may be, therefore, that deficient dietary has caused

low natural plasma proteins, and that the increase in delayed resolution, which has occurred since the introduction of chemotherapy, may be related as much to a wartime dietetic insufficiency of animal proteins as to chemotherapy which has happened to coincide very broadly with this period. In twelve of my cases who had low plasma proteins on admission and who developed delayed resolution, a subsequent estimation was performed one month after discharge from hospital. As seen from Appendix B, the values of the total plasma proteins and of plasma albumen had risen by then well above the normal minimum except in one patient who suffered from alcoholic cirrhosis of the liver which would be very likely to confuse the findings. The rise in plasma proteins might be explained by the fact that these cases had a more adequate diet while in hospital which was continued by attentive relatives in their convalescence at home.

The supposition that deficient dietary in itself might be responsible for low plasma proteins and delayed resolution has many attractions. Several observers have shown that races having a high protein intake, particularly of animal proteins, are more virile and of better physique than those with a low animal protein intake. It is also well known that malnutrition predisposes to infection, as demonstrated, for instance, in marasmic infants and again in the incidence of tuberculosis. Indeed, it seems likely that resistance to infection is related in some way to the

plasma proteins. If this be so, then in any individual with low natural plasma proteins as a result of deficient dietary, the response of the defensive mechanism to invasion with the pneumococcus would be inadequate, and delay in resolution might well result.

But again, this does not explain why it is chiefly the albumen fraction which is reduced in delayed resolution, as nutrition would affect the various fractions to an equal extent.

(3) Hepatic dysfunction

It is generally agreed that the liver is the main site of origin of the plasma proteins. The albumen seems to be formed only in the liver, whereas some globulin is produced by the reticulo-endothelial system in addition to the liver. Thus, an overwhelming toxaemia from a severe infection might well damage the liver and bring about mal-production of the plasma proteins, and the fraction chiefly affected would be the plasma albumen. It has indeed been shown that diseases of the liver such as infective hepatitis do produce this result. It may be then that low plasma proteins in pneumonia reflect the extent of the liver damage caused by the infection. In addition, the fact that the age of the patient is such an important factor in the incidence of delayed resolution and in hypoproteinaemia might find an explanation in the degeneration of liver cells, which accompanies advancing years.

(4) "Oligaemic shock"

D.P. Cuthbertson (1944) and other investigators in studying the relation of hypoproteinaemia to burns and trauma have shown that in these conditions there is a loss of blood and/or plasma to the tissue spaces accompanied by reduced blood volume and "oligaemic shock". The clinical picture in pneumonia is comparable, due to the great outpouring of plasma from the blood stream into the alveoli. Some of the typical signs of dehydration and reduced blood volume are manifest in a sharply ill case of pneumonia, for example, the dry, coated tongue and the rapid, feeble pulse. During this period of "shock" the blood flow to the organs is impaired, and, in severe cases, this results in albuminuria, myocarditis, and, if the liver is affected, jaundice. In addition, in a severe case of pneumonia there is considerable toxaemia. This toxaemia will affect the capillaries rendering them more permeable. Now, as I have already stated, the albumen is the fraction of the plasma protein having the smallest molecular weight, and it will pass through the damaged capillaries more readily, and this may explain why it is the albumen fraction which is reduced in delayed resolution. Again, on account of its smaller molecular weight, it is the albumen portion which exerts the greatest osmotic pressure. Normally, the osmotic pressure of the plasma proteins tends to attract water from tissues to blood and this is counter-balanced by the filtration pressure exerted by the blood pressure which tends to draw

water from blood to tissues. Now, where there is a marked fall in the albumen one might expect to find oedema clinically. Some of my cases had plasma albumen levels as low as 2.0 gm. per cent. and yet there was no evidence of oedema. What is the reason for this? It may readily be explained by the "shock" theory, for, in these toxic cases, there is a reduction in blood volume with a resulting fall in blood pressure. Thus it is that a fall in plasma proteins is counterbalanced by a fall in blood pressure, and no oedema results.

Now, if low plasma proteins are due to oligaemic shock, may not delay in resolution be related to this also? The best way of estimating the degree of shock is by assessing the condition of the cardio-vascular system. Thus, in the next chapter I will discuss the progress of resolution in relation to the circulation.

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APPENDIX A

Admission Plasma Protein Levels

Patient	Age	Type of Organism	Admission Plasma Proteins				Resolution
			Total Plasma Proteins	Plasma Albumen	Plasma Globulin	Plasma Fibrinogen	
W.Mc.	17	II	6.98	4.2	2.08	0.7	RAPID Resoln.
A.M.	17	II	5.6	3.2	1.75	0.65	,,
R.P.	18	"Group IV"	6.25	3.4	2.15	0.7	,,
W.E.	18	"Group IV"	7.0	4.0	2.25	0.75	,,
D.E.	19	II	7.63	4.2	2.83	0.6	,,
J.C.	20	II	6.25	4.4	1.3	0.55	,,
F.L.	21	II	6.55	3.8	2.45	0.3	,,
A.P.	22	I	6.98	4.6	1.93	0.45	,,
A.M.	24	II	4.5	2.4	1.7	0.4	,,
J.L.	28	III	7.25	3.8	2.8	0.6	,,
R.T.	29	"Group IV"	6.0	3.8	1.3	0.9	,,
W.C.	33	"Group IV"	9.14	5.2	3.19	0.75	,,
N.M.	34	"Group IV"	6.5	4.4	1.15	0.95	,,
R.T.	30	II	5.25	4.0	1.0	0.25	,,
W.Mc.	35	II	6.25	4.25	1.55	0.45	,,
W.T.	36	II	6.25	3.6	2.15	0.5	,,
W.E.	38	II	6.5	4.4	1.7	0.4	,,
D.Mc.	42	"Group IV"	6.98	3.2	3.35	0.45	,,
F.D.	43	II	6.9	3.2	3.3	0.45	,,
H.S.	45	"Group IV"	7.2	4.5	1.8	0.9	,,
J.L.	45	"Group IV"	7.5	4.8	1.4	1.3	,,
E.W.	46	III	6.55	4.4	1.75	0.4	,,
J.Mc.	47	II	7.5	4.5	1.6	1.4	,,
D.K.	51	II	7.42	4.0	2.5	0.9	,,
W.C.	64	II	7.85	3.4	3.2	1.25	,,
S.L.	33	I	5.75	3.6	1.55	0.6	FAIR Resoln.
W.S.	40	"GroupIV"	5.25	4.4	0.3	0.55	,,
J.C.	42	II	5.25	3.2	1.63	0.42	,,
T.K.	49	"GroupIV"	6.55	2.4	3.65	0.5	,,
W.S.	52	II	6.34	4.2	1.68	0.45	,,
A.C.	52	"Group IV"	5.7	3.4	1.85	0.5	,,
J.Y.	59	II	5.75	3.6	1.85	0.3	,,
J.J.	75	II	5.0	2.8	1.1	1.1	,,

APPENDIX A (Contd.)

Patient	Age	Type of Organism	Admission Plasma Proteins				Resolution
			Total Plasma Proteins	Plasma Albumen	Plasma Globulin	Plasma Fibrinogen	
A.M^{c}.	22	II	6.12	3.2	2.42	0.5	DELAYED Resol^{n}.
D.H.	35	I	5.25	2.4	2.25	0.6	,,
D.C.	41	"Group IV"	6.0	3.2	2.45	0.35	,,
J.M^{c}.	42	II	5.9	3.2	1.9	0.8	,,
J.Q.	43	I	7.63	4.5	2.63	0.5	,,
J.B.	45	II	5.25	3.2	1.4	0.65	,,
J.J.	47	II	5.25	3.2	1.7	0.35	,,
T.M^{c}.	47	" Group IV"	5.5	3.4	1.75	0.35	,,
T.P.	49	II	4.5	3.4	0.7	0.4	,,
J.C.	50	II	5.5	3.0	2.2	0.3	,,
M.K.	50	II	6.0	3.6	1.5	0.9	,,
M.C.	52	II	6.75	3.6	2.85	0.3	,,
R.S.	57	"Group IV"	6.5	4.2	1.75	0.55	,,
J.B.	61	"Group IV"	6.77	3.4	3.05	0.32	,,
S.D.	61	II	6.0	3.2	2.15	0.65	,,
J.C.	61	II	5.75	2.0	3.35	0.4	,,
W.Y.	64	II	6.98	3.6	2.48	0.9	,,
F.O.	65	"Group IV"	6.0	3.1	2.5	0.4	,,
D.G.	65	II	6.28	4.0	1.4	0.85	,,
T.W.	70	"Group IV"	4.0	2.2	1.55	0.25	,,

APPENDIX B

Comparison of Plasma Proteins on Admission and after Discharge

Patient	Total Plasma Protein		Plasma Albumen		Plasma Globulin		Plasma Fibrinogen	
	Admission	After Discharge	Admission	After Discharge	Admission	After Discharge	Admission	After Discharge
D.C.	6.0	7.42	3.2	5.0	2.45	2.17	0.35	0.25
J.B.	5.25	6.0	3.2	4.8	1.7	0.8	0.35	0.4
A.Mc.	5.6	8.06	3.2	4.8	1.75	2.86	0.65	0.4
A.C.	5.7	8.06	3.4	5.2	1.85	2.51	0.5	0.35
D.A.	5.25	6.5	2.4	4.4	2.25	1.65	0.6	0.45
J.J.	5.25	7.45	3.2	5.0	1.7	2.07	0.3	0.35
J.M.	8.06	7.2	4.4	4.4	2.81	2.45	0.85	0.35
W.S.	5.25	7.63	4.4	4.8	0.3	2.48	0.55	0.35
W.E.	6.5	7.42	4.4	4.5	1.7	2.52	0.4	0.3
M.C.	6.75	7.85	3.6	4.8	2.85	2.75	0.3	0.3
W.Y.	5.68	8.0	3.6	5.2	2.78	2.4	0.5	0.4
J.Mc.	6.12	7.42	3.2	3.6	2.42	3.32	0.5	0.5

CHAPTER VIII

THE CIRCULATION AND RESOLUTION

Section (i) : Cardio-Vascular Involvement in Pneumonia.

Section (ii) : The Relation of Cardio-Vascular Involvement to the Progress of Resolution.

It is well known that the circulatory system is often affected in pneumonia. In Section (i) of this chapter, the various manifestations of this involvement as it affects the pulse, the blood pressure, and the heart, will be reviewed. In Section (ii) these will be further investigated in respect of the progress of resolution.

SECTION (i)

Cardio-vascular Involvement in Pneumonia

During the febrile period in pneumonia one expects a rise in pulse rate. A gradually increasing rate is, however, usually of serious prognostic significance. Observers such as Chatard and Cole (both quoted by Heffron) have demonstrated that cases in which the maximum pulse rate is 120 or under have a better prognosis than others in which the rate exceeds this figure. The following table from Cole shows that, in his series of cases, the fatality rate increased sharply as the maximum pulse rate increased.

TABLE 36
(from Cole)

The Pulse Rate in Pneumonia

Maximum Pulse rate per minute	Number of Cases	Deaths	
		Number	Per cent.
Under 100 ..	28	-	-
100 - 110 ..	89	1	1.1
110 - 120 ..	114	6	5.3
120 - 130 ..	206	24	11.7
130 - 140 ..	139	28	20.1
140 - 150 ..	108	55	50.9
150 - 160 ..	41	19	46.3
160 and over.	43	27	62.8
TOTAL ..	768		

In regard to the blood pressure in pneumonia, the results of reported studies show little uniformity and vary from case to case. It seems that sudden changes of blood pressure are more important than any single absolute pressure. There is general agreement that a rapid fall in blood pressure, if associated with a persistently rapid pulse, is of bad omen.

Signs of cardiac involvement are frequently elicited. Systolic murmurs, apparently functional in origin, may appear during the course of the disease and disappear in convalescence. These are claimed to be due to dilatation of the heart but this cannot often be demonstrated - Davies,

Hodgson and Whitby, in their series of 119 cases, found only 3 cases with cardiac enlargement on radiographic examination. Again, the first heart sound may become soft and approach the second sound in quality - another unfavourable omen. The pulmonic sound may be accentuated due to back pressure obstructing the pulmonary circulation and a lessening of its intensity may indicate a failing heart. Auricular fibrillation occasionally occurs during the height of the disease. A survey of 1,456 cases by Cohn and Lewis (1935) at the Hospital of the Rockefeller Institute for Medical Research showed that auricular fibrillation occurred in 37 cases, or 2.5 per cent.

In 1915, Porter and Newburgh showed that the heart muscle is not functionally impaired in pneumonia. They perfused the hearts of dogs which had died from pneumonia with normal dog blood and showed that they contracted normally. Several observers since then have claimed that circulatory failure in pneumonia is essentially not a failure of the central but of the peripheral circulation. Warfield considered that when bacteria invade the body they produce certain histamine substances which cause capillary dilatation. In addition, the toxic products of the bacteria acting on the capillaries cause an increase in their permeability. Thus, the condition of "shock" is produced. There is vascular stasis and decreased blood volume, lowered blood chlorides, haemoconcentration, and a fall in arterial blood pressure. The heart beats rapidly

to keep up the minute blood volume, and, according to Warfield, at first it becomes smaller in size because it is not stretched during diastole. Dilatation of the heart only occurs secondarily - the coronary arteries, which are the blood supply of the heart, fill during diastole, and, when the heart beats rapidly, the coronaries receive less blood. The heart will, therefore, receive less oxygen and dilatation will then ensue.

(It is of interest here to consider the treatment of auricular fibrillation in pneumonia. There are various supporters for and against digitalis therapy. On the one hand, it is claimed that the condition is due to toxaemia, and that since digitalis has no effect on the toxic heart, there is thus no therapeutic indication for its use. On the other hand, one might argue that if anoxaemia of the heart muscle is the basis of auricular fibrillation, then by slowing conduction of the cardiac impulse with digitalis, the coronaries should fill more efficiently. As a result, the heart will receive a better blood supply and auricular fibrillation will disappear. In my series of cases, only three developed auricular fibrillation. They were rapidly digitalized with digitalis leaf (2 gm. every 6 hours) and, in three to four days, normal rhythm was resumed in each case.)

SECTION (ii)

The Relation of Cardio-Vascular Involvement to the Progress of Resolution

(a) Pulse rate in relation to resolution

Here the maximum pulse rate during the first 24 hours was chosen, excluding the first pulse rate which may be unduly raised from the excitement of admission to hospital. In Table 37, I have grouped the cases according to whether the rate was above or below 110 beats per minute. This gave approximately an equal number of cases in both groups. It is seen that a higher percentage of cases with a high pulse rate developed delayed resolution.

TABLE 37

The Pulse Rate in respect of Resolution

Pulse rate on admission	Total Cases	Rapid Resolution	Fair Resolution	Delayed Resolution
Under 110 beats per minute ..	72	35	17	20 (27.8)
110 beats per minute and over .	76	26	17	33 (43.4)

(The figures in brackets are percentages of the group total)

(b) Cardiac lesions and resolution

The term myocarditis, used in Table 38, includes

cases which displayed soft heart sounds, a shortening of the first sound and approach to the second in quality, or a marked lessening in intensity of the second pulmonic sound. It is seen that none of the 13 cases with myocarditis nor the three cases with transient auricular fibrillation showed rapid resolution. The percentage of delayed resolution in these cases was very high.

TABLE 38

Cardiac Lesions and Resolution

	Total Cases	Resolution		
		Rapid	Fair	Delayed
Myocarditis ..	13	-	2	10
Auricular fibrillation	3	-	-	3

(c) Blood pressure and resolution

Blood pressure estimations were performed on admission to hospital in only 76 cases in my series as I did not realize the possible significance of the blood pressure till the latter part of my study. Of these cases, 67 were uncomplicated by empyema, sterile effusion, or death, and the relation of these to the progress of resolution is shown in Table 39. It is seen that a low admission systolic B.P. (100mm. Hg. and under) occurred as frequently in rapid as in delayed resolution. Similarly the proportion of cases showing a low admission diastolic B.P.

(below 60 mm. Hg.) showed no significant increase in delayed resolution.

TABLE 39

Blood Pressure and Resolution

Resolution	Total Cases	Systolic B.P. (mm. Hg.)			Diastolic B.P.	
		under 110	110-140	140 +	Under 60	60-90
Rapid ...	31	7	22	2	3	28
Fair	12	1	10	1	3	9
Delayed ..	24	6	15	3	4	20
Totals..	67	14	47	6	10	57

A single blood pressure reading seems, therefore, of little practical significance in relation to resolution. It is to be noted, however, that 54 of these cases were over 40 years of age and yet the highest systolic B.P. recorded was 150 mm. Hg. In normal individuals of this age group, one would expect to find a considerable proportion of readings above this figure. Many of the cases did show signs of arterio-sclerosis, so it is reasonable to assume that the blood pressures recorded in these cases were lower than their normal values.

These findings in relation to pulse rate, cardiac lesions, and perhaps blood pressure, do tend to indicate that circulatory involvement is associated with delayed resolution. To substantiate Warfield's (1936) claim that

such involvement falls primarily on the peripheral circulation, estimations of (a) blood volume, and (b) haemoglobin levels would be valuable as an assessment of haemoconcentration. Such estimations were not performed in my series of cases and this subject requires further investigation.

Now, where there is considerable cardio-vascular involvement, particularly where there is a condition of "shock", the circulation to all the organs will be impaired, and the pulmonary circulation will share in this impairment. Absorption of the exudate into the circulation, either directly via the blood vessels, or indirectly via the lymphatics, will be less efficient, and it seems reasonable to assume that in such circumstances resolution will be inhibited.

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CHAPTER IX

SULPHONAMIDES AND RESOLUTION

Section (i) : Relation of Dosage and Duration of Administration to the Progress of Resolution.

Section (ii): The Sulphonamide Blood Concentration.

Many factors in relation to resolution have been discussed in the preceding chapters. However, I have not yet touched on the main problem, namely why sulphonamide chemotherapy per se should cause an increased incidence of delayed resolution. In the following chapter I shall correlate the progress of resolution in my series of cases with various aspects of sulphonamide therapy. From my deductions, I shall endeavour to show that the response to chemotherapy is intimately associated with the other factors concerned with the progress of resolution.

SECTION (i)

Relation of Dosage and Duration of Administration to the Progress of Resolution

(1) Dosage

(a) Initial stage. At the beginning of the study, every case of pneumonia received an initial dose of 2 gm. sulphathiazole, which was thereafter followed by 1 gm. every four hours - a total of 7 gm. sulphathiazole during the first twenty-four hours. In the latter months of the study an alternate method of dosage was employed in patients over 40 years of age, as it is in this age group that delay in resolution is most marked. This method was based on the assumption that by attaining a rapid high concentration of

the drug in the blood we might strike an overwhelming blow at the pneumonic infection and thus attain a more rapid resolution. Thus 2 gm. sulphathiazole was administered every four hours for the first twenty-four hours - a total of 12 gm. Thereafter, the amount given was 1 gm. four-hourly. Table 40 shows the results in relation to the progress of resolution in both schemes of dosage. There were 62 uncomplicated cases over 40 years of age who received sulphathiazole - 40 of these received 12 gm. during the first 24 hours, and 22 cases received 7 gm. It is interesting to note that 52.5 per cent. of cases on the higher initial dosage developed delayed resolution compared with 36 per cent. of those on the lower dosage. There was, however, only one death in the latter group whereas, in the former group, there were three deaths.

TABLE 40

Initial Dosage of Sulphathiazole and Outcome

	Dosage in first 24 hours	
	12 gm.	7 gm.
Total cases over 40 years	40	22
Deaths	1	3
Delayed resolution ..	21 (52.5)	8 (36)

(The figures in brackets are percentages of the group total.)

Now it is reasonable to assume that the speedy attainment of a high concentration of the drug in the blood stream might well lessen the fatalities by striking an overwhelming blow at the infecting organism. This may explain the small number of deaths in those receiving the higher dosage. Again, it is probable that those cases, which would have succumbed without the help of the higher dosage of sulphathiazole because their own response to the infection was poor, were just those cases which later developed delayed resolution. This would push up the percentage of delayed resolution in the group, and may explain the high figure. Nevertheless, it is evident from this experiment that a greater initial dosage of sulphathiazole does not lessen the incidence of delayed resolution but rather seems to cause an increase.

(b) Total dosage. In the vast majority of cases the total dosage of sulphathiazole administered varied between 30 gm. and 50 gm. Table 41 depicts the progress of resolution in relation to the total dosage, irrespective of the age of the patient. It is seen that a greater percentage of cases on the larger dosage showed delayed resolution. It is doubtful, however, if any significance can be attached to this finding, as it is very likely that cases who were seriously ill received more drug than cases who had only a mild attack of pneumonia. And it might reasonably be

argued that the incidence of delayed resolution would be higher in the former group due to the mere severity of the illness.

TABLE 41

Total Dosage and Resolution

Resolution	Total dosage Sulphathiazole	
	30 - 40 gm.	40 - 50 gm.
Rapid ...	32	20
Fair	11	17
Delayed ..	15 (25.8)	24 (39.5)
Totals .	58	61

(The figures in brackets are percentages of the group total.)

(2) Duration of administration of drug

Table 42 shows that the longer the period of administration of the drug, the fewer were the cases showing rapid resolution. It must be remembered, however, that the

TABLE 42

Resolution in respect of Duration of Therapy

Resolution	Duration of chemotherapy (days)				
	5	6	7	8	9
Rapid ...	17 (63)	21 (49)	14 (42)	3 (25)	1 (16)
Fair ...	2	11	8	4	3
Delayed ..	8	11	11	5	2
Totals .	27	43	33	12	6

(The figures in brackets are percentages of the group totals.)

main indication employed for stopping the drug was a temperature which had remained normal for twenty-four to forty-eight hours when this was accompanied by a marked clinical improvement in the patient's condition. Here it is of interest to study the duration of primary pyrexia in the various types of resolution. From Table 43 it is seen that most of the cases of rapid resolution had a normal temperature by the third day, and none had pyrexia more than six days after commencement of sulphonamide therapy.

TABLE 43

Duration of Primary Pyrexia in the Types of Resolution

Resolution	Total Cases	Duration of primary pyrexia (days)		
		1st - 3rd	4th - 6th	6 +
Rapid ...	61	48	13	-
Fair	34	12	15	7 (26)
Delayed ..	53	18	13	22 (43)

(The figures in brackets are percentages of the group totals.)

On the other hand, a considerable proportion of the cases showing delayed resolution (43 per cent.) had pyrexia after the sixth day, and, in some of these cases, the fever even extended into the third week. Now, a severe initial illness is often accompanied by protracted primary pyrexia. The association of a high proportion of delayed resolution with prolonged pyrexia may, therefore, be a consequence of a severe initial illness and not the result of prolonged

administration of sulphonamides.

These results indicate that no clear evidence could be found for attributing inhibition of resolution either to the quantity of drug administered or to the duration of the drug, as the severity of the initial illness tends to confuse the issue.

SECTION (ii)

The Sulphonamide Blood Concentration

The level of sulphathiazole in the blood was estimated (a) on admission, and (b) 24 hours after admission, in 102 cases of the series. The method employed was a modification of that of Bratton and Marshall and is described in Chapter I.

(a) Admission level. Table 44 shows that no sulphonamide

TABLE 44

Admission Sulphathiazole Blood Levels

	Sulphathiazole blood level (mg. per cent.)					Total Cases
	0	0-0.9	1-1.9	2-2.9	3-3.9	
Number of cases ..	78	3	6	11	4	102

could be detected in the blood in 78 of the cases. Now, the majority of patients gave a history of administration of "M. and B. Tablets" just prior to admission, from their own doctor. It must, therefore, be concluded in the light of

this finding, that, in the great majority of cases, the drug was being administered in very inadequate dosage.

(b) 24 hour blood level. Table 45 shows the twenty-four hour sulphathiazole blood level in the 102 cases.

TABLE 45

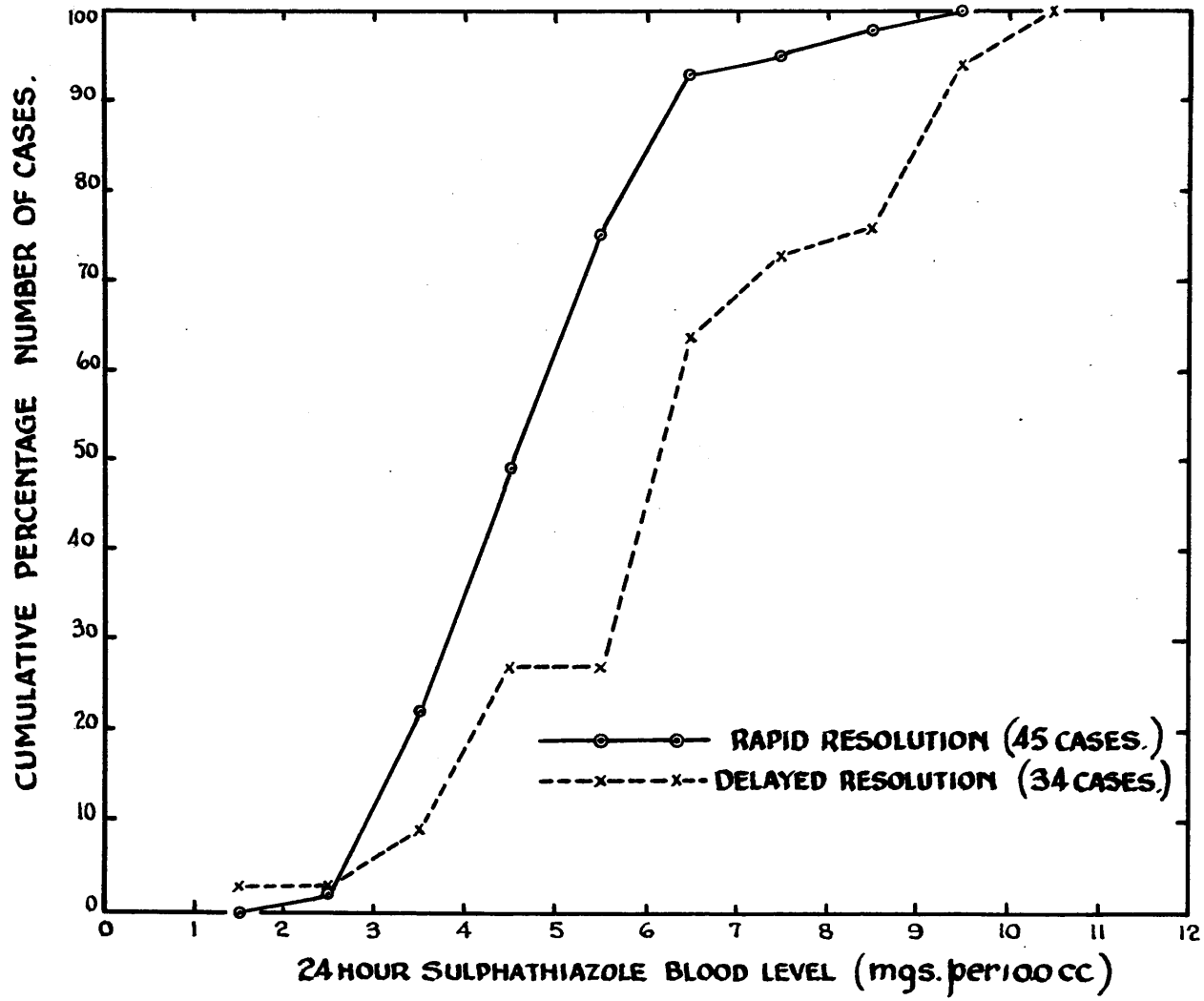
Resolution in respect of Twenty-Four Hour Sulphathiazole Blood Level

	24-hour Sulphathiazole blood level (mg. per cent.)										Total Cases
	1-1.9	2-2.9	3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-9.9	10+	
Rapid resolution	-	1	11	10	12	8	1	1	1	-	45
Fair resolution	-	1	3	2	2	4	1	-	1	-	14
Delayed resolution	1	-	2	6	-	13	3	1	6	2	34
Sterile effusion	-	-	-	-	-	3	-	-	-	-	3
Empyema	-	-	1	-	1	-	-	-	-	-	2
Deaths	1	-	-	-	-	2	1	-	-	-	4
Totals	2	2	17	18	15	30	6	2	8	2	102

This included three cases which developed sterile pleural effusions, two cases of empyema and four deaths. Of the 93 remaining cases, 51 had levels below 6 mg. per cent. and 42 cases attained levels over this figure. Table 46 shows that the percentage of cases of delayed resolution in those with a high blood level (over 6 mg.) is more than three times the number in those with a low blood level (below 6 mg.).

GRAPH V.

SULPHATHIAZOLE BLOOD LEVEL 24 HOURS AFTER ADMISSION. CUMULATIVE FREQUENCY DISTRIBUTION PERCENTAGE.



G.

TABLE 46

Delayed Resolution in respect of Blood Concentration

	24 hr. Sulphathiazole Blood Level	
	-6 mg. per cent.	6+ mg. per cent.
Total cases	51	42
Cases showing delayed resolution	9 (17.6)	25 (59)

(The figures in brackets are percentages of the group totals.)

Graph V depicts the cumulative frequency distribution percentage of the twenty-four hour sulphathiazole blood levels in rapid resolution and delayed resolution. In rapid resolution, the majority of blood levels lay below 6 mg. per cent. In delayed resolution, on the other hand, the blood level, in the great majority of cases, lay above 6 mg. per cent.

This indeed seems a strange finding, as one would expect that the higher the concentration of drug in the blood, the greater would be the therapeutic effect, and the more rapid the progress of resolution. What then is the explanation? In an attempt to solve the problem, I placed all the cases with twenty-four hour blood levels below 6 mg. per cent. on one list, and all the cases with values above 6 mg. per cent. on another list. I then studied the clinical signs in each case. And I found, as depicted in Table 47, that a high proportion of cases with high blood levels showed cardio-vascular involvement. This was in marked contrast to those with low blood levels, for, as shown from Table 48, only two cases showed an obvious cardiac abnormality, namely myocarditis.

Now, it was suggested in the preceding chapter, that cardio-vascular inefficiency was the basis of delayed resolution. It now seems that a high blood level is another indication of circulatory involvement, and, in

TABLE 47

Twenty-Four Hour Sulphathiazole Blood Level
6.0 mg. per cent. and over

Patient (age in brackets)	Sulphathiazole level at 24 hrs.	B.P. on admission		Pulse Pressure	Highest P.R. in first 24 hrs.	Cardiac Irregularities	Resolution D - delayed F - fair R - rapid
		Systolic	Diastolic				
R.C.(57)	14.5	140	80	60	90	Myocarditis Extra systoles	D.
H.C.(55)	10.35	100	40	60	120	Myocarditis	D.
A.M.(50)	9.9	90	60	30	96	Myocarditis	D.
W.X (73)	9.75	-	-	-	106	Arterio-sclerosis	D.
G.B.(61)	9.75	-	-	-	110	Myocarditis	D.
W.M.(45)	9.75	110	60	50	120	Myocarditis, Arterio-sclerosis	F.
F.O.(65)	9.0	140	80	60	110	Arteriosclerosis	D.
J.Q.(9.	9.0	100	80	20	112	Mitral stenosis	D.
J.B.(61)	9.0	130	70	50	124	Myocarditis	D.
W.C.(64)	9.0	100	60	40	84	Auricular fibrillation	R.
J.K.(32)	8.5	100	60	40	130	Myocarditis	R.
W.Mc.(50)	8.0	-	-	-	116	-	D.
J.C.(50)	7.65	120	50	70	122	Myocarditis	D.
J.D.(61)	7.5	90	50	40	108	Myocarditis	D.
J.F.(53)	7.5	130	80	50	140	Myocarditis, Auricular fibrillation	Death
W.W.(51)	7.5	120	60	60	100	-	R.
W.S.(40)	7.5	100	50	50	126	-	F.
T.K.(49)	7.2	110	65	45	98	-	D.
J.M.(46)	6.75	120	65	45	98	-	D.
V.R.(46)	6.75	120	80	40	100	-	F.
H.S.(45)	6.75	110	70	40	96	-	R.
W.T.(36)	6.75	120	80	40	110	-	R.
T.L.(21)	6.75	110	70	40	130	-	R.
W.T.(63)	6.75	90	50	40	120	Myocarditis	Death
J.B.(45)	6.75	120	80	40	108	-	D.
P.B.(56)	6.75	110	46	70	126	-	R.
G.P.(18)	6.75	-	-	-	120	-	R.
J.H.(19)	6.75	135	85	50	120	-	R.
R.W.(51)	6.6	150	80	70	98	Myocarditis	D.
W.Mc.(19)	6.45	120	70	50	124	-	R.
E.W.(46)	6.3	140	95	45	120	-	R.
S.D.(61)	6.0	130	70	60	108	Auricular fibrillation	D.

TABLE 47 (contd.)

Patient (age in brackets)	Sulphathiazole level at 24 hrs.	B.P. on admission		Pulse Pressure	Highest P.R. in first 24 hrs.	Cardiac Irregularities	Resolution D - Delayed F - Fair R - Rapid
		Systolic	Diastolic				
J.C.(61)	6.0	90	60	30	120	Myocarditis	D.
T.Mc.(58)	6.0	-	-	-	136	-	D.
T.W.(70)	6.0	150	80	70	100	Arterio-sclerosis	D.
R.P.(54)	6.0	-	-	-	124	Myocarditis	D.
J.J.(75)	6.0	120	70	50	126	Auricular fibrillation	F.
R.S.(19)	6.0	-	-	-	120	-	R.
W.Mc.(40)	6.0	120	70	50	114	Pericarditis	Death
W.B.(71)	6.0	-	-	-	100	-	D.
T.D.(67)	6.0	-	-	-	-	Myocarditis	D.
J.D.(29)	6.0	-	-	-	130	-	D.
R.H.(43)	6.0	130	60	70	110	-	F.
S.C.(48)	6.0	140	60	80	120	-	F.
T.Mc.(47)	6.0	-	-	112	-	Myocarditis	R.
D.Mc.(67)	6.0	120	50	70	110	Myocarditis	R.
W.Y.(44)	6.0	120	70	50	132	Myocarditis, pericarditis	D.

TABLE 48

Twenty-Four Hour Sulphathiazole Blood Level under 6.0 mg. per cent.

Patient (Age in brackets)	Sulphathiazole level at 24 hrs.	B.P. on admission		Pulse Pressure	Highest P.R. in first 24 hrs.	Cardiac Irregularities	Resolution D - Delayed F - Fair R - Rapid
		Systolic	Diastolic				
J.B.(20)	5.45	120	60	60	110	-	R.
F.O.(43)	5.25	130	75	55	102	-	R.
G.S.(41)	5.25	110	40	70	84	-	F.
F.Mc.(19)	5.25	100	60	40	92	-	R.
J.S.(44)	5.25	-	-	-	120	-	R.
D.K.(51)	5.25	150	50	70	100	-	R.
A.M.(24)	5.25	-	-	-	120	-	R.
M.P.(28)	5.25	-	-	-	136	-	R.
J.L.(45)	5.25	130	70	60	110	-	R.
J.J.(34)	5.25	120	70	50	110	-	Empyema
D.X.(51)	5.25	150	80	70	100	-	R.
T.Mc.(19)	5.2	110	50	60	140	-	R.
W.G.(32)	5.1	-	-	-	120	-	R.
A.E.(52)	5.1	-	-	-	120	-	R.
J.L.(28)	5.1	-	-	-	134	-	R.
W.S.(52)	5.1	110	75	35	100	-	R.
J.C.(42)	4.8	110	50	60	120	-	F.
D.K.(21)	4.8	-	-	-	104	-	R.
D.C.(41)	4.5	120	60	60	120	-	D.
M.C.(52)	4.5	140	100	40	112	Myocarditis	D.
S.L.(33)	4.5	-	-	-	140	-	F.
W.C.(33)	4.5	100	50	50	98	-	R.
W.E.(38)	4.5	120	60	60	122	-	R.
R.T.(29)	4.5	130	70	60	122	-	R.
R.P.(18)	4.5	105	70	35	112	-	R.
N.M.(34)	4.5	100	60	40	112	-	R.
R.S.(57)	4.5	150	60	90	108	-	D.
J.Mc.(47)	4.5	130	80	50	98	-	R.
C.Mc.(33)	4.5	100	65	35	100	-	R.
A.Mc.(22)	4.5	115	60	55	128	-	D.
J.J.(47)	4.5	110	70	40	100	-	D.
R.T.(30)	4.3	100	70	30	146	-	R.
P.L.(27)	4.2	-	-	-	96	-	R.
J.Mc.(42)	4.05	130	95	35	134	-	D.
A.E.(50)	3.9	130	70	60	96	-	R.
J.M.(38)	3.9	-	-	-	130	-	R.
R.S.(32)	3.75	130	70	60	120	-	Empyema
D.Mc.(32)	3.75	120	60	60	96	-	R.
P.N.(16)	3.75	120	60	60	120	-	R.
D.E.(19)	3.75	120	70	50	136	-	R.

TABLE 48 (Contd.)

Patient (Age in brackets)	Sulphathiazole level at 24hrs.	B.P. on admission		Pulse Pressure	Highest P.R. in first 24 hrs.	Cardiac Irregularities	Resolution D - Delayed F - Fair R - Rapid
		Systolic	Diastolic				
A.L.(16)	3.75	-	-	-	130	-	D.
N.P.(34)	3.45	130	90	40	124	-	R.
A.C.(54)	3.3	110	70	40	128	Myocarditis	F.
J.Mc.(52)	3.3	150	80	70	118	-	F.
J.S.(16)	3.3	110	60	50	90	-	D.
J.M.(49)	3.0	-	-	-	100	-	D.
J.C.(20)	3.0	120	80	40	124	-	R.
J.O.(17)	3.0	-	-	-	108	-	R.
D.K.(33)	3.0	-	-	-	116	-	R.
A.Mc.(16)	3.0	-	-	-	122	-	R.
W.Mc.(35)	3.0	120	70	50	124	-	R.
J.W.(36)	2.7	-	-	-	110	-	F.
R.H.(25)	2.5	130	70	60	105	-	R.
T.P.(49)	1.5	120	75	55	120	-	D.
T.A.(56)	1.5	130	75	65	128	-	Death

many cases, prognosticates slow resolution. The condition of "shock", which I demonstrated as a cause of low plasma proteins and also of delayed resolution, can again explain this mystery. For, with increased capillary permeability there will be a decrease in circulating blood volume and hence a concentration of drug in the blood. Further, vascular stasis will result in a sluggish pulmonary circulation, and, even although the sulphonamide blood level in the peripheral circulation is high, very little drug may be reaching the actual pneumonic consolidation. In addition, the renal circulation will suffer, with resulting impairment in excretion of the drug, and thus drug retention may contribute to a high blood level. Two experiments might be carried out to prove the efficiency or the inefficiency of the renal and pulmonary circulation in the presence of a high blood level:-

(1) Measurement of the quantity of drug excreted in the urine during the first twenty-four hours. It has been estimated by various observers that, normally, excretion of sulphathiazole amounts to from 75 per cent. to 100 per cent. of the daily intake. Any experiment to show this, however, would be attended by great practical difficulties in pneumonia. The total output of urine must be collected and measured, and, where the patient is acutely ill, and often incontinent, this is impossible. Again, the nursing in a pneumonia ward is extremely heavy

and the staff would find it difficult to cope with this additional burden.

(2) Measurement of the level of drug in the sputum. If a low sputum level were found with a high blood level, it could be assumed that the drug was not reaching the consolidation. Here, again, there are practical difficulties in handling sputa. In addition, the admixture of saliva with the sputum would vitiate results.

Although it was not found practical to carry out these two experiments, yet the finding of high blood levels and circulatory inefficiency in cases showing delayed resolution does suggest that these three conditions are closely allied. In this respect, a study of the pharmacology of the sulphonamides is of interest. The drug is bacteriostatic, and its action seems to depend upon the fact that it interferes with the enzyme p-amino benzoic acid which is necessary for the growth of many organisms. Sulphonamides are not therapeutic drugs in the true sense, for they do not stimulate the defensive mechanism of the body in the way that antiserum does. Indeed, as already mentioned, Anderson has shown that they seem to be almost antagonistic to antibody formation. The common toxic effects of the drug in man are well known and generally occur after a considerable dose of the drug has been administered. Sensitization phenomena (drug fever, skin rashes) may,

however, occur after the smallest dose, and the reason for this is obscure. In a recent article, Hawking has suggested that the sulphonamide-protein complex may play a part in the production of this condition.

In any case of pneumonia where there is circulatory involvement, the drug will rapidly attain a high concentration in the blood. The toxic effects of over-dosage will, therefore, tend to appear after a comparatively small amount of drug has been administered. Now, it has already been shown that impaired circulation in itself leads to delayed resolution. It seems reasonable to deduce that in these cases the tendency towards sulphonamide toxaemia will impede the body's defensive mechanism, and will inhibit still more the progress of resolution.

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DISCUSSION

A study of the results of treatment of pneumococcal pneumonia by sulphonamide chemotherapy presents an apparent paradox. From the foregoing study two opposing tendencies emerge. First, the immediate effect of the drug on the course of the disease is altogether beneficial, as shown by the reduction in the fatality rate, and by the rapid clinical improvement during the acute illness. On the other hand, a greater proportion of cases now show delay in resolution, and the period of convalescence is consequently prolonged. It has been found that it does not suffice to assume that only the patients who were seriously ill on admission, and who would perhaps have succumbed without the help of chemotherapy, are those who later develop delayed resolution.

In any previous study of delayed resolution one serious drawback was the absence of a standard whereby to measure the normal progress of resolution. Relative comparisons of the incidence of delayed resolution in cases treated by sulphonamides with the incidence in cases receiving no sulphonamide therapy have, therefore, been unsatisfactory. In the present study an attempt was made to provide a uniform standard based on radiographic findings. Resolution was arbitrarily divided into three types - rapid resolution, fair resolution and delayed

resolution. Rapid resolution included cases who showed complete clearing of the opacity by the twenty-first day. In fair resolution, clearing of the lung was complete between the 21st day and the 35th day. Delayed resolution comprised cases which required more than 35 days for complete resolution. The distribution of cases in the present series in respect of the type of resolution was compared with the radiographic findings found in a series of cases studied by Davies, Hodgson and Whitby in 1935. This comparison confirmed the clinical impression that, under sulphonamide chemotherapy, delayed resolution is now more frequent.

In order to try to understand the factors which might influence the progress of resolution, the pathological sequence of events in pneumonia was first studied. This showed that, during the stage of gray hepatization, an impairment of the pulmonic circulation occurs due to compression of the alveolar capillaries by the pneumonic consolidation. It was also found that the chief method by which the exudate is removed from the alveoli is by absorption into the circulation, either directly by means of the blood vessels, or indirectly by means of the lymphatics. If excess exudate were present in the alveoli, it is reasonable to assume that resolution would be prolonged: and, again, if the circulation supplying the

consolidated area were impaired, then absorption would be deficient, and delay in resolution could be expected.

The greater the outpouring of exudate into the alveoli the more dense is the pneumonic opacity. Further, it was found that a dense opacity was associated with a severe initial illness. That this would not in itself explain delay in resolution was apparent from the fact that the age of the patient seemed to be a determining factor. In individuals over forty years of age, a dense opacity certainly did result in delayed resolution, but, in the younger age group, an equally intense consolidation frequently showed rapid resolution. The cause of delayed resolution, therefore, seemed to lie in some factor intimately related to advancing years.

Fresh light was thrown on the subject from a study of the blood plasma proteins. It would seem likely that, in pneumonia, the great outpouring of plasma into the pulmonary alveoli would result in a withdrawal of plasma proteins from the circulation. And it was found that the blood plasma proteins on admission to hospital were indeed low. In cases showing rapid resolution the values were not usually below the limits of normal variation. On the other hand, of the cases which developed delayed resolution, a considerable proportion had low plasma proteins on admission. Further, it was demonstrated that the fall in plasma proteins was due to a diminution in the albumen fraction.

In order to discover if low plasma proteins were directly concerned with inhibition of resolution, the plasma protein values were correlated with the factors found to be intimately concerned in delayed resolution, namely, the age of the patient, the density of the consolidation, the presence of bacteriaemia, the number of days ill prior to admission, and the type of the infecting organism. It was found that here again, as in the incidence of delayed resolution, the age of the patient and the density of the consolidation were the two most important factors, which determined the occurrence of hypoproteinaemia.

In respect of the cause of low plasma proteins, several possible explanations were adduced. Two of these explanations, namely, loss of plasma in the exudate, and deficient nutrition, did not suffice to explain why it was the albumen fraction of the plasma proteins which was diminished. That hepatic dysfunction might play a part was possible, for the albumen fraction is formed mainly in the liver, whereas globulin is also partly formed by the reticulo-endothelial system. Damage to the liver from the toxaemia of the disease would, therefore, mainly affect the albumen fraction. A more adequate explanation, however, was provided by the theory of "oligaemic shock". Such a state of shock it was argued could result from the toxaemia present in any severe case of pneumonia. The consequent damage to the capillary walls would render them more permeable. As a process of degeneration in the blood

vessels accompanies advancing years, the burden of the toxaemia will fall most heavily upon older people. In addition, since the albumen fraction has a smaller molecular weight than the globulin fraction, it might be expected to pass more readily through the capillary walls.

Delay in resolution, then, is accompanied by low plasma proteins, and it is suggested that this change may be related to a state of "oligaemic shock". It remained to find some "connecting link" which might explain how inhibition of the resolution process could be caused by a state of "shock". Now, the clinical assessment of the degree of shock present is perhaps best measured by cardio-vascular efficiency, and it was found that cardio-vascular involvement, as manifested by a high pulse rate, cardiac lesions, or a low blood pressure, was invariably present in cases which developed delayed resolution. When it is remembered that absorption into the circulation is the chief method of removal of the exudate, it seems reasonable to conclude that cardio-vascular inefficiency is the ultimate cause of delayed resolution. In addition, many of the other factors concerned in the incidence of delayed resolution could also be explained by cardio-vascular involvement and they will here be briefly capitulated.

Firstly, it was shown that, of all the factors concerned in the incidence of delayed resolution, the age of the patient was by far the most important. This is

readily explained, as stated above, by the general cardio-vascular impairment which accompanies advancing years. In the older individual, degenerative changes occur in the walls of the blood vessels in virtue of which they lose their elasticity, and the circulation thereby becomes less efficient. Where delayed resolution did occur in younger individuals, it was always accompanied by marked evidence of cardio-vascular deficiency, and indeed, in some of these cases, a history of pre-existing cardiac disease was elicited.

The density of the pulmonic consolidation was the next factor shown to influence the incidence of delayed resolution. Here again, however, as already stated, the age of the patient was all-important: in the younger age group, a dense consolidation usually showed good resolution, whereas, in the older age group, resolution was frequently delayed. Now, the more dense the consolidation the greater is the quantity of exudate present in the alveoli, and the longer will be the period of time required for its absorption into the circulation. In younger individuals, where the circulation is good, resolution will not be significantly prolonged, even when there is a dense consolidation. In older individuals, however, circulatory inefficiency is more marked, so that a dense consolidation will show delay in resolution. Further, the greater the density of the opacity, the greater will

be the pressure exerted on the alveolar capillaries. As the elasticity of the capillaries in older people is impaired, a longer period of time will be required before they regain their potency. By such means the impairment of the pulmonic circulation will be further increased and the process of resolution inhibited. In addition to the density of the consolidation, the position of the consolidation was apparently of some importance, for it was found that the right lower lobe was the lobe most frequently involved in delayed resolution. But, anatomically this lobe has a poorer blood supply than the other lobes, so that, once again, a connection is found between the relative inefficiency of the circulation and the occurrence of delayed resolution.

Finally, the fact that sulphonamide chemotherapy is associated with an increased incidence of delayed resolution, and this, especially in older individuals, is most readily explained on the basis of circulatory inefficiency. In the first place, where this exists, the drug will possibly not come into contact so readily with the pulmonic consolidation. But, of more importance, the vascular stasis and "oligaemic shock" present in such cases will tend to cause drug retention and concentration of the drug in the blood stream. A toxic level will be more readily attained. The defensive mechanism of the body will then not only have to cope with the pneumonic

infection, but also with this foreign and toxic substance sulphonamide. Moreover, such concentration of the drug will tend to occur more frequently in older individuals whose response to infection is in any case less satisfactory. It is little wonder that, in such an event, inhibition of resolution results.

It would appear then that sulphonamide chemotherapy is a double-bladed weapon; its damaging attack is not confined to the bacterial cell. Nevertheless, it is evident that, in the majority of cases, the advantages of the drug outweigh its disadvantages. Undoubtedly, the bacteriostatic qualities have saved many lives and have shortened the duration of the acute pneumonic illness. The present study has demonstrated that, where cardiovascular involvement is present during the acute illness, some degree of delay in resolution must be expected. Where such involvement exists frequent blood levels should be performed in order to detect any serious degree of drug retention. In addition, the duration of administration of the drug should be limited to the minimum period compatible with effective bacteriostasis.