

T H E S I S

for the

D E G R E E o f D O C T O R o f M E D I C I N E

presented by

JOSEPH ALEXANDER BELL.

M.B., Ch. B., (Univ.Glas). F.R.F.P.S. (Glas). M.R.C.P.(Edin).

JOHANNESBURG, SOUTH AFRICA.

ProQuest Number: 13905562

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 13905562

Published by ProQuest LLC (2019). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Is Meningococcal Meningitis curable by

Chemotherapy alone?

Introduction.

The investigation of this problem was carried out in Johannesburg, South Africa, it having been suggested by numerous and various reasons of which the following are the most important:-

I. The introduction by Domagk in Germany in 1936 of p-sulphonamide and its compounds to the field of chemotherapy had opened up a field of seemingly unlimited possibilities in therapeutics.

II. The prevalence of meningococcal meningitis among the natives of South and East Africa.

III. The very large numbers of natives, both local and imported from East Africa, as labourers in the Gold Mines, and their housing in close contact in Compounds accommodating from three to five thousand men.

IV. The very close contact of these natives with the European population both in the mines and in the home, there being as a rule, at least one native servant in almost every European household in the Witwatersrand area, or rather throughout the whole of the Union of South Africa for that matter.

V. The constant travelling to and fro of these natives of both sexes from the native townships or "locations" as they are called, bringing them from fruitful sources of infection into close daily contact with the Europeans in all walks of life, industrially, commercially and domestically.

VI. The Witwatersrand area is the largest Goldmining and industrial area in South Africa and consequently the population, European, Euraffrican, Asiatic and Native (Bantu) is the most dense here.

Geography.

Johannesburg and the Witwatersrand, the latter a ridge of "kopje" or hill country running from East to West for some sixty miles is situated in the Transvaal. It is approximately some six thousand (6000) feet above sea level and four hundred (400) miles from the nearest coast line, Natal, with its seaport Durban.

Population.

The population is made up as follows:-

	European	Euraffrican	Asiatic	Native	Tot. l.
Johannesburg	285,400	23,400	16,950	208,900	528,650.

To this may be added some further 60,000 European and about 80,000 natives on the mines and Reef towns.

Native Housing and Health.

Photograph of a section of a typical native Compound



Photograph of interior of a room showing bunks.



Photograph of atypical native "location" as built by Municipalities.



Photograph of another type of location, more modern.



A glance at these pictures is sufficient to show how close the actual contact may be and it is therefore obvious that it would be no difficult matter for an epidemic of meningococcal meningitis to spread with facility and rapidity with possible dire effects upon the entire community. Furthermore the disease is endemic in this country and sporadic cases are reported throughout the country at all times of the year..

The problem of native health is here so closely bound up with that of the European population that an effective and comparatively simple cure of at least one of the possible epidemic diseases, and that one fraught with such dire consequences, would be an ineffable blessing to this or any other community.

That we South Africans are not doing as much as we might is instanced by the extract from the Rand Daily Mail of June 19th 1939. This is only one of such warnings issued from time to time.

The extract is given on the next page.



Nigerian Epidemic.

A.B. Cook, Medical officer, C.M.S. Hospital, Wusasa, Zaria, N.

Nigeria writing in the correspondence columns of the British Medical Journal of June 3rd, 1939 reports an epidemic of cerebrospinal meningitis in the Northern Provinces of Nigeria, in which thousands of deaths were reported. He tells how difficulties had to be overcome in the shape of local prejudices of the natives to European medicines, the possibility of doing lumbar puncture in only a very few cases, and the prohibitive cost of anti-meningococcal serum and meningococcal antitoxin.

He points out that the advantage of the use of Prontosil in the native territories is that the treatment can be carried out in their own homes. This is of course of the utmost importance to the Bantu populations of South Africa, the majority of whom were quite too far out of reach of what few hospitals as exist.

DEMONSTRATING THE ACTUAL
INCIDENCE OF CEREBRO-SPINAL (MENINGOCOCCAL)
MENINGITIS IN FIVE LARGE WITWATERSRAND TOWNS
- JOHANNESBURG, BENONI, SPRINGS, KRUGESDORP AND
BOKSBURG - DURING THE YEAR 1937-1938.

I. TOTAL POPULATION.

EUROPEAN	353,706
<u>NON-EUROPEAN</u>	<u>446,494</u>
<u>ALL RACES</u>	<u>800,200</u>

II. TOTAL C.S.M. CASES.

EUROPEAN	35
<u>NON-EUROPEAN</u>	<u>252</u>
<u>ALL RACES</u>	<u>287</u>

III. TOTAL C.S.M. DEATHS.

EUROPEAN	15
<u>NON-EUROPEAN</u>	<u>85</u>
<u>ALL RACES</u>	<u>100</u>

IV. INCIDENCE AND DEATH RATES.

	<u>INCIDENCE RATE.</u>	<u>DEATH RATE.</u>	<u>CASE MORTALITY RATE.</u>
EUROPEAN	0.10	0.04	43
<u>NON-EUROPEAN</u>	<u>0.56</u>	<u>0.19</u>	<u>34</u>
<u>ALL RACES</u>	<u>0.36</u>	<u>0.125</u>	<u>35</u>

INCIDENCE OF MENINGOCOCCAL MENINGITIS
AMONG MINING NATIVES OF THE RAND MINES GROUP:
TAKEN FROM THE 1938 REPORT OF DR. A.J.
ORENSTEIN. C.M.G.

	<u>TOTAL CASES.</u>		<u>DEATHS.</u>		<u>CASE</u>
	<u>No.</u>	<u>Per 1000 P.A.</u>	<u>No.</u>	<u>Per 1000 P.A.</u>	<u>MORTALITY (%)</u>
1936	65	0.62	34	0.32	52.3
1937	146	1.39	52	0.50	35.6
1938	147	1.38	27	0.25	18.4

This Mining group in 1938 employed (average figure)
106,378 mining Natives on 15 Gold Mines and one
Colliery.

Interest in Sulphonamide.

In the last three or four years a world wide interest had been raised in the new azo-dye compound sulphonamide. The number and variety of the uses to which this drug had been put, and the too often extravagant and widely conflicting claims as to its therapeutic efficacy in widely differing infections, had led to not inconsiderable confusion as to its actual utility and had led one in the course of time to take a much more conservative view of its true potentialities.

My own experience (admittedly small) with sulphonamide and its derivatives in a variety of conditions such as staphylococcal septicaemia and other staphylococcal infections, acute and chronic gonococcal and non-gonococcal urethritis etc, had been on the whole more disappointing than encouraging. It had indeed left me with the strong impression that the main field of activity of the sulphonamide products was in combating local or generalised infections produced by the haemolytic streptococcus and by it alone. In infections by this organism, such as in puerperal septicaemia, brilliant results had been obtained and its potency in this particular field is now undoubted. Such too is apparently true for the May and Baker product, M & B 693, in pneumococcal infections both pulmonary and occasionally meningeal.

Although I was well aware of the reported successes in America, in meningococcal meningitis as obtained by Willien (1937), and very occasionally in pneumococcal infections by others, I had nevertheless remained unenthusiastic, until Dr. T.T. Stone, Associate Professor of Neurology, at the Northwestern University Medical School, Chicago, greatly stimulated interest in the subject.

While on a visit to South Africa he gave a lecture in Johannesburg before the John Saner Clinical and Pathological Club in July 1938. He related his own experiences in the Cook County Hospital, Chicago, during which it was borne out in a most convincing manner that with the use of sulphomamide, the death rate in this hospital, in meningococcal meningitis had been reduced from sixty per cent and more to the amazing figure of five per cent or less.

He states that in spite of intrathecal pus, clinicians there looked upon the disease more as a meningococcaemia and treated it as such, the actual condition of the spinal canal being totally disregarded.

That the infection is blood borne, and is conveyed not by direct extension from the nose through the cribriform plate of the ethmoid, is of course an accepted theory, and that the meningococcus may frequently be cultured from the blood stream is also well known. This entire disregard for the condition of the cerebrospinal fluid was to me a startlingly novel and yet at the same time a most feasible conception, if one accepted the condition as a meningococcaemia and treated it as such, and therefore not directing so great attention purely to the interior of the skull and spinal canal as formerly.

What was even more convincing was his clear and decided reply to the question as to what he would desire to have done to himself if he was unfortunate enough to contract the disease. He said :- " Give me Prontosil and leave me alone".

Within three weeks of these remarks the opportunity arose for me to treat four cases of meningococcal meningitis in the Kensington Sanatorium, Johannesburg.

With Dr. Stone's words still vividly in mind, but nevertheless

with considerable misgiving, I decided to embark upon the present investigation, that is, to withhold anti-serum entirely and to give sulphonamide and sulphonamide alone to these cases.

It was further decided to do only one lumbar puncture for purely corroborative purposes, in order to put the diagnosis beyond all possible doubt.

In spite of the seemingly heroic doses it was proposed to use it was further decided to employ the most potent, and consequently the most toxic preparation available.

The reason for this was that it appeared quite clearly according to the researches of Cokkinis (1938) and others, that the less toxic the preparation, the less potent is its bacteriostatic powers. It was further wished to obtain the maximum possible therapeutic effect and the lethal nature of the condition was regarded as sufficient justification for these bold measures.

As this investigation was as far as I am aware the first of its kind carried out in South Africa the difficulties were consequently considerably enhanced as no guidance of any kind was obtainable.

Opinions as to the toxicity of Prontosil, the preparation it was decided to use, varies with different observers, some believing that in therapeutic doses the toxicity is very low while others hold that it is highly toxic.

As the proposed doses were to be very large the strong possibility of producing a haemolytic anaemia as described by Harvey and Janeway (1937), and other severe toxic effects such as marked met- and sulphaemoglobinaemia, acidosis, agranulocytosis, disturbances of vision such as optic neuritis, scotoma for red and blue, skin

eruptions like erythema multiforme and even bullous eruptions, and drug fever, was kept continually in mind and a watch kept for their appearance.

Prophylaxis of toxic effects.

The precautions to be observed were decided as follows:-

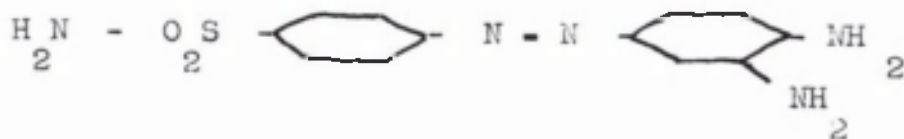
- (1) To give grain for grain of sodium bi-carbonate by mouth to prevent acidosis.
- (2) To avoid the administration of sulphates as $MgSO_4$, or of sulphur containing foods such as eggs, onions and cabbage.
- (3) To proceed with the continuous treatment for not more than eight days.
- (4) To reduce the dosage as soon as favourable clinical progress allowed.
- (5) To keep patients out of strong natural or artificial sunlight.
- (6) To keep careful watch for extreme pallor, sore throat, dyspnoea, jaundice and persistent vomiting and to carry out serial leucocyte counts daily.

No other prophylactic measures suggested themselves at this time.

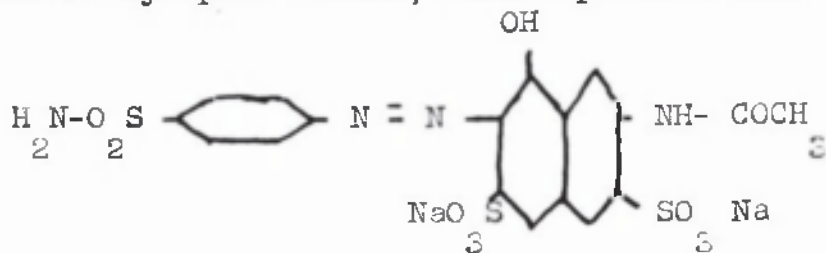
It was decided to use the Prontosil preparations of Bayer and of these to use:-

1. Prontosil Rubrum tablets by mouth.
2. Prontosil Soluble by intramuscular injection.

Prontosil Rubrum tablets intended for oral administration contain 0.5 grams of 4 - sulphonamide - 2,4 - diamino - azo - benzol :



Prontosil Soluble is given by injection and is prepared in ampoules containing 5 ccm of a 2.5 per cent or a 5 per cent solution and consists of a disodium salt of 4' - sulphonamide-phenyl-azo-7-acetyl amino-1-oxynaphthaline-3, 6-disulphonic acid.



Mode of Action.

The absorption of Prontosil is very rapid being nearly complete within four hours according to Marshall and his co-workers (1937) and appears to spread rapidly to all parts of the body as it was recovered from the saliva, bile, pancreatic juice, pleural fluid and cerebrospinal fluid. Fuller (1937) suggested that **sulphanilamide** was not completely excreted, some being destroyed in the body but Marshall concluded that after equilibrium had been established by two or three days regular dosage, about 100 per cent of the drug could be recovered from the urine.

In man it is excreted partly unchanged and partly converted into the acetylated form.

A concentration in the blood of 1:5000 to 1:10,000 could be obtained and maintained by regular and sufficiently large four hourly doses, except where there is impaired renal function where a smaller dosage will be sufficient to achieve the desired level of concentration.

Although Prontosil Soluble and Prontosil Rubrum are

known to be altered in the body to Prontosil Album, all is not so converted some being excreted in the acetylated form. On the hypothesis that the latter form too may be bacteriostatic, the two former preparations were used to gain the benefit of the acetylated form, if such power as it did possess existed. According to Donagh (1937) the acetylated compound has a low chemotherapeutic activity but this however has never been settled and its true value remains as yet unassessed. It was found by Rosenthal et alii (1937) that the rapidity of excretion of Prontosil Soluble was so great as to leave a surprisingly small amount to be activated by reduction, hence the decision to use both the oral and the intramuscular route as the best means of keeping a more or less constant amount in the blood stream at the same time having a very rapid effect.

Levaditi (1937) found that the coloured drugs, the azo-compounds, did not depend for their activity on their reduction to sulphonilamide, but were powerful therapeutically themselves, - another point in favour of the Prontosil compounds to produce a maximum action.

The true mode of action of these drugs remains as yet mysterious. It is known that the action is not bactericidal, in vitro at least. The action is regarded therefore as bacteriostatic and the action of sulphonilamides and similar other drugs is not a simple disinfectant or bactericidal action but is related in some way with the activities of the body. It seems however that the drugs exert an action sufficient to enable the phagocytes to deal with the organisms, and as far as is known the action does not seem to inhibit in any way the production of phagocytes. Nor is it known if the administration of the anti-serum containing the antibodies is helpful

in any way but it does seem that even without the meningococcal antiserum cure can be obtained with Prontosil.

In meningococcal cases numerous instances of treatment with Prontosil and serum together are quoted good results being obtained, 25 recoveries in 26 cases and in a recent report by Eldahl (1938) the mortality rate was under 25 per cent. Carey (1937) reported 5 cases in which no other treatment than Prontosil was given, and Bell and Palmer (1938) 2 cases with Prontosil alone. In all these reported cases the response to treatment was prompt and striking and encouraged the furtherance of this investigation. Apart from the above 7 cases treated purely by Prontosil no other records appear to be available in the literature.

I had considered the experiences of Morton, Erwing and Elsworth (1938) and of Van der Poel (1938) and saw the excellent results obtained using Prontosil and anti-serum together, but never the less resolved to continue with the Prontosil alone, to endeavour to ascertain whether anti-serum was necessary or not.

Reports from the Johannesburg Fever Hospital and Non-European General Hospital (personal communications) using Proseptasine and Soluseptasine were not encouraging and serum had to be resorted to in the end, but again no trial with Prontosil alone was made.

Dosage.

In extremely severe infections the dosage should be high but the maximum dosage is still unknown, and it is probable that it should be fixed were possible according to the patients body weight.

The Americans Schwickler, Clason et alii, gave one gram (15 grains) of Sulphonilamide (Prontosil Album) per 20 lbs of body weight with a maximum of 5 grains (75 grains) per day to patients suffering from streptococcal meningitis, and Prontosil soluble was given in doses of $\frac{1}{2}$ ccm of 5 per cent solution per lb of body weight per day.

Standard dosage.

For practical purposes the following standard adult dosage is regarded as sufficient in streptococcal infections with the childrens' dose one half, and the infants dose one third, of what is given below:-

Oral { Prontosil Album } I-3 tablets (0.5-1.5 grams)
 { Prontosil Rubrum } t.d.s.

Parenteral. Prontosil Soluble 10-25 (or more) ccm per
 (5% solution) 24 hours intra-
 muscularly.

Combined treatment (Prontosil soluble and Album)

In most infections combined treatment i.e.

Prontosil soluble and Prontosil Album is recommended except in urinary tract infections, erysipelas, mild conditions, and prophylaxis, when oral therapy alone suffices.

The dosage for combined treatment is somewhat as follows:-

Moderately severe case:-

Prontosil soluble 10-15 ccm 5% solution per 24 hours.
 plus Prontosil Album 1-2 tabs t.d.s.

Severe case:-

Prontosil soluble 20-25 ccm 5% solution per 24 hours.
 plus Prontosil Album 1-2 tabs t.d.s.

Combined treatment (Prontosil soluble & Rubrum)

Gravely ill.	8 tabs per day (4 grams)	By I.M. injection of 5% soln, 10 ccm every 8 hours.
Of moderate severity	4 tabs per day (2 grams)	10 ccm 5% soln every 8 hours.
Mild.	4 tabs per day	5 - 10 ccm twice daily.

As any case of true meningococcal meningitis must necessarily be regarded as "gravely ill", it was felt that not less than 70-90 grains (4.5 to 6 grams) of Prontosil soluble and Prontosil Rubrum per day, by combined method, by mouth and intramuscular injection for at least seven consecutive days should be given, and to lessen or increase the daily dose if considered advisable according to the clinical improvement, or otherwise, obtained.

Of the cases presented, three worked on Central Witwatersrand Gold Mines, two of these working underground and one in the Time Office of the Native Compound. The fourth case was a master plumber, not on the Mines. In all these cases their daily work brought them into very close contact with native labourers. They all occurred in August and September a point of some interest in that it is from about September each year onwards that an increase in the incidence of cerebrospinal meningitis may be expected to occur among the native labourers on the Mines, with all the attendant problems of treatment etc..

A detailed description of the various cases now follows.

The cases.

Case 1. J.B. Aetat, 32 years, Male, Miner, Scotsman, was first seen on the morning of July 29th 1938. He had been at work the previous day. He complained of general malaise and headache, which began at night on the 28th, but he had no clinical signs or symptoms suggestive of any definite entity. Six hours later he showed all the classical appearances of a severe case of cerebrospinal meningitis namely, hyperpyrexia (temperature 104 F), Brudzinski's neck sign, Brudzinski's leg sign, Kernig's sign, exaggerated knee jerks, extensor plantar response (Babinski's sign), severe headache and numerous well formed petechiae on the abdomen, chest and back. the breath was foul sordes present and facial appearance denoted severe toxæmia. Lumbar puncture was performed and the cerebrospinal fluid was found to be under considerable pressure and also to be frankly purulent. Prontosil by intramuscular injection was immediately given and in consultation with his medical adviser W.H. Palmer, M.B., Ch.B., (Univ Glas), permission was obtained to proceed with Prontosil alone. The doses given to this patient are tabulated below together with the serial leucocyte counts, C.S.F. cell counts, cocci present in C.S.F. etc..

5 ccm of a 5% solution Prontosil Soluble contains approximately $7\frac{1}{2}$ grains (0.5 grams, and one tablet of Prontosil Rubrum contains 2 grains (0.5 grams).

Case I.J.B. admitted 5.p.m. 30/7/38.

Day.	Time.	Dose & Preparation.	Leucocytes in blood.	C.S.F cell count.	Cocci in C.S.F	Sulphaemo Globinuria	Prontosil in urine.
1.	7 p.m	5cc&15grs	-	-	-	-	-
	12 p.m	5cc					
		Total 30grs					
2.	6 a.m	10cc&15grs					
	12 a.m	5cc	20,000	4,200	numer-	-	present
	6 p.m	5cc&15grs	per cmm	per cmm	ous		
	12 p.m	15grs.					
		Total 32grs					
3.	6 a.m	10cc&15grs					
	12 a.m	5cc	18,000	no L.P	no L.P	present	present
	6 p.m	5cc&15grs					
	12 p.m	15grs					
		Total 32grs					
4.	6 a.m	15grs					
	12 a.m	10cc&15grs	13,000	2,160 Poly	free	present	present
	6 p.m	15grs		morphs	in		
	12 p.m	5cc&15grs		256 lymph	C.S.F		
		Total 37grs		ocytes			
5.	6 a.m	5cc&15grs					
	12 a.m	10cc&15grs	9,900	-	-	present	present
	6 p.m	15grs					
	12 p.m	5cc&15grs					
		Total 30grs					
6.	6 a.m	5cc&15grs					
	12 a.m	5cc&15grs	7,800	-	-	present	present
	6 p.m	15grs					
	12 p.m	5cc&15grs					
		Total 30grs					
7.	6 a.m	5cc&15grs					
	12 a.m	15grs	15,400	-	-	present	present
	6 p.m	5cc&15grs					
	12 p.m	5cc&15grs					
		Total 32grs					
8.	6 a.m	15grs					
	12 a.m	15grs	10,000	-	-	present	present
	6 p.m	15grs					
	12 p.m	15grs					
		Total 60grs					

The leucocyte count continued to fall steadily and reached normal figures on the twelfth day, thus:-

9th day	9,700
10th "	7,200
11th "	6,700
12th "	5,600

The Prontosil was discontinued after the eighth day, a total of 570 grains or 38 grams having been administered in the 7 $\frac{1}{2}$ days. The sodium bi-carbonate was continued in doses of 90 grains per day for a further five days and the urine was a normal colour again within three days of stopping the drug. A marked rise in temperature and intense headache on the fourth day forced me to discard Dr. Stone's injunction to "leave me alone", and to relieve the obvious pressure symptoms a second lumbar puncture was performed, 35 ccm of turbid fluid, now not so frankly purulent, and still under considerable pressure was removed with an immediately beneficial result as manifested by the instant relief of the headache and a rapid fall in temperature. On the sixth day a further rise in temperature (103.2 F) and a recurrence of the intense headache induced me in the light of the experience two days previously to repeat the lumbar puncture for the third time. Some 30 cc of cerebrospinal fluid, still somewhat turbid, were removed on this occasion, and the opportunity was taken to inject some 7 cc of Prontosil intrathecally, with a corresponding adjustment of the daily dose. Apart from the marked relief of the headache due to the decompression I was unable to convince myself that any advantageous effect was obtained from the intrathecal injection of this one dose of Prontosil by this route. On the eighth day the drug was stopped as deep cyanosis and signs of marked sulphaemoglobinaemia were present, and a

slight icteric tinge on the cornea was seen, and the bleeding time too was found to be increased, indicating the presence of haemolysis in its early stages. On the ninth day the temperature rose to 103 F, but in view of the signs noted above, being present on the 8th day, I did not dare to give any more Prontosil, and I thought further that the Prontosil might in itself, through its toxic reactions, be wholly or in a large measure responsible for this febrile reaction (drug fever). That this theory probably correct in this case was shown in the next two days by the rapid fall in the temperature to normal, the disappearance of the sulphaemoglobinaemia, and of all evidences of haemolysis.

The pulse throughout varied from 60 to 80 per minute. No other medication was given apart from enemata, cascara, the occasional use of morphia, omnopon and luminal, in the appropriate symptomatic treatment of incidental symptoms as they arose. All sulphur containing compounds such as saline laxatives, Epsom and Glauber salts, Mist alba and compound Liquorice and Mist Senna Co were avoided. All eggs, and food containing eggs, and onions and cabbage were omitted from the diet.

The neurological symptoms rapidly improved, head retraction especially yielding early, being absent on the sixth day.

The Brudzinski leg sign remained as did the Babinski sign until the eleventh day, and the exaggerated knee jerks were normal on the twelfth day. He was actually able to sit up and move about in bed as early as the afternoon of the fifth day but this naturally was not encouraged. Daily ophthalmoscopic examination showed no abnormality of discs or retinae on any occasion.

The patient was allowed up on this 14th day and no sequelae in

Case I.
4 HOUR CHART.

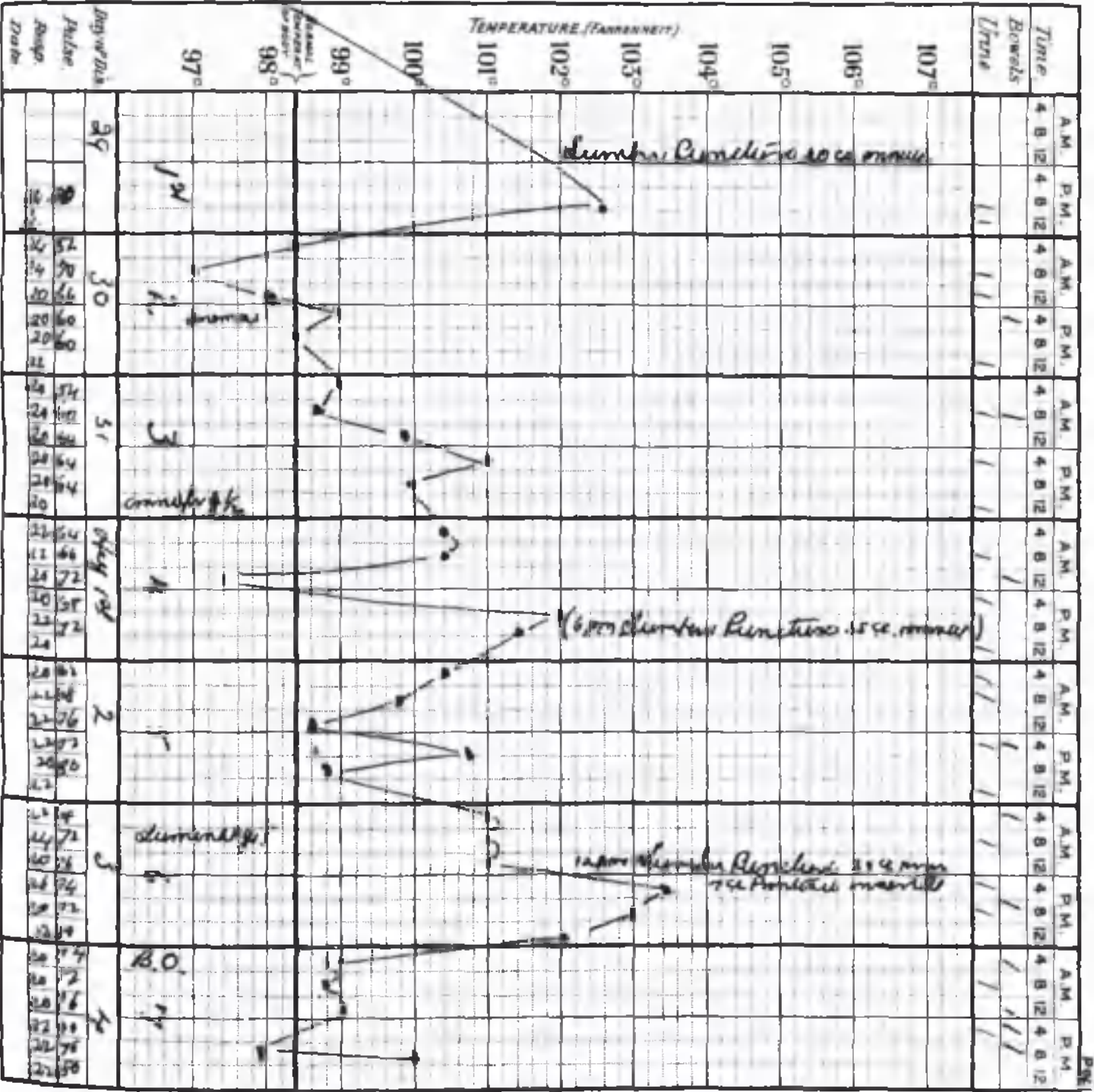
DISEASE.
MENINGOCOCCAL
MENINGITIS.

Name James
Bartolman
Age 32 Y.
Dial Blood Light.
Case Book No T.

Notes of Case.

excludes from diet.
Eggs - all eggs
containing food, also
onion, cabbage
No hydrog, milk, etc
in past 24 hours
Laminolytic.
N.A.D.

Date of admission
29: 7: 38
Russett General



Temperature (Centigrade) 35 36 37 38 39 40 41 42

4 HOUR CHART.

DISEASE.

Name {

Age

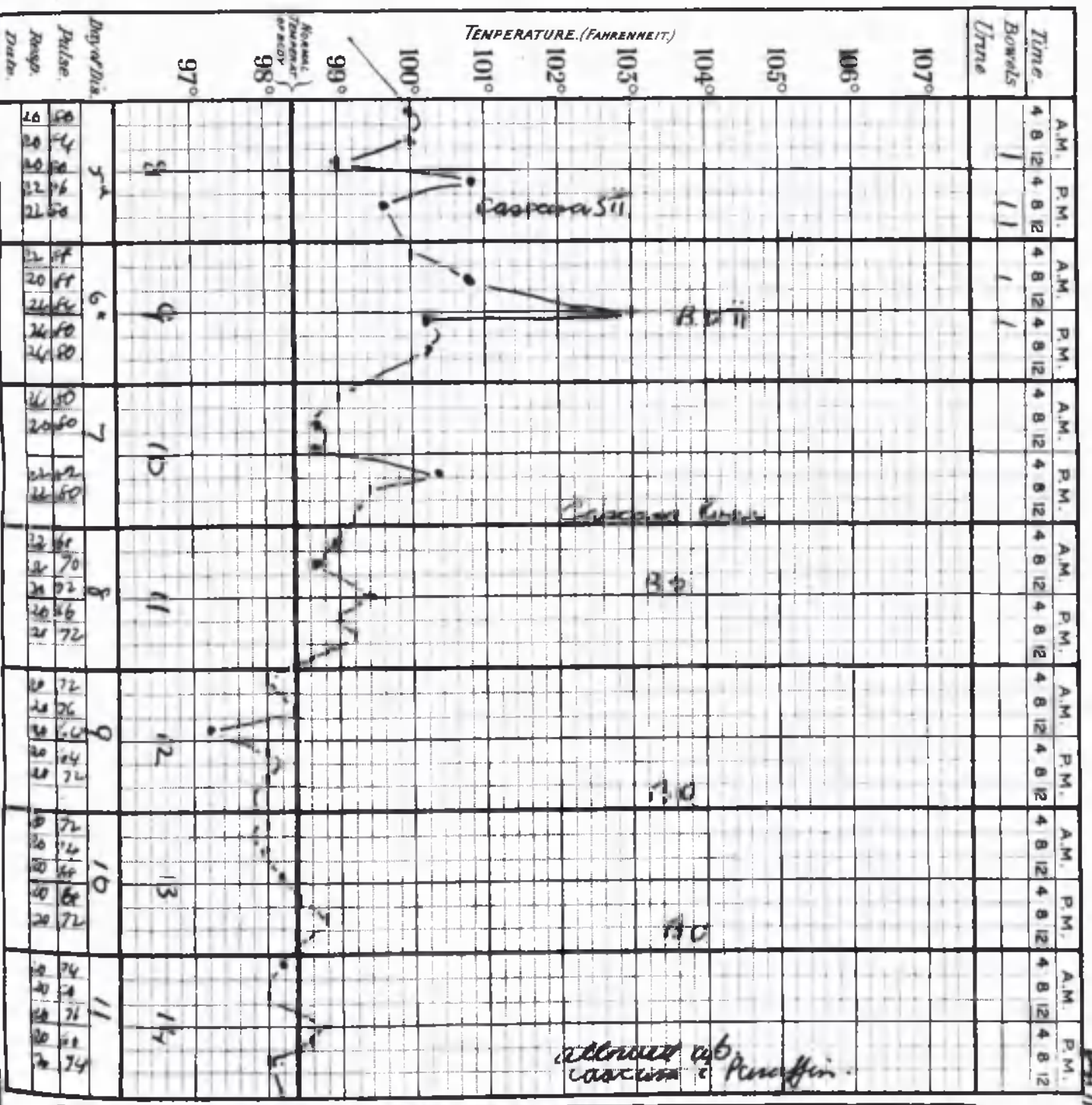
Diet

Case Book No.

Notes of Case.

Date of admission

Resident



at least 100 castor oil Penicillin

4 HOUR CHART.

DISEASE.

Name {

Age

Died

Case Book No.

Notes of Case.

Date of admission

Result

Time	A.M.		P.M.		A.M.		P.M.		A.M.		P.M.		A.M.		P.M.		A.M.		P.M.	
	4	8	12	4	8	12	4	8	12	4	8	12	4	8	12	4	8	12	4	8
Bowels	1																			
Urine																				
Temp. (Fahrenheit)																				
Normal Temperature of Body	98°																			
Day of Dis.	12		13		14		15		16		17		18							
Pulse	72	70	72	70	72	70	76	76	76	76	76	76	76	76	76	76	76	76	76	76
Resp.	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Date																				

Discharged from Hospital 16/2/38.

Page III



the shape of cranial nerve lesions or alterations of the mental state occurred. He left Hospital two days later and returned to work, well and strong and as far as could be ascertained healthy in every respect, in four weeks from the date of the onset of his illness.

Case 2.

R.W.W. Aetat 17 years, Male, Clerk in Native Time Office, was admitted from the same Gold Mine the day following the previous case. These two cases were ~~at~~ no time in contact even remotely while at work. His temperature on admission was 103.6 F. and he too showed all the usual symptoms of meningococcal meningitis. In his case however the petechial rash was much more profuse but he was certainly not so toxic and did not appear to be nearly so ill as the former man. This case too was diagnosed immediately on admission and within 12 hours of the onset of the premonitory symptoms.

Lumbar puncture was performed purely for the confirmation of the diagnoses, and in this case I was able to pursue one of my main objects, that is to do one puncture for confirmatory purposes, and the one puncture only.

The treatment in this case too was almost identical or as nearly so as possible to that in case One, except that the opportunity did not arise to enable me to give an intrathecal injection at the same stage as in the former case.

The dosage in case Two was exactly the same as in case One for the first four days, when owing to the extremely rapid and at the same time dramatic improvement as shown by the almost complete disappearance of all the signs, the intramuscular injections of Prontosil soluble were discontinued. On the 5th, 6th and 7th days he was given two tablets of Prontosil Rubrum by mouth every six hours,

that is 60 grains or 4 grams per day, the drug then being completely withdrawn.

Cerebrospinal fluid, cell and cocci counts were done on only one occasion and the progress was estimated mainly by the symptoms and by the blood leucocyte counts as tabulated below. As can be clearly seen, these latter showed a steady fall from 11,700 per cmm on the first day to 4,200 on the tenth day when they were discontinued.

Sulphaemoglobinaemia and Haemolysis, especially the latter although both were present, were very much less marked no doubt due to the smaller doses of Prontosil which were found to be necessary.

This case received in all 495 grains or 33 grams.

The striking features of this case, probably because the diagnoses was made sooner and the treatment begun more early, were:-

1. The very rapid improvement.
2. The ability to reduce the dose on the fifth day with safety.
3. The very rapid control of the infection.

Similar precautions as in case One, were exercised in regard to the ingestion of Sulphur, and the use of bi-carbonate of soda etc, and the patient was allowed up on the eleventh day and left hospital on the fourteenth day. The neurological signs improved very rapidly indeed, there being no rigidity present on the fifth day and all other signs previously present were either absent or had reverted to the normal condition by the eighth day, the knee jerk again being the last to reach its normal excursion. The petechiae had vanished entirely by the fourth day of the treatment, notwithstanding their profuseness, howbeit small in diameter. The leucocyte count, never so high as in case One fell steadily each day and returned to normal on the tenth day.

The figure of 4,200 appeared to be on the low side on the ninth day and prompted the count on the tenth day, a possible tendency to agranulocytosis being recognised.

Case 2. R.W.W. admitted 4 a.m. 31/7/39.

Day.	Time.	Dose & Preparation.	Leucocytes in blood.	C.S.F. cell count.	Cocci in C.S.F.	Sulphaemo Globinuria	Prontosil in urine.
1.	6 a.m.	10cc&15grs					
	12 a.m.	5cc	11,700	3,100	Numerous	-	-
	6 p.m.	5cc&15grs					
	12 p.m.	15grs					
		Total 82½ grs					
2.	6 a.m.	10cc&15grs					
	12 a.m.	5cc	10,200	-	-	-	present
	6 p.m.	5cc&15grs					
	12 p.m.	15grs					
		Total 82½ grs					
3.	6 a.m.	15grs					
	12 a.m.	10cc&15grs	8,400	-	-	Present	present
	6 p.m.	15grains					
	12 p.m.	5cc&15grs					
		Total 87½ grs					
4.	6 a.m.	5cc&15grs					
	12 a.m.	5cc&15grs	7,200	-	-	present	present
	6 p.m.	15 grs					
	12 p.m.	5cc&15grs					
		Total 90 grs					
5.	6 a.m.	15grs					
	12 a.m.	15grs	5,900	-	-	present	present
	6 p.m.	15grs					
	12 p.m.	15grs					
		Total 60 grs					
6.	6 a.m.	15grs					
	12 a.m.	15grs	5,600	-	-	present	present
	6 p.m.	15grs					
	12 p.m.	15grs					
		Total 60 grs					
7.	6 a.m.	15grs					
	12 a.m.	15grs	5,200	-	-	present	present
	6 p.m.	15grs					
	12 p.m.	15grs					
		Total 60 grs					

Case 4 HOUR CHART.

DISEASE.

MENINGOCOCCAL
MEINGITIS.

Name *R.W. WALKACE*
Age *17 yrs*
Diet *Blawid diet.*
Case Book No *11*

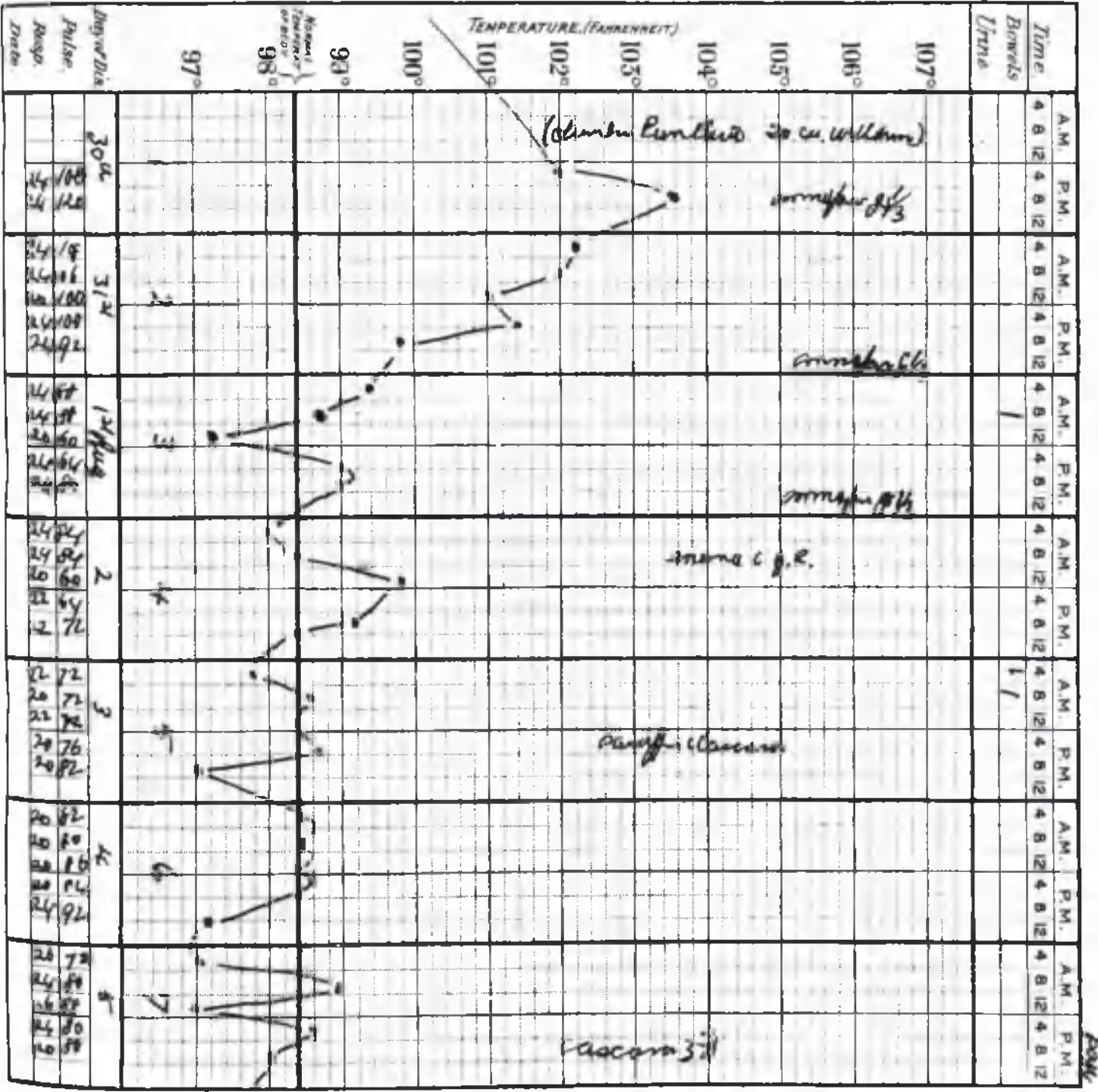
Notes of Case

Exchange diet eggs.
all egg foods, also over
colleges.

No MGA, but Allen
must learn to.

Lumbar: NAD.

Date of admission
30 : 7 : 38
Rupture Curved.



Temperature (Centigrade) 35 36 37 38 39 40 41 42

4 HOUR CHART.

DISEASE.

Name {

Age

Died

Case Book No

Notes of Case.

Date of admission

Resort

Time	Bowels		Urine	Temp. (Fahrenheit)		Notes
	A.M.	P.M.		A.M.	P.M.	
4	8	12	4	8	12	100°
4	8	12	4	8	12	
4	8	12	4	8	12	102°
4	8	12	4	8	12	
4	8	12	4	8	12	104°
4	8	12	4	8	12	
4	8	12	4	8	12	106°
4	8	12	4	8	12	
4	8	12	4	8	12	99°
4	8	12	4	8	12	
4	8	12	4	8	12	97°

Day	Temp. (F)	Temp. (C)	Notes
6	100.4	38.0	B
7	100.2	37.9	C
8	100.1	37.8	D
9	100.0	37.8	E
10	99.8	37.7	F
11	99.6	37.6	G
12	99.4	37.5	H
13	99.2	37.4	I
14	99.0	37.3	J

B.O. II

B.O.

Cocaine & Paraffin

B.O. III

Alimentus

B.O.

Cocaine & Paraffin

B.O.

→ Cocaine & Paraffin 16th day



Leucocyte count continued gave the following figures:-

8th day	5,100
9th "	4,200
10th "	5,200

Case 3.

N.A.G. Aetat 26 years, Male, South African Dutch, Miner, was admitted to hospital on 25th March 1938. He had been ill for two days previously suffering from severe headache and noisy delirium. On admission he was found to be extremely ill. There were numerous petechiae present, some cyanosis, very marked nuchal rigidity, and noisy restless delirium were observed. It was very difficult to keep him in bed and two special nurses had to be engaged to do day and night duty with him.

Lumbar puncture was done immediately and the fluid was found to be frankly purulent, not very thick, and under great pressure. There was a mild degree of papilloedema of both discs and paralysis of the internal rectus muscle of the left eye. He was however still quite able to swallow and there was no incontinence of urine or faeces. All the other neurological signs of meningeal irritation were markedly present and the case was obviously dangerously ill.

He was given 20 ccm of Prontosil Soluble intramuscularly and 15 grains of Prontosil Rubrum by mouth and the dosage was then carried out as in the accompanying table.

The delirium continued until the fourth day of treatment and the restlessness for another day. A fair amount of omnopon was used to control the restlessness and violence, and to prevent his injuring himself by throwing himself about the bed.

Diet had to be liquid in nature but it was not found necessary to resort to nasal feeding as had appeared to be likely in the beginning.

The first four days found the patient critically ill and deeply toxic but on the fifth day marked improvement began and was maintained continuously to the end of the treatment.

The papilloedema disappeared on the fifth day and the ocular symptoms were again quite normal on the sixth day. Absolutely no sequelae of any kind resulted from the severe intracranial infection he had weathered so well. The administration of the Prontosil was continued for seven days but the dose was reduced during the last two days. It seemed as if the doses might have been given in even smaller quantities but it was considered inadvisable to reduce the total quantity too greatly as some slight rise in temperature persisted.

This patient was allowed up on the fourteenth day and left hospital two days later. He returned to work within four weeks of the date of the onset of his illness and to all intents and purposes as far as could be determined clinically he was perfectly well.

Sequelae of a neurological nature could reasonably have been expected to eventuate with such a very severe infection but these fortunately did not occur in any shape or form.

In this case too, lumbar puncture proved to be necessary on only the one occasion and no opportunity arose to do any further counts of the cells and cocci present in the C.S.F., or to discover when the latter were to be found to be floating free in the C.S.F.

The total quantity of Prontosil given was 562 grains or 37.5 grams.

The leucocyte count was continued for four more days with the following results:

9th day	6,100
10th "	7,000
11th "	5,300
12th "	5,600

these counts were then discontinued.

Case 777
4 HOUR CHART.

DISEASE.

Meningococci
Meningitis.

N. A.

Name Greenstein

Age 26 years

Died 11-10-1918

Case Book No 111

Notes of Case.

Excluded fructid

eggs. all egg containing

also steam. Culture

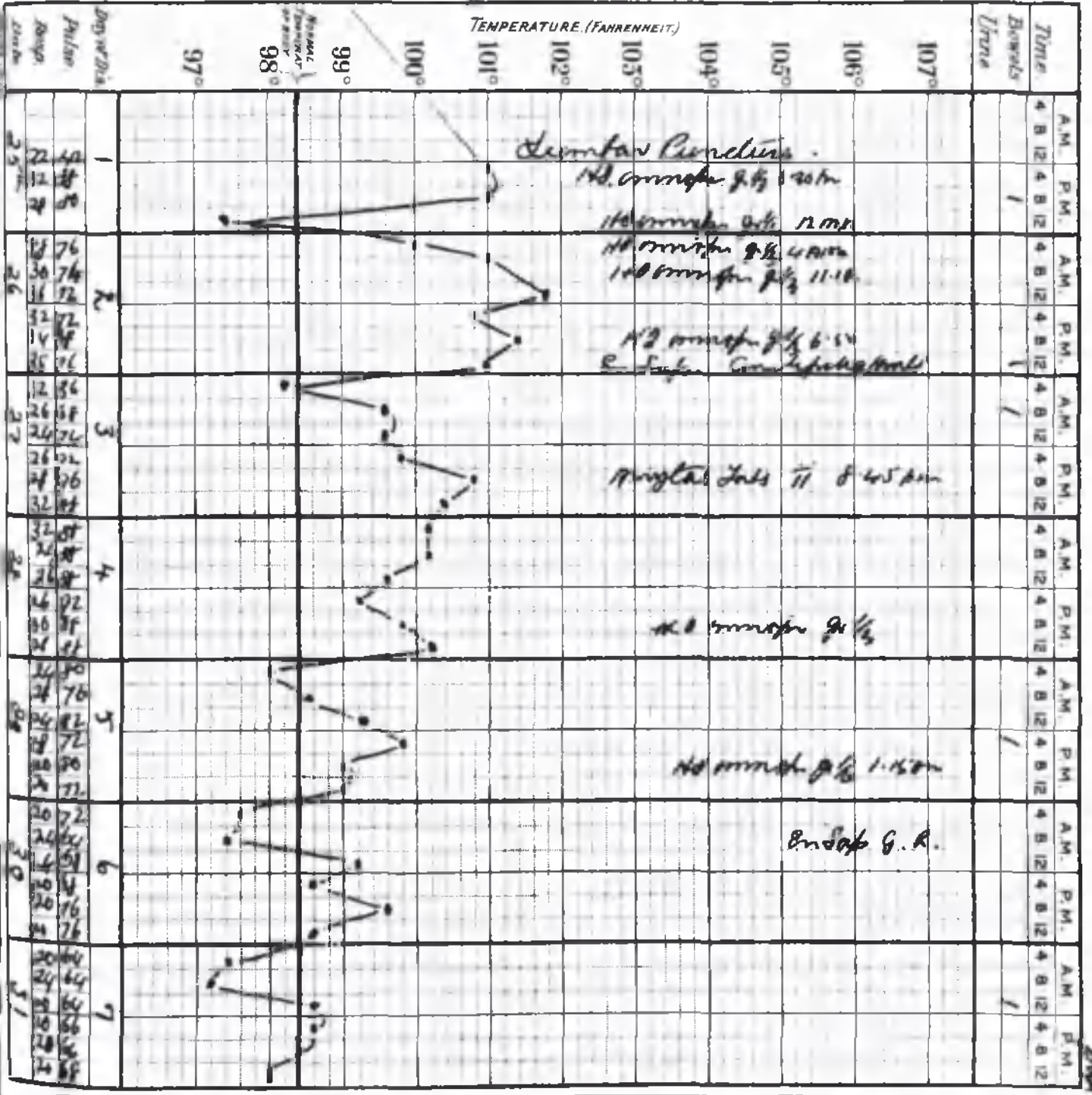
No night, health

in Philadelphia Co

Leontopos N.A.D.

Date of admission
25. 3. 39

Revised Case.



4 HOUR CHART.

DISEASE.

Name {

Age

Diet

Case Book No

Notes of Case.

Date of admission

Resident

Time	A.M.		P.M.		A.M.		P.M.		A.M.		P.M.		A.M.		P.M.	
	4	8	12	4	8	12	4	8	12	4	8	12	4	8	12	4
Bowels																
Urine																
107°																
106°																
105°																
104°																
103°																
102°																
101°																
100°																
99°																
98°																
97°																
Normal Temperature of Body																
Day of Dis.	8		9		10		11		12		13		14			
Pulse.	94	94	94	94	81	81	76	76	70	70	75	75	76	76	70	70
Resp.	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Temp.	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2	98.2

TEMPERATURE (FAHRENHEIT)

Normal Temperature of Body



Case 3. N.A.G. admitted 25/3/39.

Day.	Time.	Dose & Preparation.	Leucocytes in blood.	C.S.F cell count.	Cocci in C.S.F.	Sulphaemo Globinuria	Prontosil in urine.
1.	6 p.m	20ccm					
	12 p.m	22grs	23,000	-	-	-	-
		Total 52grs					
2.	6 a.m	10cc&15grs					
	12 a.m	15 grs	21,300	6,100	numerous	-	present
	6 p.m	10cc&15grs					
	12 p.m	15grs					
		Total 90 grs					
3.	6 a.m	10cc & 15 grs					
	12 a.m	15grs	19,000	-	-	-	present
	6 p.m	10cc&15grs					
	12 p.m	15grs					
		Total 90 grs					
4.	6 a.m	10cc&15grs					
	12 a.m	15grs	12,000	-	-	present	present
	6 p.m	10cc&15grs					
	12 p.m	15grs					
		Total 90 grs					
5.	6 a.m	5cc&15grs					
	12 a.m	15grs	9,700	-	-	present	present
	6 p.m	5cc&15grs					
	12 p.m	15grs					
		Total 75 grs					
6.	6 a.m	5cc&15grs					
	12 a.m	15grs	7,600	-	-	present	present
	6 p.m	5cc&15grs					
	12 p.m	15grs					
		Total 75 grs					
7.	6 a.m	15grs					
	12 a.m	15grs	7,800	-	-	present	present
	6 p.m	15grs					
	12 p.m	15grs					
		Total 60 grs					
8.	6 a.m	15grs					
	12 a.m	15grs	6,200	-	-	present	present
		Total 30 grs					

Case IV.

Child Van Wyk, aetat 20 months, South African Dutch, was seen by me on the 22nd July 1939 for the first time. He had taken ill two days previously suffering from an injected throat, pain in the right ear and some restlessness but no pyrexia. When seen by me he was pulling at his left ear, had petechiae on hands and arms, had a marked Kernig's sign, Brudzinski's leg and neck signs and bilateral Babinski's sign. He was semi-comatose and was screaming loudly.

The ears were washed out and on inspection per otoscope both drums were found to be red but not bulging and the middle ears were not infected. The infection appeared to be of a pneumococcal type.

Lumbar puncture was performed immediately in the house and the fluid was seen to be frankly purulent and under pressure. Ten ccs of fluid were removed at once with obvious and immediate relief to the patient, who stopped crying and soon fell asleep.

His medical attendant had already given the child one tablet of M & B 693 and was anxious to continue this four hourly as he considered the case to be one of pneumococcal meningitis next day however the meningococcus was found to be present in the C.S.F. and treatment by Prontosil was begun giving one third of the usual adult dose namely thirty grains per day both by mouth and parenterally as described in the previous cases.

The table of doses and serial leucocyte counts is given below.

As the temperature continued to be sustained at a fairly high level the dose of Prontosil was increased on the sixth day. On the fifth day a complication in the shape of a marked synovitis of the left knee appeared, which did not seem at any time to be painful,

but it was nevertheless thought that this complication partly or wholly was responsible for keeping up the leucocytosis which was seen to increase at this time. The increase in the leucocytosis lead to the decision to increase the dosage.

Another striking feature of this case was the amazing tolerance displayed by this child to the very large doses of Prontosil which were given in the last few days. No signs of toxaemia were noticed at any time during the eight days of treatment. Cyanosis was minimal and the degree of sulphaemoglobinaemia was of the slightest. Nor was the urine so deeply coloured by the drug as in the cases of all the Adults previously treated.

This case then seemed to illustrate that Prontosil was safe and effective even in very young children and that the administration of the drug in large doses up to and above the expected effective dose as calculated as one third of the dose for Adults suffering from a similar attack.

The synovitis was treated purely by aspiration of the knee joint and this treatment alone was effective and did not leave any sequelae in the shape of stiffness or injury to the surrounding bony parts.

Dosage table is given overleaf.

It will be seen that this child received 55 grains of M & B 693 and 240 grains of Prontosil over the eight days but it was felt that in the absence of the synovial complications a dosage of approximately 30 grains per day would have been sufficient.

Case IV. Child Van Wyk, admitted

Day.	Time.	Dose & Preparation.	Leucocytes in blood.	C.S.F. cell count.	Cocci in C.S.F.	Sulphaemo globoinuria in urine.	Prontosil
1.	11 a.m.	M&B 1 tab.					
	12 a.m.	2cc Pront.	18,000	-	-	-	-
	6 p.m.	1 tab. M&B					
	12 p.m.	1 tab. M&B					
		Total 32½ grs					
2.	6 a.m.	M&B 1 tab.					
	12 a.m.	M&B 1 tab.	17,500	-	numerous	-	-
	6 p.m.	1 tab Pront					
	12 p.m.	1 tab Pront					
		Total 22 grs					
3.	6 a.m.	7½ grs					
	12 p.m.	2.5cc & 7½ grs					
	6 p.m.	7½ grs	14,700	-	-	-	-
	12 p.m.	2.5cc & 7½ grs					
		Total 35 grs.					
4.	6 a.m.	2½cc & 7½ grs					
	12 a.m.	7½ grs	12,500	-	-	slight	present
	6 p.m.	2½cc & 7½ grs					
	12 p.m.	7½ grs					
		Total 35 grs					
5.	6 a.m.	2½cc & 10grs					
	12 a.m.	7½ grs	20,800	-	-	slight	present
	6 p.m.	2½cc & 7½ grs					
	12 p.m.	10 grs					
		Total 40 grs.					
6.	6 a.m.	2½cc & 10 grs					
	12 a.m.	10 grs	25,000	-	-	slight	present
	6 p.m.	2½cc & 7½ grs					
	12 p.m.	10 grs.					
		Total 45 grs.					
7.	6 a.m.	2½cc & 10 grs					
	12 a.m.	10 grs	17,500	-	-	slight	present
	6 p.m.	2½cc & 10 grs					
	12 p.m.	10 grs					
		Total 50 grs.					
8.	6 a.m.	2½cc & 10 grs					
	12 a.m.	7½ grs	12,000	-	-	slight	present
	6 p.m.	7½ grs					
	12 p.m.	7½ grs					
		Total 37½ grs.					

Case IV
4 HOUR CHART

DISEASE:
On Stone & Hill

Membranococcal
hemipilis

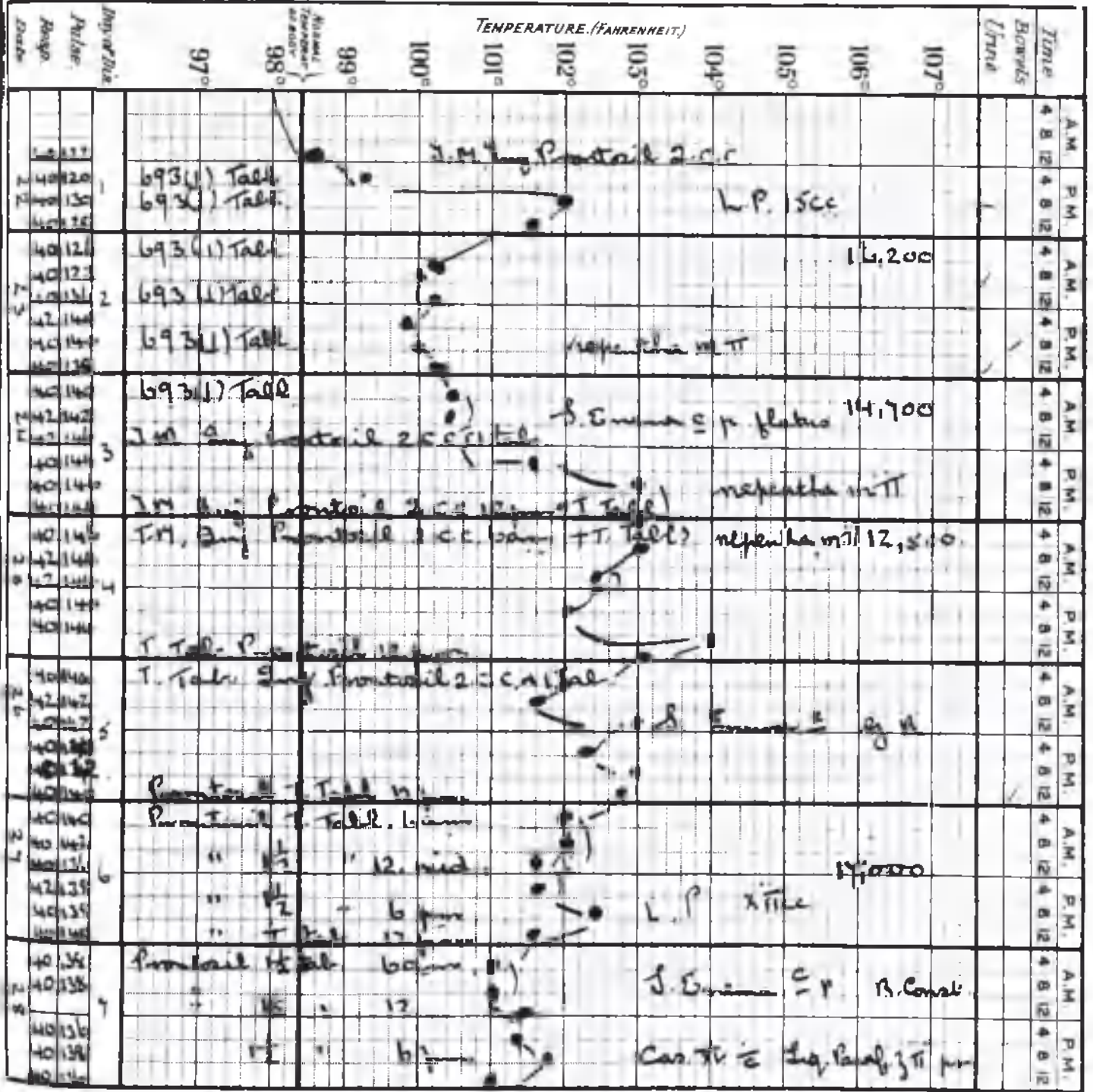
Name: (none)
van Wyk

Age: 2 yrs

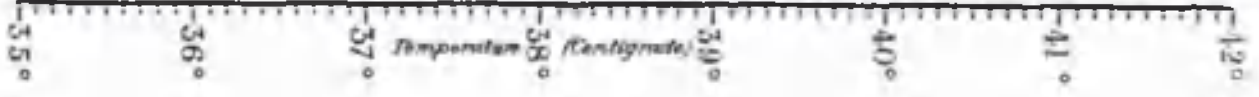
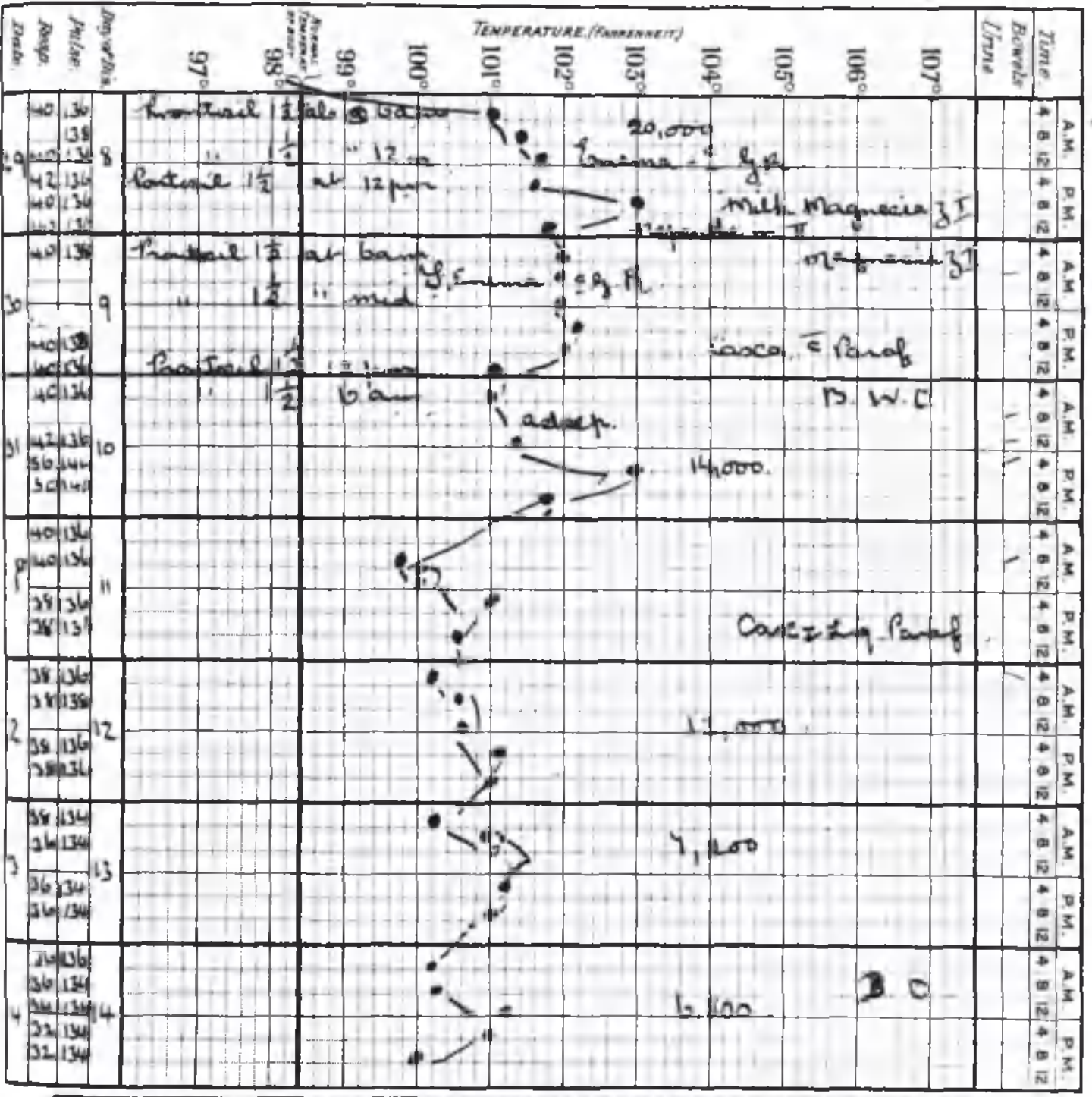
Diid
Case Book No

Notes of Case

Date of admission
22-7-39



Temperature (Centigrade) 35° 36° 37° 38° 39° 40° 41° 42°



Case 5. J.G.P. aetat 22 years, Male, South African Dutch, was taken ill in the morning of August 22nd 1939, he had a headache on arriving but proceeded to his work as a Miner underground in his usual fashion. At work the headache became greatly intensified and was soon accompanied by severe pain in the back. The headache and backache grew worse as the day progressed and he walked from his work to consult his doctor. He was seen at 5.p.m this same day and was then found to have all the signs and symptoms of a well developed case of cerebrospinal meningitis, with ~~neck~~ rigidity, Kernic's sign, Babinski sign etc, He was sent to hospital at once and lumbar puncture was performed soon after arrival. The fluid was found to be under pressure becoming purulent and markedly turbid.

This case was one of the earliest in which a positive diagnoses was made and treatment was consequently begun very early after the onset of the symptoms. The actual treatment was commenced ten hours from the onset of his first and earliest symptom namely the headache.

A rapid response to treatment was now confidently expected and as the accompanying charts show one was rapidly enabled to reduce the dosage, on the seventh day however a recurrence of the headache and a slight rise in temperature forced one to increase the dose somewhat and as less than the usual amount of Prontosil had been given it was continued up to and including the ninth day. In this case too no sequelae of any kind eventuated and the response to treatment was again both rapid and dramatic. After two days of treatment the outcome as a very favourable result never seemed to be in any possible doubt.

Case 5. J.G.P. admitted 22/8/38.

Day.	Time.	Dose & Preparation.	Leucocytes in blood.	C.S.F. cell count.	Coeci in C.S.F.	Sulphaemo globinuria in urine.	Prontosil
1.	6 p.m.	20cc & 15grs					
		Total 30 grs.					
2.	6 a.m.	15grs	18,200	-	numerous	-	-
	12 a.m.	10cc & 15 grs					
	6 p.m.	5cc & 30 grs					
	12 p.m.	15grs					
		Total 97½ grs.					
3.	6 a.m.	5cc & 15grs					
	12 a.m.	7½ grs	17,000	-	-	-	present
	6 p.m.	15 grs					
	12 p.m.	15 grs					
		Total 52½ grs.					
4.	6 a.m.	15grs					
	12 a.m.	15grs	12,000	-	-	-	present
	6 p.m.	15grs					
	12 p.m.	15grs					
		Total 60 grs.					
5.	6 a.m.	15grs					
	12 a.m.	15grs	10,000	-	a few	-	present
	6 p.m.	15grs					
	12 p.m.	15grs					
		Total 60 grs					
6.	6 a.m.	15grs					
	12 a.m.	--	8,000	-	-	slight	present
	6 p.m.	15grs					
	12 p.m.	15grs					
		Total 45 grs.					
7.	6 a.m.	15grs					
	6 p.m.	15grs	7,000	-	-	slight	slight
		Total 30 grs					
8.	6 a.m.	15grs					
	12 a.m.	15grs	7,200	-	-	slight	slight
	6 p.m.	15grs					
		Total 45 grs					
9.	6 a.m.	15grs					
	2 P.M.	15grs	6,800	-	-	slight	present
	6 p.m.	15grs					
		Total 45 grs					

DISEASE.

Meningitis

Notes of Case.

Name *J. R. Palmer*

Diet

see next page.

Date of admission

Result

Temp	Pulse	Resp	Days of Dis	Temperature (Fahrenheit)		Remarks
				Rectal	Oral	
107°						
106°						11 6 am
105°						11 6 am
104°						11 6 am
103°						11 6 am
102°						11 6 am
101°						11 6 am
100°						11 6 am
99°						11 6 am
98°						11 6 am
97°						11 6 am

Case V
4 HOUR CHART.

DISEASE.

Protonyctocæle
Peritonitis

Name Mr. G. G.

Age 29 yrs.

Diet _____

Case Book No. _____

Notes of Case.

Temp. Test

Place - Amber

Sp. 58. 1894

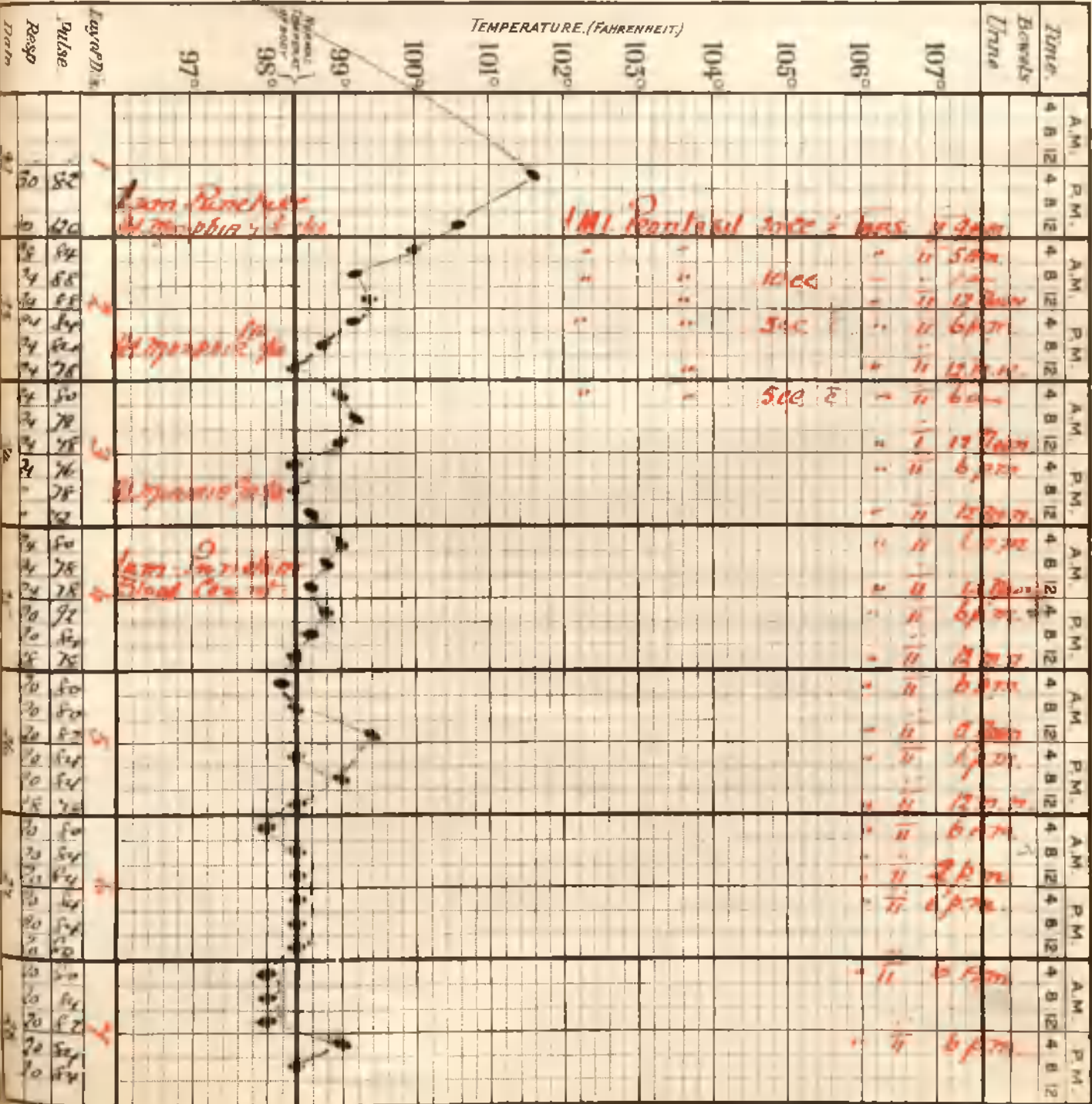
Place - Tent

All - Nil

Signs - "

Diagnosis - "

Date of admission
92 - 5 - 39



Case 6.

This last case occurred about the same time and the investigation was carried through in the same manner as the preceeding cases, and is included in the series by way of contrast, arising out of a mis-diagnosies.

This man W.J.D. aetat 50 years, Master plumber, British South African, was seen at his own home in Johannesburg by a general practitioner on 14th September 1938.

He was found at that time to have an intense headache, photophobia/severe pains in the limbs and body/and nasal and bronchial catarrh. He was diagnosed as a case of influenza and treated by means of Salicylate of Soda and a sedative cough mixture. These symptoms continued more or less unabated for two more days when he was admitted to hospital. He was then given one 5ccm injection of Prontosil Soluble intramuscularly, Empirin compound, and Prontosil by mouth in doses of eight tablets or 60 grains daily for three days, as a treatment for the influenza with the intense headache. He had a rigor on the second day after admission and developed some nuchal rigidity. I saw him for the first time on the seventh day of the illness when he was seen to present all the signs and symptoms of a moderate attack of meningitis. He did not however have a very toxic appearance. His temperature was 101 F. and Kernig's sign, Brudzinski's neck and leg sign, and Babinski's sign were all present. Photophobia was marked and headache was intense. In spite of this, signs of mental abnormality were absent, and he was quite lucid. It did not appear from the mode of onset and the absence of toxicity to be a true meningococcal meningitis, but it was thought advisable to treat it as such.

Lumbar puncture was performed and the fluid was seen to be somewhat cloudy, under moderate pressure, and not purulent. 20ccm were removed for the purpose of diagnosis and to relieve the pressure and the Combined Prontosil treatment for meningococcal meningitis begun with doses larger than had been used at the beginning of his illness.

Although no ^{real} improvement had been noted on the earlier oral Prontosil treatment, such improvement began almost immediately on beginning and the intramuscular injections in combination with the oral route. Treatment in this case produced the same marked improvement on the fourth day of introducing the larger doses and augmenting the action of the drug by the use of the combined method. The leucocytosis in this case was not so marked as in the other cases but as some three days treatment had already been given the initial figure was consequently unknown. It soon became apparent that the 60 grain doses by mouth were not enough, and this is well seen by a reference to the accompanying temperature charts.

VI
24 HOUR CHART.

DISEASE.

*Influenza
Menigitis*

Name *W. J. Dukes.*

Age *50 yr*

Diagnosis *Blind*

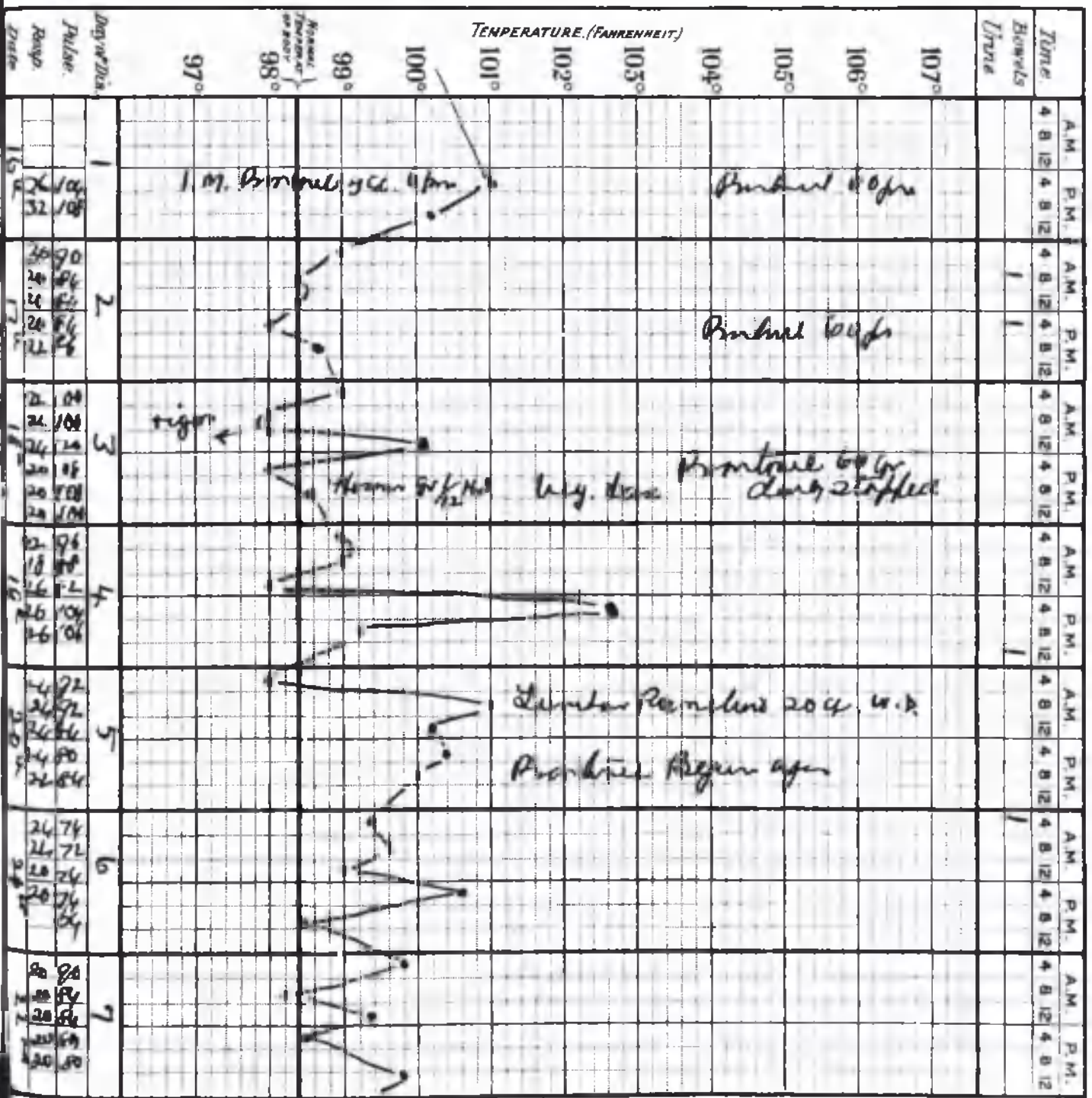
Notes of Case.

*Stomatitis
de Galla.*

*Several prescants
for Antinal.*

Date of admission

16 : 9 : 38



4 HOUR CHART.

DISEASE.

Name {

Age

Diets

Case Book No

Notes of Case.

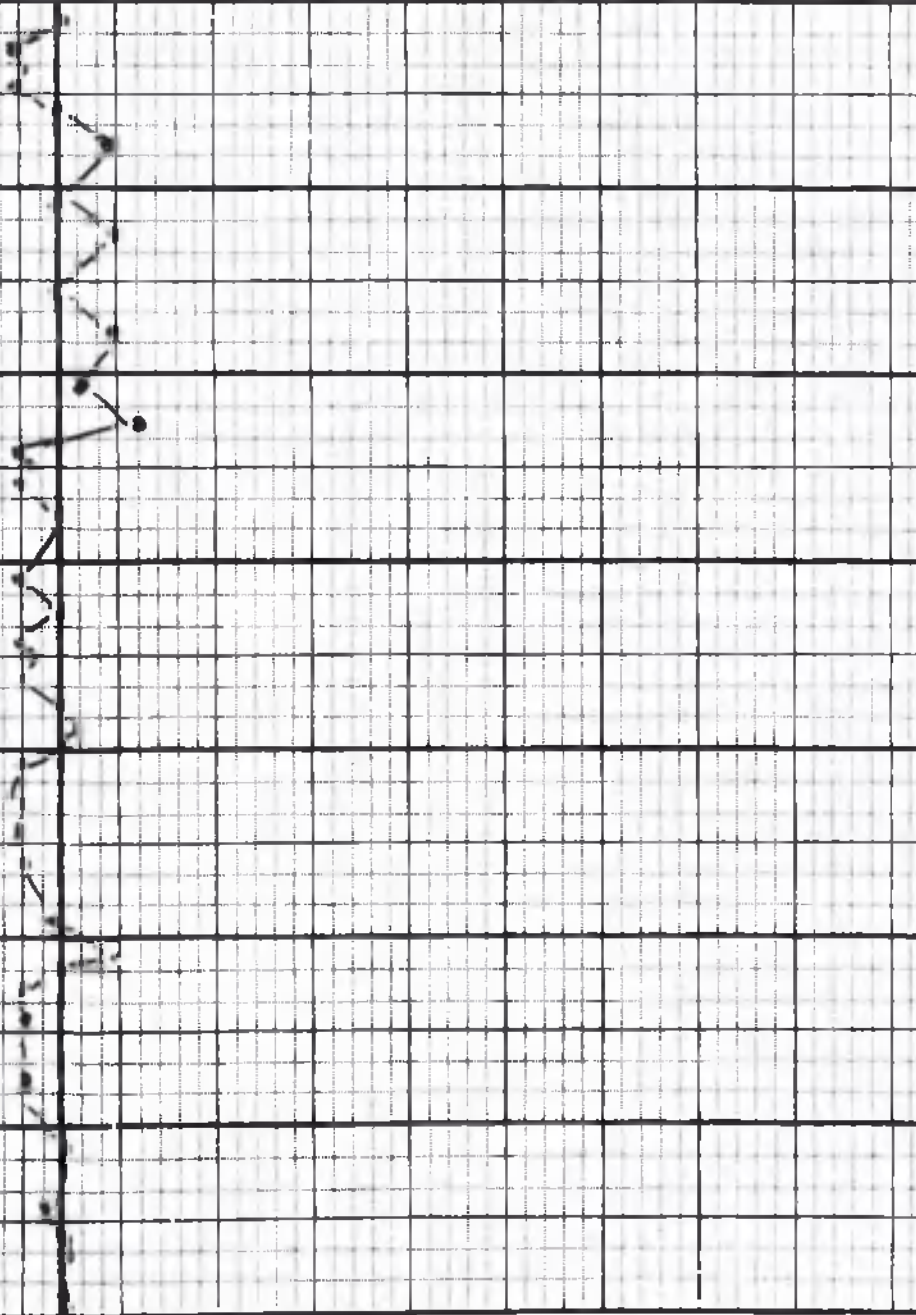
Date of admission

Time.	A.M.		P.M.		A.M.		P.M.		A.M.		P.M.		A.M.		P.M.	
	4	8	12	4	8	12	4	8	12	4	8	12	4	8	12	4
Bowels																
Urine																
Temp.																
Day of Dis.	5		6		7		8		9		10		11		12	
Pulse.	88	76	76	76	80	80	80	80	88	88	84	84	76	76	76	76
Resps.	22	22	22	22	20	20	20	20	22	22	24	24	20	20	22	22
Date	2-22		2-23		2-24		2-25		2-26		2-27		2-28		2-29	

TEMPERATURE (FAHRENHEIT)

107°
106°
105°
104°
102°
101°
100°
99°
98°
97°

Normal Temp. of Body



Temperature (Centigrade)

37 36 35 40 41 42

Case 6. W.J.D. admitted 16/9/38.

Day.	Time.	Dose & Preparation.	Leucocytes in blood.	C.S.F. cell count	Cocci in C.S.F.	Sulphaemo Globinuria	Prontosil in urine.
1.	6 p.m	5cc & 7½ grs					
	12 p.m	15 grs	-	-	-	-	-
		Total 30 grs					
2.	6 a.m	15 grs					
	12 a.m	15 grs	-	-	-	-	present
	6 p.m	15 grs					
	12 p.m	15 grs					
		Total 60 grs					
3.	6 a.m	15 grs					
	12 a.m	15 grs	-	-	-	-	present
	6 p.m	15 grs					
	12 p.m	15 grs					
		Total 60 grs					
4th- No Prontosil given.							
5.	10 a.m	5cc & 15grs					
	12 a.m	15grs	15,000	4,300	-	-	present
	6 p.m	15 grs					
	12 p.m	5cc & 15grs					
		Total 75 grs					
6.	6 a.m	5cc & 15grs			B. Influenza		
	12 a.m	5cc & 15grs	14,300	-	<u>present</u>	-	present
	6 p.m	15grs					
	12 p.m	5cc & 15grs					
		Total 82½ grs					
7.	6 a.m	10cc & 15grs					
	12 a.m	5cc & 15grs	11,000	-	-	present	present
	6 p.m	15 grs					
	12 p.m	5cc & 15grs					
		Total 90 grs					
8.	6 a.m	5cc & 15grs					
	12 a.m	15grs	8,500	-	-	present	present
	6 p.m	15grs					
	12 p.m	5cc & 15grs					
		Total 83½ grs					
9.	6 a.m	5cc & 15 grs					
	12 a.m	15grs	6,200	-	-	present	present
	6 p.m	5cc & 15grs					
	12 p.m	15grs					
		Total 75 grs.					

Chart Case 6 continued:

10th	6 a.m	5cc & 15grs					
	12 a.m	15grs	6,000	-	-	present	present
	6 p.m	5cc & 15grs					
	12 p.m	15grs					
	Total 75 grs.						
11th	Nil		5,600	-	-	present	present
12th	Nil		5,300	-	-	present	present

It was not surprising to see from the bacteriological report by the South African Institute for Medical Research that the Bacillus influenza was found to be the causal organism and that the condition here was that of influenzal meningitis.

No improvement was noted until the larger doses were instituted and the combined treatment instituted.

Only one lumbar puncture was done, again for purely confirmatory purposes and the usefulness of this procedure was here made obvious, demonstrating the presence of the Influenzal bacillus and not the Meningococcus. In this case no anti-serum could have been of any benefit and for that reason the Prontosil was persisted in, especially as there was no other known effective treatment.

The excellent reaction to the treatment by Prontosil of this bacillary organism was not expected and came as a distinct surprise, and it is still difficult to believe that, in spite of all appearances the Prontosil in the larger doses did actually bring about the alleviation of rather the cure of this case of Influenzal meningitis

as seemed to have been so convincingly demonstrated.

In this case too no sequelae of any kind were noted but in view of the appearance of the C.S.F, they were really not to be expected in the event of a recovery, as it happened, taking place.

Conclusions.

Although I have had only these few cases to investigate it would appear that the uniformly excellent results obtained demonstrated that we have now a potent remedy in our possession for the simple and successful treatment of a dreaded and all too often fatal infection which up to the present time, with any form of treatment has had an appalling death rate of anything from 50-80 per cent. Two of these cases investigated were undoubtedly infections of the very greatest severity in which with any other form of treatment would have appeared most likely to have ended fatally.

I think then that I have definitely been able to demonstrate fairly conclusively that meningococcal meningitis is curable by chemotherapy alone.

I feel too that I may further with strong justification and with confidence conclude that:-

1. With the ~~use~~ of Sulphanilamide, meningococcal meningitis need not now be so greatly feared as formerly.
2. Sulphanilamide, preferably as Prontosil, may be regarded as almost a specific for ~~this~~ disease.
3. Large doses are necessary, a minimum of ~~from~~ 60 to 90 grains (4 to 6 grams) daily, and for at least seven days, are required.
4. Careful watch must be kept for toxic effects around the

fifth to the seventh day, and the drug stopped after the seventh day, even if the temperature remains elevated.

It may be continued again if necessary after a "rest" of two or three days.

5. A falling leucocyte count of the circulating peripheral blood offers an easily performed and fairly reliable test of progress.
6. The use of the anti-serum is apparently not necessary.
7. Lumbar puncture may be entirely unnecessary or limited to one, for diagnostic purposes only, or for the relief of headache due to pressure of excess fluid.
8. The disease may be regarded as a meningococcaemia and treated as such, the state of the cerebrospinal fluid being entirely disregarded.
9. The treatment has been greatly simplified, and the course of the disease greatly lessened, and very much less fatal.
10. In epidemics large numbers of patients could be treated with this remedy at a fraction of the often prohibitive cost of anti-serum, a perishable commodity in tropical or subtropical climates.

REFERENCES.

- Bell J.A. and Palmer W.H. (1938), S.A. Med.Jour. Vol XII
No.20 p 745 - 747.
- Carey B.W. (1937). J. Pediat II, 202.
- Cokkinis A.J. (1938) B.M.J. No. 4038, p. 1151 et seq.
- Domagk G. Z.Klin. Med. 132, 775.
- Eldahl A. (1938) Lancet I. 712.
- Harvey A.A. and Janeway C.A. (1937). J.A.M.A. 109, 12.
- Marshall K. Emerson K. Culby W.T. (1937) J.A.M.A. 108. 953
- Morton T.C. Ewing V.S. and Elsworth J.D. (1938) B.M.J. No 4042
p. 1362 et seq.
- Rosenthal S.M. (1937). Publ. Hlth. Rep. Wash 52, 192
- Rosenthal S.M. Bauer H. and Branham S.E. 52, 552.
- Van der Poel A. (1939) S.A. Med. Jour. Vol.13, 59-60
Jan. 28th 1939.

List of References on all early work on this Subject.

1. "Meningococcal meningitis: Sulphanilamide therapy - 3 cases". T.C. Norton, V.S. Ewing and J.D. Elsworth, Brit. med. J. vol.1, 1362-1364, June 25th, 1938.
2. "Sulphonamides for meningitis (use of soluseptasine)". A. H. Winchester, Brit. med.J., vol.2, 70, July 9th, 1938.
3. "Sulphanilamide therapy in cerebrospinal meningitis". G. Lemaire, Gillot and Raynal, Algeri med. vol.42, 465-469, August 1938.
4. "Meningococcal meningitis: Sulphanilamide treatment". J.A. Bell and W.H. Palmer, South African Med. J., vol, 12, 745-747, October 22nd 1938.
5. "Meningococcal meningitis: Treated with soluseptasine and proseptasine, 9 cases". R.M. Hahhah and F.G. Hobson, Lancet, vol.2, 937-941, October 22nd, 1938.
6. "Meningococcal meningitis: Treatment with M & B 693". F.G. Hobson and D.H.G. Mac Quaids, Lancet, vol.2, 1213-1217, November 26th, 1938.
7. "Meningococcal meningitis: Sulphanilamide and sulphopyridine therapy". P.F. Armand- Delille, J. de med. et Chir. prat, vol. 110, 5-10, January 10th 1939.
8. "Treatment of meningococcal meningitis: Use of soluseptasine (Benzyl sulphanilamide derivative)". A.Van der Poel, South African Med. J., vol. 13, 59-60, January 28th, 1939.
9. "Meningococcal meningitis Sulphanilamide." G.J.Levy J. Tennessee, med. Ass., vol. 32, 1-8, Jan 1939.
10. "Cerebrospinal meningitis due to meningococcus B; cure by sulphanilamide therapy alone; case." A. Germain and G. Guiron, Bull. et mem. Soc. med. de hop. de Paris, vol.55, 103-109, February 6th 1939.