

REVIEW OF A CEREBRO-SPINAL FEVER EPIDEMIC

AMONGST TROOPS IN FRANCE.

by

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## P R E F A C E .

These observations were made in the early months of 1940, during an epidemic of cerebro-spinal fever amongst Troops of the British Expeditionary Force then stationed on the Lines of Communication in France. At that time the author was serving as Officer in Charge of the Infectious Diseases Block of No. 4 General Hospital.

All cases, in this review, were direct admissions from billets or camps to the above-named Hospital. Thus they were observed and treated from the earliest possible moment, and not, as in most Base Hospitals in France, after a lapse of days spent in travelling.

The circumstances of our military service during this period made a survey of the relevant literature impossible, access being had only to such textbooks as were contained in the small medical library of the Hospital. These observations, therefore, were based, almost entirely, on clinical experience.

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CEREBRO-SPINAL FEVER.

Period  
of  
Observa-  
tions

Material for this Thesis was obtained from observations made on all cases of cerebro-spinal fever which came under the care of No. 4 General Hospital. In all, 44 cases of cerebro-spinal fever were admitted, the first on 5th January and the last on 10th June, 1940.

INCIDENCE.

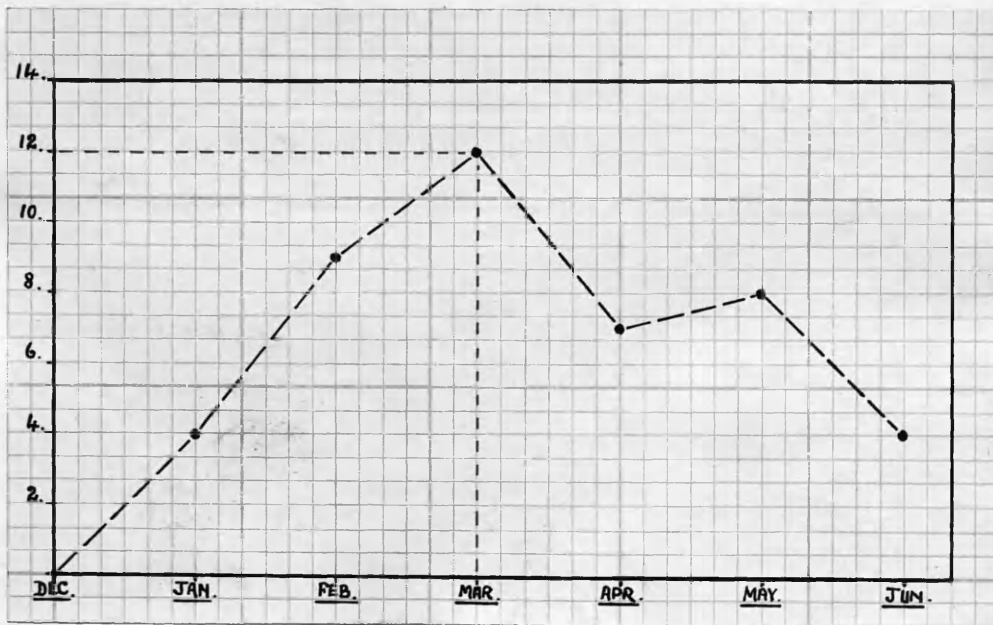
Numerical

The 44 cases described comprised all those who developed cerebro-spinal fever, during the period stated, from amongst a body of men totalling 29,000. This represents an incidence of 1.5 cases per 1,000 troops, and is no greater than the usual rate in civilian epidemics.

Seasonal

The number of cases per month reached a maximum in March, during which month 12 cases of cerebro-spinal fever were admitted to Hospital. This is demonstrated by the following graph of admissions, month by month, over the period covering the epidemic:-

Number  
of  
Cases

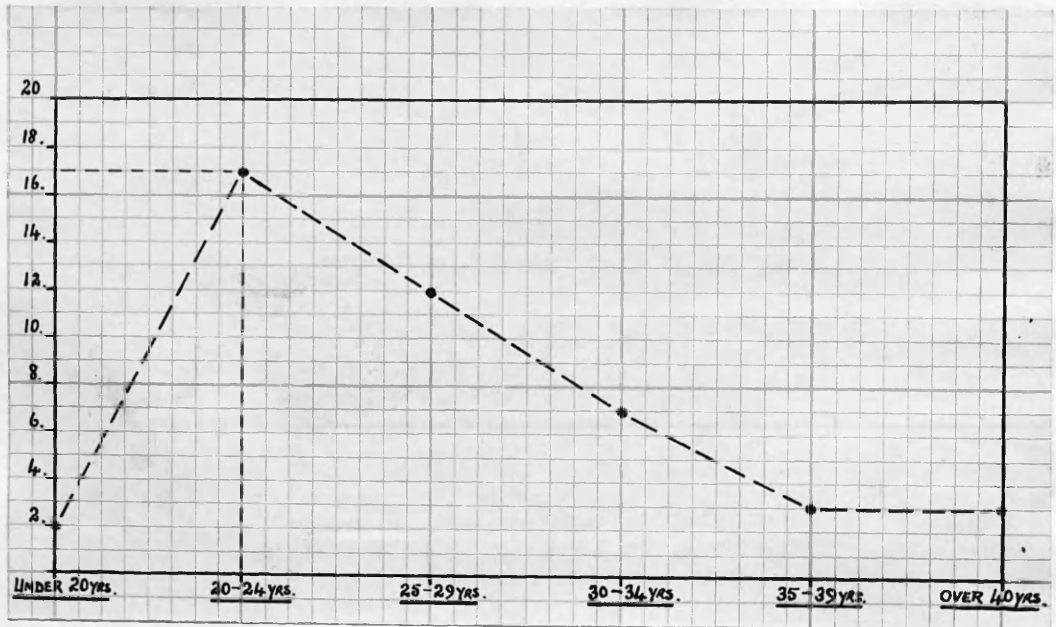


It is noteworthy that during November, December and January, there was a widespread prevalence amongst Troops of common cold, yet no case of cerebro-spinal fever occurred until January 5th, and, from subsequent cases, only four gave any history of a possible naso-pharyngeal infection immediately preceding cerebro-spinal fever.

### Age

Typical limitation of the disease to young adults was much in evidence during this epidemic, occurring, as it did, amongst men of widely varying ages. There were a few isolated exceptions as is shown in the following graph :-

Number  
of  
Cases



### SPREAD OF INFECTION.

It was definitely established that no one case had been in contact with any individual who shortly thereafter developed cerebro-spinal fever. Direct spread of infection, therefore, from case to individual was not considered to be the means responsible for promulgation of this epidemic. This would appear to accord with the accepted theory that healthy Carriers are mainly responsible for

spread of the disease. Yet, of the 151 individuals swabbed as contacts of these 44 cases, only fourteen revealed meningococci in the naso-pharynx. Whilst it is true that, until the height of this epidemic had been reached in March, the Carrier Rate was 17%, a noteworthy fact is that this rate steadily diminished thereafter to such an extent that the figure for the whole period of this epidemic (Jan. - June) was only 9.2%. Actually during Jan., Feb. and March 12 Carriers were found, whilst in Apr., May and June only 2 more were discovered amongst contacts of cerebro-spinal fever cases.

### ONSET.

In each case, details of the onset of illness were obtained by interrogation of patients themselves and/or by communications from Regimental Medical Officers.

#### Stage of Invasion

For the most part, onset was characteristic of any acute infective process with shivering, aching limbs, headache, nausea and pyrexia. The duration of this 'stage of invasion' was found to vary within relatively wide limits, ending with development of signs of 'meningeal irritation' as evidenced by increasingly severe headache, muscular stiffness, head retraction, photophobia. Thus, in one case, only an hour elapsed between commencement of illness and development of meningeal irritation, whilst in another, this 'stage of invasion' was prolonged over twenty-one days. By the end of 72 hours, however, 60% of all cases had begun to show signs of meningeal irritation.

#### Stage of Meningeal Irritation

#### Remission of Symptoms

An interesting fact brought to light by study of case histories was the occurrence, in the early course of disease, of complete or partial remission of all symptoms. This is clearly demonstrated in the following selection of case histories :-

CASE I. Sapper Lewis was well until 12 a.m. February 29th, when he felt shivery and complained of headache. He stayed in bed for two days, then, feeling better, returned to duty on March 3rd. He worked until 4 p.m. when shivering and



headache returned with neck stiffness. Thereafter he became steadily worse until admission to Hospital on March 4th with obvious signs of meningitis.

CASE II. Private Trickett's illness began with slight headache, shivering and muscular stiffness on March 26th. This "nasty cold", as he described it, passed off in four days, and he moved with his Unit to another station. At the end of the day's travel he was feeling out of sorts, and by next morning had headache and shivering once more. Vomiting and muscular stiffness ensued, and he arrived at No. 4 General Hospital on April 6th with meningitis of moderate degree.

CASE III. Private Thorley was attending a court-martial on morning of April 2nd when symptoms of "Influenza" came over him. From then until April 5th he was kept in bed complaining of headache and dizziness during which time he had two transient rises of temperature. On April 5th he was allowed back to work, feeling well, but that night headache and stiffness of back became troublesome, and temperature was found to be 101°F. His illness thereafter showed no remission, and he was brought to Hospital on April 6th in a state of restless delirium.

CASE IV. Private Richards reported sick on March 17th with malaise and headache which, however, passed off after a day's rest in a nearby Medical Reception Station. Next day, symptoms re-appeared only to ameliorate again next morning. Both these exacerbations of illness were accompanied by general aching and transient muscular stiffness. For three days thereafter he had no complaints, then began, once more, to suffer from headache with pyrexia. This time illness progressed to a state of coma before he reached Hospital on March 25th.

The last, and most extreme, example of remissions of disease is of particular interest in that progressive changes were observed in his cerebro-spinal fluid at intervals throughout illness.

CASE V. Gunner Thornton began with shivering and vomiting on February 21st, to which was added headache two days later. He was admitted to Hospital on February 24th as ? Enteric Fever. Symptoms abating spontaneously in a few days, he was allowed up and out of doors. On March 1st, he was lumbar punctured for recurrence of headache with herpes of lip and slight neck stiffness. Cerebro-spinal fluid was clear and under normal pressure though containing 40 mononuclear cells per c.m.m. No diplococci were seen on smear examination. Once more he was up and about feeling well until development of pyrexia on March 8th, yet still there was no clinical evidence to substantiate a diagnosis of cerebro-spinal fever. Headache became intense on March 11th, lumbar puncture yielding clear fluid under slightly increased pressure, with 3,810 cells per c.m.m. (63% polymorphs). No diplococci were discovered on smear examination. Next morning neck rigidity and Koernig's sign were unmistakable, and a third lumbar puncture, 21 days from commencement of illness, gave turbid fluid under pressure, containing many Gram-negative intra and extra-cellular diplococci. In this case, no specimen of cerebro-spinal fluid yielded meningococci on culture.

Ambulant Cases.

A consideration of these cases suggested that patients showing such remission of symptoms were strongly resisting bacterial invasion and became, for the time being, ambulant cases of cerebro-spinal fever. Only after a lapse of some considerable time, often days, did the organism succeed in producing the picture of cerebro-spinal fever in these individuals.

In all, 17 of the 44 cases of cerebro-spinal fever dealt with during this epidemic showed remissions of symptoms over periods varying from days to weeks.

CLINICAL FEATURES OF NOTE IN TYPICAL CASES.

Reflexes

Absence or impairment of abdominal reflexes was a feature of these cases. Tendon reflexes were exaggerated in 75% patients, though none of the 44 cases displayed extensor plantar responses reputedly occurring in 10% of cerebro-spinal fever cases.

Pupils

In all cases the pupils were dilated, in many responding sluggishly to light and on accommodation.

Pulse Rate

True bradycardia was present in comparatively few patients, four to be exact, and then only in those whose illness was most severe. 50% of patients, however, had a pulse of slower rate than might be expected from their temperature and gravity of illness.

Eruptions

Herpes of lips and chin was a constant feature of all severe cases, though not common in those of mild degree. Of rashes, two types were observed; firstly, isolated, large, raised erythematous spots - Rose spots - scattered over the body surface; secondly, small petechial spots at times profusely, at others scantily, distributed over the body but predominantly on limbs. In one patient both types of rash were present on admission, the Rose spots fading in thirty-six hours whilst petechiae persisted for days.

The 44 cases were classified as to severity of condition on admission, in one of three groups: coma, marked stiffness with presence of petechial spots being taken to indicate a severe case.

- (a) Mild case.
- (b) Moderate case.
- (c) Severe case.

On this basis the analysis of severity was as follows:-

<u>SEVERITY</u> <u>OF</u> <u>ILLNESS</u>	<u>NUMBER</u> <u>OF</u> <u>CASES</u>
(a) <u>MILD</u> .	8.
(b) <u>MODERATE</u> .	24.
(c) <u>SEVERE</u> .	12.

Almost 73% of cases, therefore, were of mild or moderate degree.

DIAGNOSIS.Stage of Invasion

In the stage of invasion onset of this disease was similar to that of any other acute febrile illness where shivering, malaise, headache, nausea and pyrexia are the rule.

Stage of Meningeal Irritation

Later, the clinical features were those of meningeal irritation and increased intra-cranial pressure. Thus muscular spasm, photophobia, intensity of headache and mental changes pointed to an ultimate diagnosis. Most had reached this stage when first seen, whilst a few isolated cases, admitted in the early stage of disease as Influenza, developed this second phase in general medical wards of the Hospital.

In all cases, diagnosis was confirmed by lumbar puncture within one hour of admission to the Infectious Diseases Block, and by subsequent examination of the cerebro-spinal fluid.

Macroscopic appearance of the fluid was, in practically all cases, pathognomonic of meningitis. Thus in all, with one exception, the cerebro-spinal fluid was obviously opalescent, turbid or purulent and under increased pressure. In this exceptional case the fluid appeared clear and under slightly raised pressure, but demonstrated scanty Gram-negative intracellular diplococci on smear examination.

LABORATORY INVESTIGATIONS.Microscopic Examination

In every case a direct, stained smear of cerebro-spinal fluid demonstrated Gram-negative extra and intra-cellular diplococci. Not every specimen yielded a subsequent growth of organisms, successful cultures of meningococci being obtained in 50% cases; but it must be borne in mind that the Laboratory was equipped for, and was working under, field service conditions. In all meningococcal cultures obtained, with two exceptions, the infecting organisms were found to be of Group I variety. These exceptional cases yielded Group II meningococci.

CulturesGroup of Organism

Cell Counts

Cell counts were not made on all specimens of cerebro-spinal fluid, but were confined to doubtful cases and such specimens as showed scanty or absent organisms on direct smear examination. One case - Gunner Thornton, mentioned above - was of particular interest in that cytological changes were observed over a long invasion period before outward signs of cerebro-spinal fever became evident. The initial preponderance of lymphocytes and the ultimate preponderance of polymorphs in the infected fluid was specially interesting.

Cell Changes ObservedTREATMENT.Lumbar Puncture

In all cases an endeavour was made to reduce cerebro-spinal fluid pressure to normal as indicated by one drop of fluid from the lumbar puncture needle in three seconds. This was considered a measure of great importance, being performed at the earliest possible moment in every case.

Specific Therapy

Immediately following establishment of a diagnosis of cerebro-spinal fever, routine, intensive, specific therapy was inaugurated. This took the form of administration of Sulphapyridine parenterally and orally over a period of not less than seven days. In all cases the parenteral preparation used was SOLUDAGENAN, an aqueous solution of Sulphapyridine supplied in 3 c.c. ampoules, each containing one gram of active principle. Orally, the drug was used as M. & B. 693 tablets, each containing 0.5 gram of active principle.

Chemo - Therapeutic Agents UsedConcurrent Serum Therapy

In the first ten cases Sulphapyridine treatment was supplemented by daily administration of Anti-Meningococcal Serum for six days. All subsequent cases were treated with Sulphapyridine alone, since results suggested that no benefit was to be obtained by this additional use of Serum.

Details of the mode of drug administration in this treatment of cerebro-spinal fever may best be appreciated by reference to the following tabulated

summary where -

i.v. indicates Intravenous Administration  
 i.m. ----- Intramuscular -----  
 o. ----- Oral -----

<u>DAY.</u>	<u>FIRST 10 CASES. —</u>		<u>SUBSEQUENT CASES.</u>
	<u>ANTI-MENINGOCOCCAL</u> <u>SERUM.</u>	<u>SULPHAPYRIDINE.</u>	<u>SULPHAPYRIDINE.</u>
1 <sup>ST</sup> .	100 ccs. i.v.	6 gms. i.M.+O.	8 gms. i.M. + O.
2 <sup>ND</sup> .	50 ccs. i.v.	4 gms. O.	6 gms. O.
3 <sup>RD</sup> .	50 ccs. i.M.	3 gms. O.	5 gms. O.
4 <sup>TH</sup> .	25 ccs. i.M.	3 gms. O.	4 gms. O.
5 <sup>TH</sup> .	25 ccs. i.M.	3 gms. O.	3 gms. O.
6 <sup>TH</sup> .	25 ccs. i.M.	3 gms. O.	2 gms. O.
7 <sup>TH</sup> .	—	3 gms. O.	2 gms. O.
<u>TOTAL.</u>	<u>275 ccs.</u>	<u>25 gms.</u>	<u>30 gms.</u>

Detailed  
Daily  
Dosage

The principle adopted in administration of Sulphapyridine was to secure rapid production of an effective concentration of the drug in blood and cerebro-spinal fluid as quickly as possible, with maintenance of this level of concentration for the period required to overcome the acute infective process. Thereafter the drug was slowly withdrawn until its administration was considered to be no longer necessary. In practice, the most efficient

scheme of dosage was found to be that embodied in the following table where -

i.v. indicates Intravenous Administration  
 i.m. ----- Intramuscular -----  
 o. ----- Oral -----

<u>DAY OF TREATMENT.</u>	<u>HOURS.</u>	<u>MILD OR MODERATE CASE.</u>	<u>FULMINATING CASE.</u>
1 <sup>ST</sup> DAY. (VIII GMS.)	ZERO.	II GRAMMES. I.M.	I GRAM IV. + I GRAM I.M.
	4.	II " I.M.	II GRAMMES. I.M.
	8.	I GRAM. O.	I GRAM. I.M.
	12.	I " O.	I " I.M.
	16.	I " O.	I " I.M.
	20.	I " O.	I " I.M.
2 <sup>ND</sup> DAY. (VI GMS.)	ZERO.	I " O.	I " O.
	4.	I " O.	I " O.
	8.	I " O.	I " O.
	12.	I " O.	I " O.
	16.	I " O.	I " O.
	20.	I " O.	I " O.
3 <sup>RD</sup> DAY. (V GMS.)	ZERO.	I " O.	I " O.
	4.	I " O.	I " O.
	8.	I " O.	I " O.
	12.	I " O.	I " O.
	16.	I " O.	I " O.
	20.	OMIT EARLY A.M. DOSE.	OMIT EARLY A.M. DOSE.
4 <sup>TH</sup> DAY. (IV GMS.)	ZERO.	I GRAM. O.	↖  AS FOR MODERATE CASE.  ↘
	6.	I " O.	
	12.	I " O.	
	18.	I " O.	
5 <sup>TH</sup> DAY. (III GMS.)	ZERO.	I " O.	
	8.	I " O.	
	16.	I " O.	
6 <sup>TH</sup> DAY. (II GMS.)	ZERO.	I " O.	
	12.	I " O.	
7 <sup>TH</sup> DAY. (I GMS.)	ZERO.	I " O.	
	12.	I " O.	

General Principles

During the initial twenty-four hours when headache was still troublesome Morphia was given without stint.

In less troublesome cases Aspirin relieved the condition considerably. Where pulse was feeble or irregular, Coramine was administered, in some cases four-hourly during the first day, with good effect. Importance was attached to administration of fluids, an endeavour being made to keep fluid intake up to four pints daily from the start.

Retention of urine was troublesome in two cases and catheterisation had to be resorted to until normal function returned, which it did after a few days in both cases.

Constipation was relieved, on the third day, by an enema followed by daily administration of Liquid Paraffin. In early treatment where vomiting was still frequent, temporary reversion was made to intramuscular Sulphapyridine administration, oral treatment being re-established on cessation of all tendency to sickness.

In only one case was it considered necessary to give the initial dose of Sulphapyridine intravenously.

Such was recovery in many cases that further lumbar puncture was unnecessary. It was found necessary, on clinical grounds, to repeat spinal drainage in sixteen cases after commencement of specific therapy. These further lumbar punctures were made necessary by persistence of, or recurrence of, signs of increased intra-cranial pressure, e.g. slow pulse, headache, vomiting, coma. The relative frequency of these signs amongst the sixteen cases which did require a second lumbar puncture is shown here :-

<u>FURTHER DRAINAGE</u> <u>INDICATED BY:-</u>	<u>NUMBER</u> <u>OF</u> <u>CASES.</u>
<u>VOMITING.</u>	8.
<u>HEADACHE.</u>	3.
<u>COMA.</u>	2.
<u>SLOW PULSE.</u>	2.
<u>RELAPSE.</u>	1.

Repeat  
Lumbar  
Puncture

Indications



After relief of pressure by a second lumbar puncture, recovery in these sixteen cases, too, was rapid and maintained.

Whilst repeated lumbar puncture was found to be unnecessary in twenty-eight of the 44 cases treated by Sulphapyridine, it was considered of utmost importance to watch carefully during the first few days for signs of persistence or recurrence of increased intracranial pressure, and, in the presence of such evidence, to relieve this pressure by spinal drainage without delay.

### Routine Blood Counts

In every case a routine blood count was performed on the 7th day of treatment, or earlier if indicated by the patient's condition, to detect the occurrence, if any, of Granulopenia. In only two cases following treatment was anything in the nature of a Leucopenia produced. In these two, white cell counts on 7th day were in the region of 5,000 cells per c.m.m., but showed an increase to 6,000 cells per c.m.m. two days later, during which time both patients felt very well.

### Leucopenia after Sulpha- pyridine

### Effect of Sulpha - pyridine on Meningococcus Vitality

In three cases, where diagnosis seemed certain on clinical grounds alone, the Officer i/c of a General Medical Ward inaugurated Specific Therapy at once pending transfer to Isolation Block, lumbar puncture being performed as soon thereafter as possible. This did not interfere with subsequent growth of meningococci in culture, probably because lumbar puncture was performed, in each case, within one hour of Sulphapyridine administration. On another occasion repeat lumbar puncture was done twenty-four hours after beginning treatment, i.e. the patient had received 8 grammes of Sulphapyridine intra-muscularly, and cerebro-spinal fluid culture then failed to yield meningococci, although still turbid and under increased pressure. Cerebro-spinal fluid obtained from this case at diagnostic lumbar puncture was purulent and gave a growth of Group I meningococci on culture.

### TOXIC MANIFESTATIONS FROM SULPHAPYRIDINE.

#### Cyanosis.

Many of the cases treated exhibited cyanosis of varying degree, but, in absence of other disturbances, treatment was not interrupted on this account.

#### Vomiting

In early treatment vomiting was mostly of a cerebral nature, being relieved by lumbar puncture.

Until it ceased, intra-muscular administration of Sulphapyridine was continued.

Rash On two occasions, eleven days after commencing treatment, patients developed widespread maculoerythematous eruptions, with mild pyrexia. These conditions resolved in forty-eight hours, having caused no physical disturbance to the individuals.

Pyrexia Continuance of mild pyrexia during Sulphapyridine administration, with disappearance on its withdrawal, was observed once in the series.

Leucopenia No severe Leucopenia occurred in any of the cases treated.

### CONVALESCENCE.

#### Abatement of Symptoms

In this series of cases treated in the manner outlined, arrest of the infective process and resolution of symptoms occurred with striking rapidity. Thus, in twenty-one cases, temperature had returned to normal within twenty-four hours, the maximum time required being 3 days in two of the cases. By this time, too, headache had abated considerably, and comatose patients showed signs of returning consciousness. After 3 - 4 days, headache had completely disappeared and within 7 days of commencing treatment, all subjective evidence of cerebro-spinal fever had gone. Before a second week elapsed patients became restless and desirous of being allowed up.

#### Time in bed

All uncomplicated cases were allowed out of bed twenty-one days after the commencement of treatment, and within a few days were cheerily helping with light ward duties. Mild cases, encountered later in the epidemic, were allowed up on the 15th day. Thereafter, it was necessary to obtain negative naso-pharyngeal swabs on three occasions from each individual preparatory to his evacuation for further convalescence in the United Kingdom.

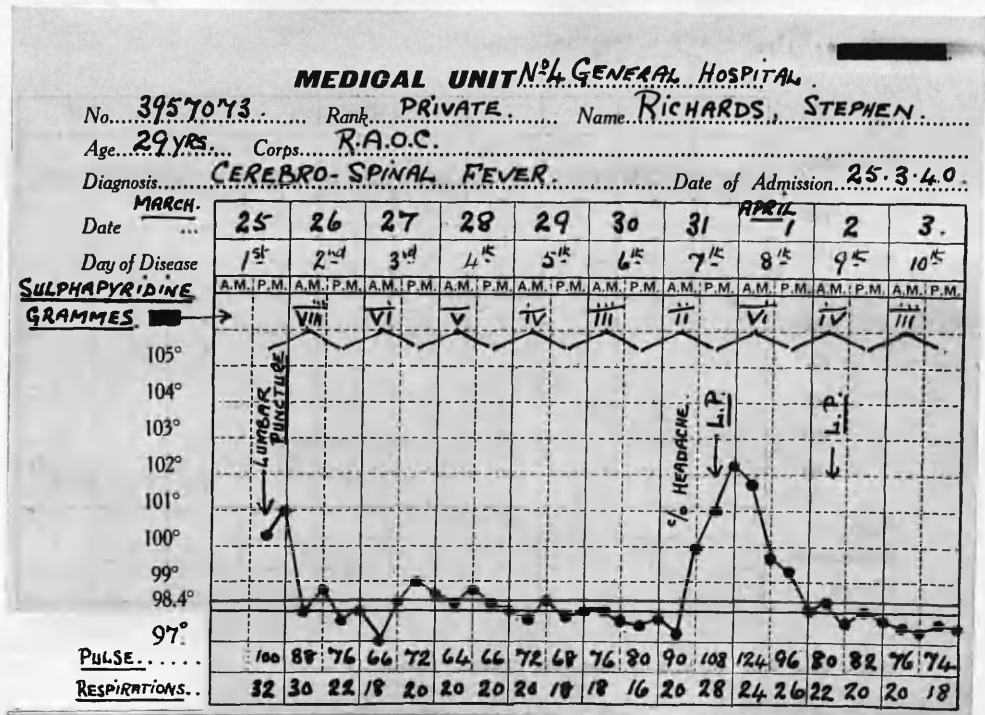
### ATYPIC CONVALESCENCE.

Acute  
Exacerbation  
of  
Symptoms A noteworthy development occurred in convalescence on one occasion when the patient, in his seventh day of recovery, began to complain once more of intense "pain behind the eyes". Temperature and pulse rate rapidly rose to 102.4°F. and 124 per minute respectively.

Lumbar puncture demonstrated opalescent cerebro-spinal fluid under increased pressure. Fifteen c.cms. of fluid were removed and M. & B. 693 dosage increased to 1 gram four-hourly for two days, then slowly withdrawn again. By next day, temperature and pulse rate were once more normal, lumbar puncture a day later revealing clear cerebro-spinal fluid under normal tension with a content of 30 cells per c.m.m. Thereafter, he improved steadily and showed no further exacerbation of symptoms.

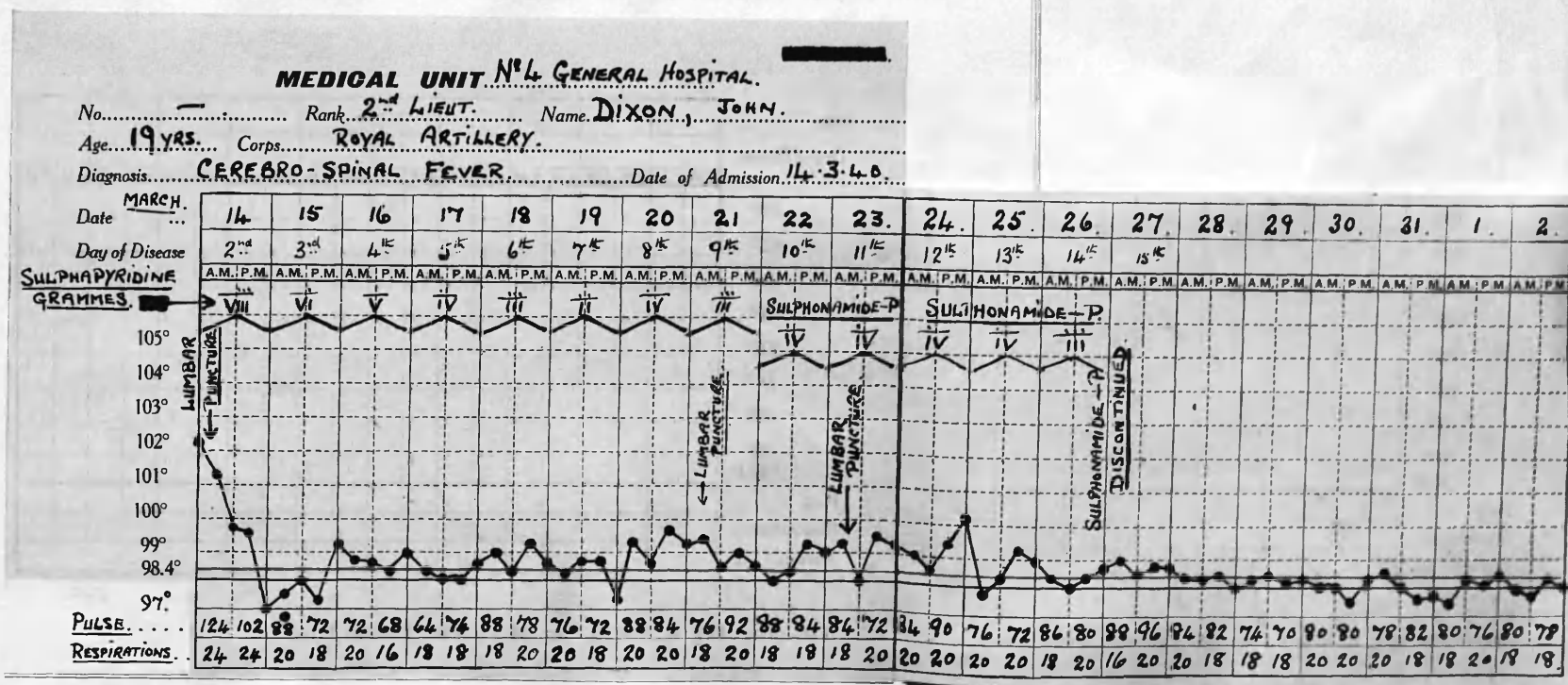
The particular temperature chart showing this exacerbation of disease is reproduced below :-

RICHARDS.



Drug  
Pyrexia

The persistence, at times, of a mild pyrexia during Sulphapyridine administration is well recognised, and one such case was encountered in this series. His temperature fell from 102.4°F. to normal within twenty-four hours of commencing treatment, but thereafter proceeded to oscillate between normal and 99.5°F. without any apparent reason. Lumbar puncture on the eighth day yielded clear cerebro-spinal fluid under normal tension. Change was made to Sulphonamide - P administration at this stage without any improvement resulting. On the thirteenth day of convalescence all drugs were discontinued, whereupon these oscillations of temperature steadily diminished and, within two more days, had settled completely, convalescence thereafter being uneventful. This particular temperature chart is shown here :-

DIXON.

SEQUELAE.

In this series of cases sequelae were few. Those which did occur were, with one possible exception, not of a permanent nature. Nine patients showed sequelae, details of which are given below :-

- (1) Synovitis of Elbow. These occurred in two cases, one treated by Serum + Sulphapyridine, the other by Sulphapyridine alone. Both developed during early convalescence and were resolved by simple application of Ichthyol and Glycerine dressings, leaving no disability.  
Synovitis of Knee.
- (2) Auditory Nerve Deafness. This sequel arose in a further two cases, each developing unilateral nerve deafness of moderately severe degree. During ensuing weeks in Hospital, both showed such marked improvement that anything in the nature of a permanent disability was improbable.
- (3) Corneal Ulcer. This condition developed in one case during his second week of convalescence. It began as a group of discrete, minute, shallow ulcers which later fused to form a Dendritic Ulcer of the Cornea. Healing was naturally slow but had progressed to such an extent before his evacuation that corneal opacity was obviously slight, and impairment of vision trivial. Unilateral conjunctival anaesthesia accompanied this condition without further evidence of facial paresis or anaesthesia.
- (4) Foot-drop. In this case, during his third week of convalescence, following combined Serum and Chemotherapy, he complained of loss

of power in his left foot with difficulty in walking. Examination revealed presence of a typical Peroneal Nerve Palsy, with resultant foot-drop. After a week's immobilisation the affected muscles had regained tone, but motor power had not returned. Thereafter, a plaster support was applied to foot and leg, the patient then being allowed up. The permanence or otherwise of this lesion is, at the time of writing, still uncertain.

- (5) Surface Anaesthesia. Three instances of this condition arose in patients convalescing from cerebro-spinal fever. Once, three weeks after beginning treatment, a patient experienced aching pains in left Triceps muscles, with numbness of forearm. No disturbance of motor power or reflexes was detected, but touch and pain senses were impaired over a limited area of flexor surface of left forearm, just above the wrist. The second condition occurred in a patient already up and about, in his fourth week of convalescence, when he complained of tingling and numbness in his right thigh. Examination revealed complete loss of skin sensations over a patch on the outer aspect of right thigh, just above the knee, with no motor disturbance. The third patient, a moderate case with preceding chronic septicaemia history of 4 weeks' duration, experienced aching of right shoulder over the Deltoid muscle 6 days after commencing treatment. Examination revealed no loss of power but presence of a vertical strip of skin anaesthesia at

at the site indicated. Ten days later he complained of tingling and numbness on the outer aspect of his left thigh just above the knee. This region showed another patch, 3" in diameter, of complete loss of skin sensation to pain, touch and temperature.

These sequelae in no way impeded patients' convalescence and had so improved during further stay in Hospital that a permanent lesion was unlikely.

It is noteworthy that, of these seven nerve lesions, four occurred as sequelae of combined Serum and Chemotherapy.

ONSET OF SEQUELAE.

<u>1<sup>ST</sup> WEEK.</u>	<u>2<sup>ND</sup> WEEK.</u>	<u>3<sup>RD</sup> WEEK.</u>	<u>4<sup>TH</sup> WEEK.</u>
<u>ARTHROPATHY</u> <u>(ELBOW).</u>	<u>ARTHROPATHY</u> <u>(ANKLE).</u>	<u>PERONEAL</u> <u>PALSY.</u>	<u>AUDITORY NERVE</u> <u>DEAFNESS.</u>
<u>AUDITORY NERVE</u> <u>DEAFNESS.</u>	<u>CORNEAL</u> <u>ULCER.</u>	<u>ANAESTHESIA</u> <u>(ARM).</u>	<u>ANAESTHESIA</u> <u>(THIGH).</u>
<u>ANAESTHESIA</u> <u>(SHOULDER).</u>	—	<u>ANAESTHESIA</u> <u>(THIGH).</u>	—

Study of these sequelae, excluding the arthropathies, showed that all must be attributed to localised lesions of peripheral nerve trunks and that onset of these conditions occurred relatively late in the course of disease at a time when all evidence of acute infection had subsided. Their close resemblance to

lesions occurring in acute disseminated encephalo-myelitis was striking, as also was occurrence of facial herpes in the path of 5th nerve distribution several days after onset of acute meningitis symptoms.

The theory that such lesions are produced by direct spread of organisms along nerve roots and trunks does not satisfactorily explain occurrence of isolated, localised, peripheral nerve lesions such as must have been responsible for production of a peroneal palsy, or of a patch of cutaneous anaesthesia. Nor can their occurrence at so late a stage be explained by haemorrhage into nerve-sheaths. These sequelae represent the effects of damage, permanent or otherwise, to peripheral nerve trunks.

On the other hand, there have been made, from time to time, investigations whose results cast doubt on the current belief that meningococci produce no exotoxin.

In our opinion, therefore, one of two explanations must be responsible for these sequelae :-

Either (a) they have been produced by a concomitant myelitis of virus origin;

or (b) they are to be attributed to a meningococcal toxæmia, giving rise to lesions closely resembling those of a local myelitis.

#### MORTALITY.

Using the scheme of treatment outlined above, mortality of the 44 cerebro-spinal fever cases treated during this epidemic was Nil.

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CHRONIC MENINGOCOCCAL SEPTICAEMIA.

In recent years this condition has come to be recognised as a definite clinical entity presenting a clear-cut group of symptoms whose origin has been proved, from time to time, by isolation of meningococci from patients' blood. Several such cases were encountered during this epidemic, particularly towards its end. Unfortunately, diagnosis was not confirmed bacteriologically by successful blood culture in any of these cases although there could be little doubt as to their real nature. One case, undergoing treatment in Hospital, actually developed acute meningitis of meningococcal origin before the true nature of his preceding prolonged illness was recognised.

The following case histories proved interesting as illustrative of this prolonged chronic blood infection with its characteristic periods of remission and possible termination in development of acute meningitis.

CASE I. Pte. Spence suddenly - at 9 p.m. on 1st May, 1940 - developed shivering, aching limbs and headache. Next morning headache was worse and he experienced definite muscular stiffness. He came to Hospital on 2nd May, 1940 as ? cerebro-spinal fever having a temperature of 102.8°F., pulse 96 per minute, and showing moderate stiffness of leg and neck muscles with slightly exaggerated knee jerks. His most striking feature was a widespread, profuse, papulo-erythematous and petechial eruption on trunk and limbs. Lumbar puncture gave clear cerebro-spinal fluid under normal tension. From this fluid a count showed 8 mononuclear cells per c.m.m. no organisms being found on direct smear or by culture. Blood culture at the same time proved sterile. Naso-pharyngeal swabs from the same patient yielded no meningococci on culture. Thereafter, he was treated with Sulphapyridine orally for 5 days. Within 12 hours temperature had returned to normal and by the second

day all headache and stiffness had disappeared leaving only fading petechiae as an indication of the infection. This patient made an uninterrupted recovery being allowed up 7 days after admission to Hospital.

CASE II. Pte. Mitchell was admitted to a General Medical Ward with "Acute Rheumatism" on 30th March, 1940. A week previously he had developed, suddenly, weakness of legs and aching calf muscles. Next day he had a rigor, broke out in profuse sweat and was found to have a temperature of 103°F. After two days' detention in a Medical Reception Station he felt well and returned to his Unit. During his second day at duty he fainted 'on parade' complaining once more of aching limbs, shivering and weakness. Thereupon he was sent to No. 4 General Hospital. After 10 days' rest with symptomatic treatment in a General Medical Ward he felt well but 3 days later had recurrence of headache, bodily aching and rigor with a temperature of 102°F. This quickly subsided but within a few days more he developed painful swelling of the right metacarpal joints. On 26th April he exhibited, for the first time, crops of raised erythematous spots on his legs. Fresh spots appeared daily although he had no discomfort beyond occasional sweating at night. On examination many of these spots were found to be petechial in nature and tender to touch. Thereupon he was transferred to the Infectious Diseases Block where he was subjected to a



(23)

Ward next day temperature was 101.4°F. and pulse rate 120 per minute, with no evidence of disease beyond a macular rash on trunk and a recent, clean, vaccination scar on his arm. Temperature soon settled and he was well thereafter until 14th March when he complained of painful swelling of both knee-joints. This lasted for 3 days after which he again felt well though weak. On 23rd March his temperature rose suddenly to 103°F. accompanied by slight cough and spit. X-Ray and sputum investigation revealed no evidence of pulmonary disease. Once more he was relatively well and uncomplaining though exhibiting occasional, transient pyrexia until 14th April when he developed painful swelling of his right ankle. On 17th April his temperature rose sharply to 103.4°F. Serum agglutination tests, done during that day for Typhoid, Paratyphoid and Undulant Fever groups of organisms, gave no evidence of such infection. Blood count was within normal limits showing 7,550 white cells per c.m.m. and red cells 5,210,000 per c.m.m. with considerable variation in size and colour. Blood culture on 24th April, during another pyrexial stage, proved sterile. On 25th April he exhibited discrete, red, tender spots on thighs and shoulders, many having central petechiae. The condition, thereafter, was regarded as one of chronic meningococcal septicaemia despite further failure to culture the organism. Thereupon Sulphapyridine therapy was instigated



Thereafter, at intervals of a few days, he suffered headaches, bouts of stiffness and sweating with recurrent crops of large, red spots on his legs, disappearing in 24 hours and leaving "bluish marks in the skin". On 9th May he experienced headache which became, this time, progressively more intense and to which was added stiffness of neck and legs. On admission to Hospital next morning he presented signs of mild cerebro-spinal fever and showed several well-marked petechial spots on legs and trunk. Examination of cerebro-spinal fluid revealed a cell content of 1,627 polymorphs. per c.m.m. and scanty Gram-negative diplococci (intra-cellular) on slide examination. No meningococcal growth was obtained on culture. Routine Sulphapyridine therapy brought about a satisfactory recovery.

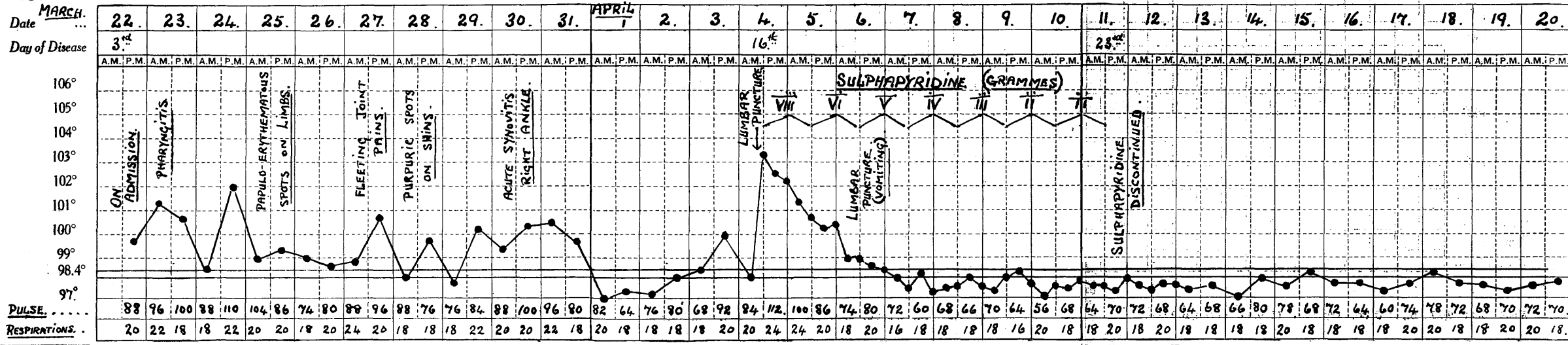
CASE V.

Dvr. Turner came to a General Medical Ward on 22nd March complaining of sore throat, shivering and fever of 3 days' duration. By 24th March his nasopharyngeal condition had subsided but next day he developed large, red spots on his limbs. Two days later he experienced joint pains of a transient nature and next morning exhibited definite purpuric spots over both shins. On 30th March his right ankle became painful, swollen and stiff. Thereafter his condition improved, temperature remaining normal, until 4th April when he suddenly developed intense headache, stiffness and spasticity of neck and leg muscles with fresh eruption of erythematous and petechial spots. At this stage spleen was just palpable. He was transferred, at once, to the Infectious Diseases Block where lumbar puncture gave turbid cerebro-spinal fluid under considerable pressure. Extra and intra-cellular Gram-negative diplococci were seen on direct smear and obtained from fluid

culture. On 4th April routine intensive Sulphapyridine therapy, as for the other cerebro-spinal fever cases, was inaugurated the patient making an uneventful and complete recovery.

Temperature Chart (Dvr. Turner).

MEDICAL UNIT No. 4 GENERAL HOSPITAL.  
 No. 123394 Rank DRIVER Name TURNER, JAMES  
 Age 20 YRS Corps R.A.S.C.  
 Diagnosis CHR. MENING. SEPTICÆMIA → C.S.F. Date of Admission 22.3.40



Symptoms

Thus it was observed that this blood infection produced a typical group of symptoms, sometimes extending over a long period of weeks, the course of which disease was characterised by acute intermittent pyrexias and rigors of short duration, by accompanying muscular pains and stiffness, by periodic skin eruptions of erythematous and petechial nature, by

acute synovitis or arthritis of single large joints and, in some untreated cases, by development of cerebro-spinal fever itself.

Response to Sulpha-pyridine

A characteristic feature of all these chronic blood infections was rapid and certain response to Sulphapyridine administered orally in relatively small doses (1 gram four hourly during the first day then thrice daily thereafter) by which a disease of many weeks' duration was cut short in as many days.

Development of Acute Meningitis

From the 44 cerebro-spinal fever cases observed, no less than 8 gave a history of illness prolonged over many weeks immediately preceding onset of meningitis. In each, this history was typical of chronic meningococcal septicaemia as described above but it was development of cerebro-spinal fever symptoms in every case that occasioned admission to Isolation Block of No. 4 General Hospital. Two examples will serve to demonstrate the typical history of these cases.

CASE I.

Sgt. Watkins first felt ill 8 weeks before admission when he developed shivering and malaise with a temperature of 103°F. This condition resolved in 36 hours but thereafter he suffered recurrent attacks of shivering, aching limbs and general muscular stiffness. On isolated occasions he developed acute synovitis of single large joints at times a knee, at others a shoulder-joint being involved. During this period, too, he noticed crops of large, red spots on arms and legs. He received treatment for Rheumatism at his Unit but remained at duty since he had intervening periods of relative freedom from illness. He continued in this manner until 28th April when a fresh crop of spots appeared on his legs. Next morning limbs were aching and he complained of headache with shivering. By 30th April headache was intense and he suffered rigors with marked stiffness of legs and vomiting. On admission to Hospital next morning he exhibited signs of meningitis of moderate degree with a profuse petechial eruption on limbs and trunk. Diagnosis of cerebro-spinal fever was confirmed by laboratory investigation of his cerebro-spinal fluid.



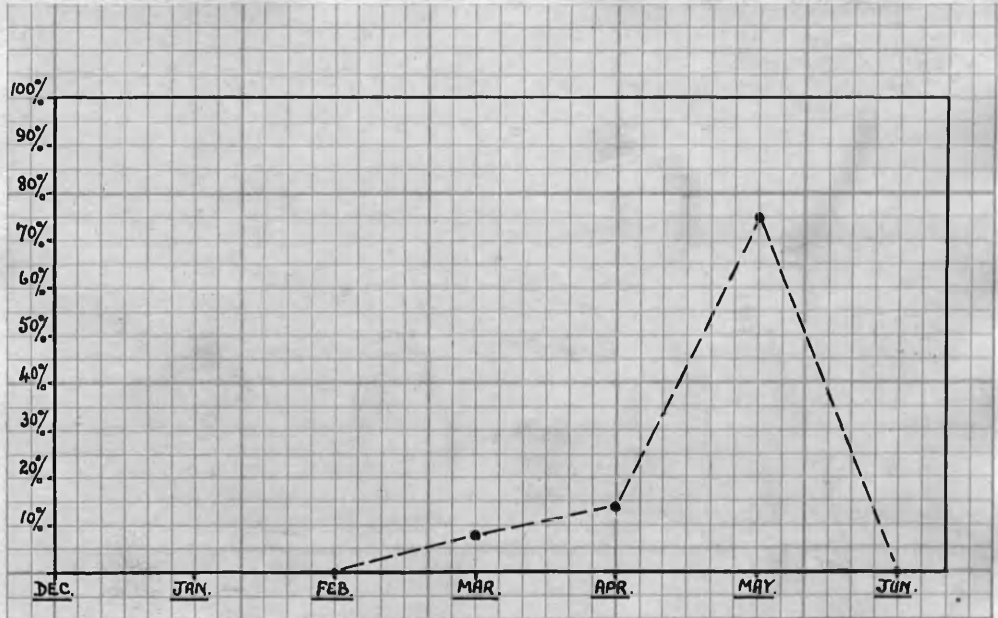
CASE II. Spr. Edwards began with headache, sweating and some stiffness of limbs 6 weeks prior to admission. These symptoms abated in 48 hours but from then on, at intervals of 3 - 4 days, he suffered ailments of similar nature accompanied frequently by aching "shin-bones" and fleeting joint pains. On two occasions his left knee became swollen, painful and stiff, and once, a week before admission, his right ankle was similarly affected. During the two weeks prior to admission he noted frequent appearance, on his arms and legs, of large, red "blotches" which disappeared in 1 - 2 days leaving "purple marks" in the skin. Such was his history until 15th May when he developed intense headache, stiffness of neck and later vomiting, being admitted on 17th May to the Infectious Diseases Block with cerebro-spinal fever of mild degree.

Relation to  
Spread of  
Cerebro-spinal  
Fever

It is one's opinion, in the light of these case histories, that sufficient importance has not, heretofore, been attached to this manifestation of disease in relation to spread of infection nor to its frequently unrecognised existence during epidemics of cerebro-spinal fever. From their study it was observed that several cases were ambulant for a relatively long period carrying meningococci presumably in the nasopharynx and exhibiting symptoms only at intervals when these organisms, for some reason, gained access to the blood-stream. Such individuals, it appeared to us, must have played a part in transmission of meningococcal infection to others who may themselves have developed a like condition, who may have become remission cases of cerebro-spinal fever or who may immediately have developed acute meningeal invasion.

The preponderance, in the later stages of this epidemic, of cerebro-spinal fever cases

with a preceding chronic septicaemia history may best be demonstrated by the following graph :

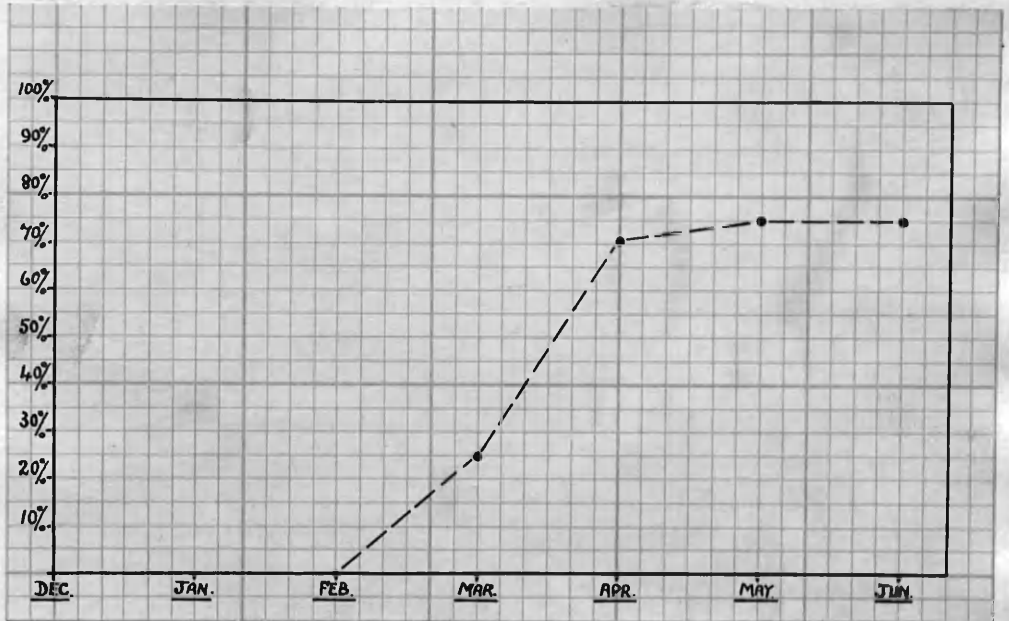


Amelioration  
of the  
Epidemic

It became more and more apparent, as this epidemic drew to a close, that its disease character was undergoing change from an initial severe one to that of diminished severity with appearance of many atypic and frankly mild forms. Thus cases occurring at the beginning and during the height of this epidemic were characterised by sudden onset, short invasion period and relatively severe meningeal involvement. Later, as the epidemic passed its height, the predominant form of disease was found to be that of a prolonged intermittent illness, either of chronic septicaemia or remission type, extending over several weeks to culminate, eventually, in

cerebro-spinal fever of moderate or mild degree. This progressive increase in incidence of 'delayed' cases is shown here :-

% Age  
'Delayed'  
Cases



Further, many of these later cases failed to present typical symptoms of cerebro-spinal fever as seen in earlier and more acute cases. Absence of definite muscular rigidity and of pyrexia were encountered in several, presence of headache and skin eruptions alone indicating the true nature of their illness.

One regards cerebro-spinal fever, therefore, not as an isolated entity of disease, but as the 'end-point' in a chain of manifestations arising from meningococcus infection. The rapidity with which this 'end-point' is reached and the number of manifestations that occur before it is reached must depend on individual resistance to that specific infection, and on the virulence of the infecting organism itself.

The character change in this disease occurring, as it did, in the late stages of the epidemic must

be attributed, in one's opinion, to attenuation of the particular strain of infecting meningococcus with diminution of virulence or to actual change of organism strain from that of high virulence to one of relatively low pathogenicity. The part played by individual specific resistance cannot be easily estimated, but it seems reasonable to believe that this too will have some bearing on the modifications of disease observed. Moreover, it is one's opinion that these factors not only lead to termination of a particular cerebro-spinal fever epidemic but, at the same time, give rise to many low-grade and unrecognised chronic infections probably septicaemic in nature. These forms of disease, persisting amongst a few individuals throughout the rest of that year, will regenerate at a later date producing a virulent organism again, so providing the nucleus for a fresh epidemic when the requisite factors and circumstances once more coexist.

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CARRIERS AND THEIR TREATMENT.

In the Army, contacts of an infectious case are those occupying adjoining beds in Hut or Barracks; if sleeping in tents or Billets, all occupants are regarded as Contacts.

During this epidemic, contacts of each cerebro-spinal fever case were investigated for presence of meningococci in the nasopharynx. In all, 151 contacts were examined and, of these, 14 were admitted to the Infectious Diseases Block for isolation as cerebro-spinal fever Carriers, each having yielded meningococci on culture from nasopharyngeal swabs. There they were subjected to a course of Sulphanilamide administered orally (Sulphonamide - P: 1 gram eight-hourly) for 6 days in an effort to terminate this Carrier state. Cultures were made from nasopharyngeal swabs taken on 6th, 13th and 15th days after commencement of treatment, absence of meningococci from three such consecutive swabs being regarded as the indication of termination of this Carrier state. Results were of some interest in view of the problem formerly presented by such members of a community.

Eleven Carriers gave consecutive negative swabs after one course of Sulphanilamide, being then discharged as 'clean'.

Three cases proved resistant to Sulphanilamide - two courses at intervals of a week, in each, failing to influence meningococcus vitality. Following these failures Sulphapyridine orally was substituted and the course repeated. All three cases, thereafter, gave consecutive negative nasopharyngeal swabs (i.e. no meningococcal growth on culture) and they too were discharged no longer stigmatised as cerebro-spinal fever Carriers.

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SUMMARY.

- (1) Study was made of cases occurring in an epidemic of cerebro-spinal fever amongst Troops, numbering 29,000, stationed on Lines of Communication in France.
- (2) This epidemic lasted from January until June, 1940, the maximum number of cases per month occurring during March.
- (3) Forty-four cerebro-spinal fever, 14 Carrier and 4 chronic meningococcal septicaemia cases were observed and treated by chemotherapy.
- (4) Incidence of cerebro-spinal fever was 1.5 cases per 1,000 men.
- (5) 66% cases occurred amongst men between 20 and 29 years of age.
- (6) Carrier rate during the first half of this epidemic was 17% but over the entire epidemic period was only 9.2% of contacts.
- (7) It was established that no individual had contracted cerebro-spinal fever shortly following contact with an existing case. Such a mechanism, therefore, could not have been responsible for promulgation of this epidemic.
- (8) Existence of ambulant and remission cases of cerebro-spinal fever was demonstrated.
- (9) With two exceptions, all positive cultures from cerebro-spinal fluid of these cases yielded Group I meningococci. These exceptional cases gave Group II meningococci.
- (10) Combined serum and chemotherapy, applied in the first 10 cases of this series, was discarded in favour of intensive chemotherapy alone.
- (11) Toxic manifestations, following Sulphapyridine treatment, of a mild nature only, were observed.
- (12) Repeated lumbar puncture was unnecessary in 64% cases treated.

- (13) Rapidity of recovery and remarkable freedom from permanent sequelae, obtained by sulphapyridine treatment of these cases, was outstanding.
- (14) Sequelae occurred in 9 cases, 7 being of nerve origin, only one leading to possible permanent disability.
- (15) Of 10 cases treated by serum and sulphapyridine 4 developed sequelae, 1 possibly permanent. Of 34 cases, treated by intensive sulphapyridine alone, 5 developed sequelae.
- (16) The nature of these sequelae and their relatively late onset was considered due to a toxic neuritis or to a concomitant, local, neurotropic virus myelitis rather than to direct infection of or haemorrhage into nerve trunks.
- (17) Mortality amongst these 44 cases of cerebro-spinal fever was NIL.
- (18) Four cases of chronic meningococcal septicaemia and 14 Carriers were successfully treated by chemotherapy.
- (19) Response of chronic meningococcal septicaemia to sulphapyridine treatment was dramatic and satisfactory.
- (20) Chemotherapy provided an effective method of dealing with cerebro-spinal fever Carriers.
- (21) From 44 cerebro-spinal fever cases, 8 gave a chronic meningococcal septicaemia history prolonged over many weeks immediately preceding the onset of meningitis.
- (22) Cerebro-spinal fever preceded by chronic meningococcal septicaemia or by frequent remissions was the predominant form of disease encountered towards the end of this epidemic.
- (23) Relation of remission and chronic meningococcal septicaemia cases to spread of cerebro-spinal fever, during this epidemic, was considered of greater importance than hitherto recognised.
- (24) Existence of atypic and low-grade manifestations of meningococcal infection was observed in the late stages of this epidemic.
- (25) It was considered that such cases might be responsible for maintenance, amongst adults, of this disease until a future epidemic of cerebro-spinal fever might develop.

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