CEREBROSPINAL FEVER

ANALYSIS OF 124 CASES

BY

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The cases herein analysed were admitted to the Military Isolation Hospital, Aldershot, during the winter of 1939 to the end of May, 1940. The type of case seen in this period appeared to show some clinical deviations from the normal as exhibited in the war of 1914-18 and it was thought worth while to analyse the cases and report on the treatment with soluseptasine by the intravenous route.

Onset and Incidence

The onset of the fever was very sudden. Many went to bed feeling quite well and awoke in the morning with intense headache, frequently accompanied with vomiting. The actual incubation period cannot be definitely stated, but it appears to be of very short duration, mostly from twenty-four to forty-eight hours. Some cases, however, had various symptoms, especially sore throat, lasting from one to seven days before the appearance of the headache. Others complained of a feeling of general malaise for a similar period of time. The fulminating septicaemic type is even more sudden than this. A man may be stricken to the ground in a fit simulating petit mal, others suddenly become unconscious and fall into various stages of coma. The following tables show the incidence according to age, length of service, and date of occurrence.

Age Incidence				Service Incidence			
Age (yrs.)	Cases	Age (yrs.)	Cases	Period	Cases	Period	Cases
1	1	25	2	1 wk.	1	9 mths.	2
14	1	26	2	2 wks.	1	10 "	2
15	1	27	2	3 "	8	11 "	5
16	1	28	1	1 mth.	4	1 yr.	4
17	1	29	3	2 mths.	4	2 yrs.	1
18	4	32	2	3 "	12	4 "	1
19	18	36	1	4 "	18	6 "	1
20	26	38	1	5 "	16	7 "	1
21	29	40	1	6 "	24	10 "	1
22	14	43	1	7 "	14	25 "	1
23	7	44	1	8 "	3		
24	3	51	1				

Time Incidence

Week ending	No. of Cases Admitted	Week ending	No. of Cases Admitted
11/11/39	1	17/3/40	2
18/11/39	1	24/3/40	8
23/12/39	4	31/3/40	4
7/1/40	2	7/4/40	5
14/1/40	3	14/4/40	9
21/1/40	12	21/4/40	3
28/1/40	8	28/4/40	2
4/2/40	8	5/5/40	2
11/2/40	14	12/5/40	3
18/2/40	7	19/5/40	2
25/2/40	7	26/5/40	4
3/3/40	8		
10/3/40	5		

124

The types of cases were classified as slight, 28; moderate, 49; severe, 41; fulminating septicaemic, 6.

Signs and Symptoms

The clinical picture was that of an extremely ill patient with the anxious expression of one in distressing pain. The lips and cheeks were pale and grey, showing a definite toxæmia with much blood destruction, leading in the worst cases to an apparently moribund state. The skin was damp with perspiration. The commonest and most distressing symptom was that of intense and intolerable

headache. On approaching the bedside or stretcher one was frequently met with an urgent appeal for something to relieve the headache, which the patients said they could not stand any longer—one man actually asked for a razor with which to cut his throat. This symptom was so constant and distressing that one could almost diagnose the case on that alone, and perform an immediate lumbar puncture in confidence of finding a turbid cerebrospinal fluid under pressure. The removal of anything from 30 to 50 c.cm. of fluid would relieve the distressed condition immediately.

The next important sign was that of nuchal rigidity with intense pain on attempting to approximate the chin to the chest. This was noted in 116 cases, and 34 of them were described as having "marked rigidity." Retraction of the head was absent in 42, and only 5 showed anything like marked retraction. No condition of opisthotonos as described was seen in any case. Vomiting was fairly constant and sometimes appeared as quite an early sign contemporaneous with the headache. This was noted in 56 cases, being severe and prolonged in 24. Strange to report, we had a number of bad and persistent vomiters, all admitted in one week in April. Nothing was discovered to account for this. The vomiting generally lasted from one to four days. During this stage soluseptasine was found to be extremely valuable.

The mental condition of the patient was very often abnormal. Two definitely distinct types existed. One type had considerable cerebral irritation. My notes show that 2 patients were very violent and required constant and forcible restraint, 4 were noisy, 13 rambling and delirious, 10 irrational and disorientated. The other type showed varying degrees of mental depression and were very sorry for themselves: 4 were unconscious in coma; 37 were stuporous, confused, and lethargic; 11 were just drowsy and apathetic. Fifteen patients were conscious and rational, and 2 were actually mentally alert. The 4 cases in coma were *in extremis*, collapsed, with cold extremities, and very cyanosed and practically pulseless. They all recovered.

The temperature was no guide in establishing a prognosis or a conception of the severity of the case. Only 3 cases had a temperature of 103° on admission; 102 cases were below 100°, and in 64 the temperature was not above 99°. The pulse rate was almost like a temperature chart and much more indicative of the severity of the infection, and in its charted rate was more informative of the progress of the case than the temperature chart. A slow pulse rate was evident only in cases of increased pressure of the cerebrospinal fluid or in full dosage of the sulphonamide drug used. The volume was noted as "poor" in 28 cases, but hard in 17. The reflexes were not very valuable from the point of view of diagnosis—for example, Kernig's sign was noted as doubtful or absent in 47 cases, knee-jerks were absent in only 18 cases, sluggish in 24, and exaggerated in 7. Brudzinski's sign was present in only 8 cases. Plantar reflexes were: 5 flexor, 42 extensor. Ankle clonus was present in 4 cases. Respirations were a little altered from the normal. Purpuric and petechial rashes on the trunk and limbs were present in 28 cases; 2 extremely severe cases had extensive areas of haemorrhagic purpura; and 24 had the "spotted fever" petechiae, 12 of them very extensive and marked.

Joint Signs.—3 patients had rigid spine, 7 had stiffness and pain on manipulation of joints in upper and lower limbs, 7 complained of pain in the back and 2 of abdominal pain, in 1 the jaw was locked, and 9 had their teeth strongly clenched. One patient who was unconscious had his fists strongly clenched and his arms firmly fixed in flexion at the elbows.

Ocular and Auditory Signs.—4 had conjunctivitis, 13 strabismus with diplopia, and 31 a marked photophobia; 2 showed ptosis of one or other eye; 1 developed a severe condition of iridocyclitis and lost the vision of that eye. 2 were deaf on admission and 5 others had a transitory partial deafness.

General Signs.—In fulminating cases all showed meningeal signs; but the predominant clinical picture was one of acute generalized toxæmia, and some were presumably septicaemic in nature. In other cases the clinical picture simulated typhoid with pyrexia and a macular rash: in these one could isolate the meningococcus by blood culture.

Pathology and Bacteriology

The cerebrospinal fluid was turbid in varying degree. Slight turbidity pointed to lumbar puncture having been performed at an early stage of the disease, and often it became more turbid on later lumbar puncture. In some cases the fluid was almost too thick to pass through the needle. Mostly the fluid was under pressure—and in some cases to such a degree that it actually spurted through the needle. In a cell count the polymorphs varied from 2 to 52,600 per c.mm., this maximum being in a soldier's child aged 3 months: 27 had up to 5,000 polymorphs per c.mm., 44 had 10,000, 38 had 20,000, 12 had 30,000, and 3 had over 30,000. A small polymorph count indicates a localized infection, and one not particularly invading the theca.

The globulin was constantly increased in amount; and sugar was decreased, down to total absence: in 16 cases it was normal; in 38 reduced in quantity; and in 70 nil. Protein was constantly increased, excepting in cases of a very low polymorph count. Any haemorrhage into the spinal canal, accidental or otherwise, gives a definite increase in amount commensurately with the polymorph cell count. The actual amount shown was: 46 up to 200 mg. per ml., 26 up to 300 mg., 20 up to 400 mg., 25 up to 500 mg., 3 up to 600 mg., 2 up to 700 mg., 1 up to 1,100 mg., and 1 up to 1,200 mg.

Chlorides were constantly diminished, varying between 600 and 700 mg. per ml.

The meningococcus was nearly always found in direct smears, but was scanty or absent in culture in cases with a low polymorph cell count or in cases in which treatment had been started before lumbar puncture was performed. In some cases in which symptomatic reasons necessitated repetition of lumbar puncture within twenty-four to forty-eight hours the laboratory reported an almost normal cerebrospinal fluid. Blood culture showed that 3 cases had normal cerebrospinal fluid, but the meningococcus was isolated in blood culture and in blood films peripherally.

In all cases save one the differential blood count showed a total white cell count varying from 10,000 to a maximum of 52,000 per c.mm. The polymorph percentage was high, varying from 70 to 94. The one case showed a leucopenia. Lymphocytes invariably decreased from normal 30% to as low as 2%. There was no change in eosinophils or myelocytes, and the mononuclear count was not altered to any appreciable extent. This is not of much prognostic value.

Differential Diagnosis.—Cases in which the initial diagnosis of cerebrospinal fever or "suspected cerebrospinal fever" was changed were: influenza, 8; scarlet fever, 1; tonsillitis, 6; pharyngitis, 3; chronic bronchitis and emphysema, 1; acute enterocolitis (infant), 1; rheumatism with rheumatic purpura, 1; acute belladonna poisoning (accidental), 1. Cases of cerebrospinal fever previously diagnosed otherwise were: post-epileptic state, 1; ? diphtheria, 1; early pneumonia, 1.

Course of the Illness

After the initial intravenous injection of soluseptasine, with lumbar puncture, within twenty-four or even twelve hours in the majority of cases the picture was entirely changed. The temperature fell to normal, the intensity of the headache was diminished and in some cases entirely eliminated, nuchal rigidity lessened, and vomiting ceased or lessened in persistence and severity. By this time sulphapyridine is given orally without subsequent vomiting, in diminishing strength of dose, until in eight or nine days treatment is stopped and the patient proceeds to a sustained and uneventful recovery, is allowed up in from thirteen to twenty-one days, and is discharged on five weeks' convalescent leave after four to five weeks' hospital treatment. Vomiting ceased in most cases after the initial dose of soluseptasine and lumbar puncture. In 4 cases it continued for two days, in 9 for three days, and in 7 for four days. The period during which headaches persisted was: three days, 2 cases; five days, 2 cases; six days, 3 cases; seven days, 4 cases; nine days, 4 cases; ten days, 2 cases; twelve days, 1 case; seventeen days, 3 cases; twenty-three days, 1 case. The length of time patients were kept in bed was thirteen days and fifteen days in 1 case each, sixteen in 2 cases, nineteen in 2, twenty in 18, twenty-one in 17, and twenty-four in 12. They were generally up and about all day in four weeks. No physical signs of cerebrospinal fever were present after eight days in 1 case, ten in 2 cases, eighteen in 4, nineteen in 12, twenty-five in 26, twenty-seven in 5, thirty-two in 7, thirty-six in 10, and thirty-seven in 11.

Post-convalescent Condition.—After five weeks' convalescent leave 25 declared themselves perfectly well and fit; 48 complained of early fatigue on exercise and occasional dizziness; and 6 complained of pain in the back. 42 exhibited the effort syndrome in varying degree of severity: these cases gave only a fair response to the exercise-tolerance test, with some distress. 6 were found unfit for duty at present and were sent to the general hospital for further treatment and final disposal by a medical board; 48 were recommended for a period of light duty under the supervision of a regimental medical officer, and 25 were returned to their unit as "fit for duty." In the examination of these cases and in the decision as to their further disposal consideration was given to the psychological aspect of the situation. The majority of the cases consisted of young militiamen who had unfortunately contracted the infection after a very short period of service; and after four to five weeks' hospitalization followed by five weeks' convalescent leave at home were, as it were, conscripted again, with the ensuing shock to their nervous system. It was decided, and I think reasonably, that after a period of light duty to enable them to settle down once more into military service they would very shortly "make good" as soldiers.

Mortality.—Among the 124 cases there were 4 deaths, which gives a fatality rate of 3.2%. Since the end of May there have been 11 more admissions, and as no other deaths have occurred the total rate is brought down to 2.9%.

Treatment with Sulphonamides

The introduction of the chemotherapeutic agents known as sulphonamides, or sulphanilamide, for the treatment of cerebrospinal meningitis has completely changed the clinical and prognostic pictures of the disease. Whereas it was previously greatly dreaded because of its high mortality figure of 30 to 60%, or even 80% in fulminating cases, this terror has largely been lost, since the mortality rate is reduced by less than 3% in all cases. In pre-sulphonamide days patients remained in hospital for at least six

weeks, with a further six weeks' convalescence, and often were invalided out of the Service. Under the new treatment men have been discharged from hospital in four to five weeks, and after five weeks' convalescence have been returned "fit for duty" or, in some cases, "fit for light duty" under the supervision of the regimental medical officer, being returned to full duty after a short period.

In treatment it is essential to achieve a high concentration of the drug at the earliest possible moment and to maintain this concentration at an effective level over a predetermined period of time to suit the particular case. As soon as a case is even suspected of being one of cerebrospinal meningitis, and even before lumbar puncture is performed, treatment should be begun. There is no doubt that by adhering to this principle many lives are saved.

Sulphonamides can be given by all routes—orally, subcutaneously, intramuscularly, intravenously, or intrathecally. There are three chief drugs in this order of merit: soluseptasine, sulphapyridine, and sulphanilamide.

1. *Soluseptasine* (M & B 137): disodium para (γ -phenylpropylamine) benzene-sulphonamide- α , γ -disulphonate.—This drug is supplied in ampoules of 5% and 10% solutions for intramuscular or, better still, intravenous injection. Soluseptasine is a sulphonamide with the addition of a benzyl group, which very greatly reduces its toxicity. If the patient is comatose or too ill to take anything by the mouth, or is vomiting, 20 c.cm. of 5% or 10 c.cm. of 10% soluseptasine is injected intravenously into one of the veins over the antecubital fossa. This can be repeated in four to eight hours, according to the severity of the case, and may be continued for three or four days, until the patient's initial signs and symptoms have disappeared. The results are so constantly good and the effects so speedy that this is the drug to be recommended for routine treatment at the outset in all cases except perhaps the mildest. It is certainly preferable to any other form of chemotherapeutic drug that has been produced up to the present time. Further research work is being done in this field. 85% of the cases either at the onset or at some subsequent period were treated by soluseptasine intravenously.

2. *Sulphapyridine* (M & B 693, Dagenan): 2-sulphanilylaminopyridine.—This is made up in the form of compressed tablets for oral administration, each containing 0.5 gramme of active substance. The adult dosage is: initial dose, 3 grammes (six tablets) finely crushed, in milk (or, even better, taken in the tablet uncrushed), followed in six hours by 2 grammes, repeated four-hourly for twenty-four hours, day and night, then reducing to 1½ grammes four-hourly for twenty-four hours; then to 1 gramme at the same intervals for the same period. Later 1 gramme may be given three times daily. If the patient vomits or suffers from nausea give a teaspoonful of sodium bicarbonate in warm water half an hour before the dose is due, or 2 minims of liquor atropinae in water or 2 minims of acidum hydrocyanicum dilutum. It may be necessary to split the dose, giving half the number of tablets two-hourly instead of the full number four-hourly. Sometimes a second lumbar puncture may have to be undertaken to reduce the pressure in the cerebrospinal canal. Treatment should be continued without remission for three to five days after the temperature has fallen and headache has been absent or very mild for a period of nine days.

Sulphapyridine Soluble (Dagenan Sodium).—This is merely the sodium salt of sulphapyridine, and is soluble. It may be introduced intravenously in those patients who cannot take the insoluble form of the drug by mouth or in whom it has been found difficult to obtain an adequate blood concentration by means of oral administration. Each ampoule contains 1 gramme of the drug in 3 c.cm. of diluent; this dose may be given at four-hourly intervals to a total of 4 or 6 grammes, after which it should be possible to continue treatment per os. Sulphapyridine soluble must be diluted in three or more volumes of normal saline. There are very grave drawbacks to the intramuscular route in the administration of this drug. Unless injected very deeply into the muscle it may give rise to subcutaneous necrosis of tissues with abscess formation and ulceration. Furthermore, intramuscular injection often gives

rise to a considerable amount of pain. Attempts have been made to anaesthetize with novocain the whole site of the injection, including the entire track of the needle. Considering the unfailing results and the simple safe operation of injecting the rival drug soluseptasine intravenously, it is difficult to find justification for advocating the use of sulphapyridine soluble.

3. *Sulphanilamide* (synonyms: sulphonamide P, colsulanyde, streptocide, prontasil album): *p*-aminobenzene-sulphonamide.—This preparation is put up in 0.5-gramme tablets. The initial dose is 4 grammes (eight tablets), followed after four hours by a dose of 2 grammes, and the same dose thereafter, four-hourly, day and night, as with sulphapyridine. The tablets should be powdered and taken in milk. If there is no sign of reaction to this treatment the course should be repeated or be changed to soluseptasine. In all cases it is recommended that a change over be made to the oral compound as soon as possible, but, at least with soluseptasine, there need be no hesitation about reverting to the intravenous route should vomiting recur or "gagging" at taking the drug by the mouth. When the meningitis appears to be controlled, as judged by the fall in pulse rate and temperature and the disappearance of clinical signs, the treatment should still be continued in doses of 0.5 gramme three times daily for three to five days, to prevent any chance of relapse.

Often the reaction to treatment, especially in those cases which appear at first sight to be *in extremis*, is truly dramatic, the picture changing completely within twenty-four hours or even overnight. One evening a sergeant was brought in with his fists tightly clenched and elbows so strongly flexed that three orderlies found difficulty in straightening his arms so that an intravenous injection could be given. 20 c.cm. of 5% soluseptasine was administered, and this dose was repeated after four hours. In the morning the patient was quite conscious, and was found actually sitting up in bed.

Another striking case was a man who on admission was practically dead. He looked like a corpse, and smelt like one. He was pulseless and hardly breathing. His body was covered with large patches or areas of purpura. His veins were so collapsed that it was very difficult to gain an entry with the needle, and the blood withdrawn into the syringe was almost black. His life was saved by two doses of soluseptasine, within the first four hours. He was eventually transferred to the Cambridge Hospital for further "tonic" treatment.

Once the diagnosis has been made no further lumbar punctures are performed unless signs of intracranial pressure arise, when the operation can be repeated and the pressure in the cerebrospinal canal registered; also, at this or any subsequent lumbar puncture, the concentration of soluseptasine in the cerebrospinal fluid can be determined. This should be from 4 to 5 mg. per 100 c.cm. for several days after treatment is initiated. Further, the percentage of concentration in the blood itself can be estimated, and future dosage thus decided.

Some cases persist in showing a small rise of temperature for some days after they have obviously reacted satisfactorily to treatment. This need give rise to no apprehension, for the temperature will eventually settle down to normal and remain there. Adverse reactions reported in the medical papers, with cyanosis, acidosis, drug fever, dermatitis, dizziness, headache, leucopenia, haematuria, jaundice, neuritis, agranulocytosis, or haemolytic anaemia, are never even seen after repeated doses of soluseptasine, which has been used throughout in cases of initial and persistent vomiting lasting for two or even four days.

With drug treatment some further important matters require attention. Where persistent vomiting occurs, whether due to the meningitis or to the drug, the patient rapidly becomes dehydrated, and fluids so lost must be

made good so that a satisfactory balance may be maintained between blood concentration and ordinary excretion. To establish this approximately four pints of fluid should be taken daily. With sulphapyridine some clinicians have found jagged arrow-shaped crystals in the urine, with haematuria, pyelitis, and other signs of renal damage.

It is important, further, to see that the diet offered contains no sulphur; for instance, eggs are dangerous, as are other foods with a high sulphur content. For a similar reason magnesium sulphate and other sulphur-containing drugs are contraindicated. A good laxative for these patients, who are often constipated, is liquid paraffin or a simple enema. Treat the patient kindly, for a drastic purge may lead to intractable diarrhoea, with consequent dehydration and its unhappy results.

The following rough outline of treatment may be of value when dealing with some of the complications seen after administration of full doses of sulphapyridine:

Cyanosis.—This should not be taken too seriously. Do not withdraw the drug, but see that the diet is sulphur-free. Give 0.5 to 1 gramme of methylene-blue daily.

Retention of Urine.—Catheterize until bladder functions naturally.

Insomnia.—Chloral and bromide or pulv. ipecac. co. Paraldehyde or morphine only if urgently required.

Herpes Labialis.—Often seen in patients who have been given sulphapyridine in a crushed form. Soluseptasine ointment has been advocated, but has not proved satisfactory. Other more serious complications such as deafness, iritis or ophthalmia or other intra-ocular infections, synovitis, etc., require the specialist's attention.

From beginning to end a complete record of the treatment must be kept on A.F.I. 1237, giving the date and hour, the drug and dose administered, and the route of entry, and this document or a copy must accompany the patient if he is transferred from one medical unit to another, so that overdosage may be avoided. More particularly is this necessary when the transfer takes place from a small medical unit—for example, a medical reception station—to a general or isolation hospital.

Technique for the Intravenous Injection of Soluseptasine

It is advisable to have one or two orderlies present to steady the patient's arm, especially if he should be restless, resistive, or irrational. Choose the arm which appears to be furnished with the best veins. Extend the arm fully at the elbow. In applying the tourniquet round the upper arm leave one end in a loop instead of pulling it right through; thus when it comes to removing the tourniquet one tug of the free end will loosen the knot.

The soluseptasine (20 c.cm. of 5% or 10 c.cm. of 10%), previously warmed to blood heat, should be ready in the syringe, with all the bubbles of air carefully excluded. Wash the skin over the chosen vein with surgical spirit, penetrate the vein, withdraw a little blood into the syringe, release the tourniquet; then, watching the patient's face, slowly inject the solution. Withdraw the needle, place a thick pad of gauze over the site of puncture, and flex the arm. If the veins fail to fill satisfactorily on applying the tourniquet repeated flexing of the arm at the elbow will bring about the desired result. Should it prove difficult to insert the needle into a vein, another vein should be chosen, perhaps on the other arm, but care should be taken not to "blow up" the vein.

I wish to give full credit to the excellent and untiring professional care and ability shown by the medical and nursing staff of this hospital, and thanks to Lieut.-Colonel Little, O.B.E., the Assistant Director of Pathology, Aldershot Command, who has done all the pathological investigations, and to others for their kind co-operation.

EXAMINATION OF THE HEART IN RECRUITS

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The routine examination by the medical boards of many healthy young men called up for military service has brought into prominence various physical signs and symptoms referable to the heart. These are often slight, but their presence raises questions as to whether they can be ignored or whether they are important enough to justify the rejection of the man as unfit for service or his relegation to an inferior physical category. The following is an attempt to enumerate and to explain these signs and symptoms.

Cases met with in these circumstances can be divided into three groups:

1. The heart is normal in size and shape when examined radiologically; no symptoms are present, but minor variations in the heart sounds cause suspicion of disease.

2. The heart is normal clinically and radiologically, but the history or symptoms suggest present or potential effort syndrome or neuro-circulatory asthenia. These, if passed for full active service, are likely to break down and to become a prolonged and severe charge upon the community and upon themselves. An attempt should be made to pass the slighter cases for clerical or other non-violent work, or to find them official work similar to that which occupies them in civil life.

3. Exercise tolerance is normal, but physical abnormalities of the heart, either congenital or acquired, are detected. The diagnosis of the commoner congenital abnormalities is described and an attempt is made to indicate the manner of dealing with the organic cases.

I. The Normal Heart without Symptoms

Excitable young adults at the time of a medical examination often have an excessive sympathetic tone, presumably largely due to an increased output of adrenaline. One result of this is a transient glycosuria, but other manifestations are found in the cardiovascular system. The heart rate is increased, often up to 120 or more. The muscular thrust of the apex of the left ventricle is abnormally vigorous. This produces several physical signs, each of which may suggest a cardiac abnormality. On inspection the impulse extends into two or more spaces and may be visible in the epigastrium. On palpation a false impression of enlargement may be obtained in the following way: The vigorous impact is transmitted by the rib to a point outside the true apex beat; therefore when the hand is placed over a rib rather than in a soft interspace a false conclusion is arrived at. In determining the point furthest to the left and furthest downwards where the heart action is felt great care must be taken in these cases to locate it with the finger-tips in the soft interspace.

Another abnormality produced by overaction of the normal heart is an impurity of the first sound. This change may be so definite as to suggest a short presystolic murmur. The chief points upon which to fix the attention are the pitch of the sound and the absence of any early sound in diastole. In mitral stenosis the pitch is high, like that of a drum stretched tight, but here the pitch is low, like that of a looser and more booming drum. Moreover, in the vast majority of cases of mitral stenosis a mid-diastolic murmur is audible after exercise with the patient lying on his left side.

An associated nervous increase in the blood pressure is found in some of these cases. The increase is presumably due chiefly to increased output, and thus,