6. Surgical Excision.—We tried a small group of cases by this method. Those in Stage I do well, healing by first intention and requiring about ten days' hospitalization followed by a week's convalescence. Early Stage II cases can be treated by excision too, but the wound is liable to become moist, and in the brawny stage surgical intervention is contraindicated, the wound always breaking down.

Comments on Treatment

The untreated Stage II case will never resolve spontaneously—it tends to linger in Stage II for weeks and then the mass breaks down. Treatment by local heat hastens this breaking-down process but rarely encourages resolution. The various drug methods, on the other hand, cause a large proportion to resolve—often quite quickly; but even where this does not occur the mass breaks down quickly, and so in either event a prolonged Stage II is avoided. The majority of cases treated with anthiomaline, sodium antimony tartrate, sulphonamides, or T.A.B. are cured, apart from a little residual thickening in the groin, and fit to return to their units in 3 to 4 weeks; anthiomaline is perhaps the best by a few days, but it is expensive. Its chief advantage is that, where constitutional reaction is not great, it can be given to the man in his unit M.I. room, whereas the others require bed treatment. However, as most Europeans do get a marked constitutional disturbance, the point is not so important.

Stage III has been treated in many ways, and there is a natural temptation to incise the fluctuating swelling. This, however, is the worst possible treatment, for experience shows that secondary infection rapidly develops and the wound continues to discharge for weeks. All are agreed that under no circumstances should incision ever be practised. The best treatment is aspiration, which may have to be at several points because of the tendency to loculation, and it may have to be repeated once or twice. It must be carried out with aseptic precautions, and the punctures should be covered with a patch of sterile gauze and elastoplast. Another method is to use a seton, and a piece of silkworm-gut transfixing the cavity serves well, though the device is not so satisfactory as aspiration.

The treatment of Stage IV is really the treatment of the secondary infection; a combination of dry heat and sulphonamides, with rest in bed, is necessary, and is eventually effective.

Recurrence.—A small proportion of our 300 cases showed recurrence of the glandular swelling, but this soon subsided under the influence of a second, shorter, course of the original treatment.

I should like to acknowledge the work of the various officers who successively took charge of the V.D. Department, and to express thanks to Colonel L. A. Harwood, T.D., the commanding officer of this unit, for permission to publish these cases.

ARSENICAL ENCEPHALOPATHY A COMPLICATION OCCURRING DURING THE TREATMENT OF SYPHILIS

BY

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The results obtained from the adequate treatment of syphilis with arsenical compounds are among the most gratifying in medicine. Most of the lesions disappear rapidly, and in the primary and secondary stages the Wassermann reaction is quickly reversed to normal, while subsequent treatment in these stages invariably results in a complete cure. The treatment, however, is not without the risks attendant on the administration of a powerful drug, and the toxic effects of arsenical therapy are many and varied. Fortunately the vast majority are mild, and the more severe types, such as deep jaundice and exfoliative dermatitis, are relatively uncommon. But it is to one of the rarest and most fatal complications, haemorrhagic encephalopathy, that we wish to draw attention.

During the past 18 months we have had opportunity of witnessing four cases which we consider typical of this condition. These patients were admitted to the wards after treatment as out-patients at the local clinics, and they are the first cases recorded during the nine years' existence of the wards.

Case I

A man aged 50 first attended the out-patient department on Nov. 21, 1940, with lymphopathia venerea. A positive test to Frei antigen was obtained. A Wassermann test was made as a routine measure; the result was doubtful. Four days later the test was repeated, and a strongly positive reaction was obtained. The patient gave a vague history of a penile ulcer in 1910. On Nov. 28, 1940, he began a course of mapharside and bismuth consisting of alternating bi-weekly doses of 0.04 g. and 0.06 g. of mapharside, and bismuth 0.2 g. bi-weekly. Five injections were given, and on the day following the last he was admitted to hospital in deepening coma. The pupils were small and equal, but responded to light. His knee- and ankle-jerks were present and equal, and the plantar response was flexor. His respirations were stertorous and he was doubly incontinent. There was no paralysis of the limbs, and the attitude of the hands and feet was at times strongly suggestive of tetany. Lumbar puncture showed that the fluid was under slight pressure. Fifteen c.cm. was removed, and 1 c.cm. of adrenaline was given four-hourly. Subsequent examination showed the cerebrospinal fluid to be normal. The temperature, which was 100.4° F. on admission, rose within a few hours to 104.2° F., and the man died.

At necropsy the brain was extremely congested on the surface. The cut surface showed very marked congestion of the small blood vessels in the white matter of both hemispheres. Microscopical examination revealed minute haemorrhages surrounding the small vessels. The only other positive finding was a pronounced fatty change in the liver.

Case II

A woman aged 22 attended the clinic with a gummatous ulceration of the hard and soft palates and ulceration of the left tonsil. Her father had a history of syphilis, and she was considered to be a case of congenital tertiary syphilis. She was 27 weeks pregnant. Her Wassermann reaction was strongly positive. Treatment began on March 10, 1942, with N.A.B. 0.3 g. and Bi 0.2 g. The patient returned on March 17 and was given N.A.B. 0.45 g. and Bi 0.2 g. On March 19 she complained of some headache and dizziness. She relapsed into coma and was admitted to hospital with athetoid movements of the left hand. On lumbar puncture the cerebrospinal fluid was under slight pressure. About 10 to 15 c.cm. was removed, and adrenaline 1 c.cm. was given. A slight increase in protein was found in the fluid. In a few hours the temperature had risen to 109° F., and the patient died.

Examination of the brain showed haemorrhages arranged in a symmetrical fashion in the medulla, both hemispheres, and the corpus callosum. The haemorrhages were punctiform and grouped together, occasionally coalescing to form a larger haemorrhage. They were particularly numerous in the white matter surrounding the basal ganglia, but were also present in the basal ganglia themselves.

Case III

A 24-year-old multipara was admitted to hospital on Jan. 29, 1941. It was her third pregnancy, the previous two having been stillbirths. She showed no clinical signs of either acquired or congenital syphilis. The Wassermann reaction and the Meinicke test were both strongly positive. She was then 32 weeks pregnant.

Treatment was given as follows. Jan. 30: N.A.B. 0.15 g., chlorostab 0.16 g. Feb. 3: N.A.B. 0.3 g. Feb. 6: N.A.B. 0.3 g., chlorostab 0.16 g.

Subsequent Course of Events.—Feb. 7: Patient complained of headache and nausea, vomiting once or twice. Feb. 8: The vomiting restarted and increased in severity. Eventually she became irrational and delirious. On examination there was no evidence of oedema or of renal tenderness. Her blood pressure was 155/90. A catheter specimen of urine showed no albumin, but sugar a trace and acetone ++. On auscultation the foetal heart was heard. A provisional diagnosis of toxæmia of pregnancy was made. An intravenous saline drip was set up and morphine given. Feb. 9: The patient was now comatose. There was spasticity of the arms, pupils were unequal, and the right plantar reflex gave an extensor response. Nothing abnormal was observed in the fundi. A lumbar puncture was done for diagnostic purposes. The cerebrospinal fluid was clear and not under pressure. There was no blood present. Treatment was given to reduce the cerebral oedema—viz., 50 c.cm. of 50% glucose intravenously and a solution of mag. sulph. 50% P.R. In the evening of Feb. 9 the patient died, the temperature rising to 104.4° F. before death.

Post-mortem Report.—Brain: There were punctate haemorrhages in the centrum ovale and in the roofs of the lateral ventricles. Microscopical examination showed multiple haemorrhages into the white matter. These usually had an obvious perivascular distribution.

Both "ring" and "ball" haemorrhages were present. Perivascular demyelination as described by Russell (1937) was particularly looked for, but no evidence was found with either the Marchi or the Loyez modification of the Weigert-Pal method. *Liver*: Microscopical examination showed marked cloudy swellings with occasional subcapsular haemorrhages. *Spleen*: Enlarged and soft; subcapsular haemorrhages and petechiae on the cut surface. *Kidneys*: Right showed subcapsular haemorrhages. The cortex was pale, with engorged vessels and glomeruli. The left kidney showed similar changes but no subcapsular haemorrhages. The *suprarenals* appeared normal.

The foetus was examined, particularly the liver. No *Spirochaeta pallida* were demonstrated, nor was there any evidence of syphilitic cirrhosis.

CASE IV

A primigravida aged 18 was admitted to hospital on Oct. 29, 1941. She was then 20 weeks pregnant. On examination she was found to have a primary sore of the vulva (*Sp. pallida* +). The Wassermann reaction and Meinicke test were both weakly positive. Treatment was given as follows: Oct. 30: N.A.B. 0.15 g., chlorostab 0.16 g. Nov. 4: N.A.B. 0.3 g. Nov. 7: N.A.B. 0.3 g., chlorostab 0.16 g.

Subsequent Course of Events.—On the evening of Nov. 9 she complained of slight headache, and retired early to bed. The following morning she was stated to have had a fit. When seen a few hours later she was stuporous. There was no neck rigidity; the pupils were equal and reacted to light. Both plantar reflexes gave a flexor response. Heart and lungs were clear. Her blood pressure was then 150/90. A catheter specimen of urine contained a trace of albumin only. The blood urea was 42 mg. per 100 c.cm.

A diagnosis of haemorrhagic encephalitis was made. Treatment consisted of repeated drainage of the theca. The first lumbar puncture was done within five hours of the fit.

C.S.F. Laboratory Data

	10/11/41	11/11/41	12/11/41	14/11/41	21/11/41
Amount withdrawn	45 c.cm.	30 c.cm.	20 c.cm.	10 c.cm.	5 c.cm.
Appearance	Clear	Clear	Clear	Clear	Clear
Fibrin clot	None	None	None	None	None
Total protein	0.09%	0.12%	0.14%	0.09%	0.04%
Globulin	Increased	Sl. inc.	Sl. inc.	Sl. inc.	Normal
Sugar	Normal	Normal	Normal	Normal	Normal
Chlorides	Normal	Normal	680 mg.	650 mg.	Normal
Lange	Negative	Negative	Negative	Negative	Negative
Cells (lymphocytes)	2 per c.mm.	2 per c.mm.	2 per c.mm.	2 per c.mm.	2 per c.mm.
W.R.	Neg. in all dilutions				Neg. in all dilutions

In addition to drainage of the theca by lumbar puncture 10 c.cm. of mag. sulph. 20% was given intravenously twice during Nov. 10, and thereafter hypertonic mag. sulph. P.R. The patient was kept under the influence of morphine. On Nov. 11 a morbilliform rash appeared on the neck, breasts, and shoulders. This rash disappeared within 24 hours. The maximum temperature was 101.2° F. on Nov. 12; on Nov. 13 and thereafter it was normal. Gradually the patient improved, and two days after the onset of the condition was fully conscious and alert. For a further four to five days she remained irritable and restless. Finally she became her usual self in behaviour and intelligence. A blood Wassermann reaction and Meinicke test done on Nov. 25 were both negative. Antispecific treatment with bismuth was started on Nov. 28, and thereafter was continued at the out-patient department.

On March 11, 1942, she was delivered spontaneously of an apparently healthy full-time male infant, whose weight at birth was 6 lb. 13 oz. The Wassermann reaction of the cord blood was negative and no *Sp. pallida* were demonstrated in the umbilical cord. On April 24 a blood test was done on the child, the Wassermann reaction and the Meinicke test being negative. Radiographs of the long bones revealed nothing abnormal.

Discussion

The so-called haemorrhagic encephalitis is the most fatal of all complications resulting from arsenotherapy. Fortunately it appears to be very rare. Stokes (1934, 1939) observed one case in 63,000 injections. Glaser, Imerman, and Imerman (1935) in a review of the subject found one death due to cerebral complications in every 5,398 cases treated and in every 28,768 injections. Paley and Pleshette (1939) reported one fatality from haemorrhagic encephalitis among 1,200 treated cases of pre-partum syphilis. It is stated that males are slightly more often affected; but of females reported over 70% were pregnant. They were apparently healthy adults, the average age being 22.5 years. The ante-natal cases were usually primigravidae, and the average duration of pregnancy was 5.5 months. In our series of cases the ages were 50, 22, 24, and 18 years. All three females were pregnant. The periods

of gestation were 27 weeks, 32 weeks, and 20 weeks respectively. From our own limited experience we suspect that the condition is not so rare as the figures quoted suggest. It is conceivable that such cases might be admitted to medical and ante-natal wards, where, in ignorance of recent antispecific treatment having been given, the diagnosis is not made.

The mortality rate is high. Most cases terminate fatally, although recovery has been reported in several instances by David Lees (1940), Netherton (1934), Dickens (1928), and Parnell and Dudley (1920).

Pathology

The pathological changes are most pronounced in the white matter of the brain, although similar lesions are found to a less extent in the grey substance. It is stated that the sites most frequently involved are the corpus callosum, the caudate and lenticular nuclei, the pons, and the medulla. Globus and Ginsburg (1933) in their description of two cases following arspenamine therapy indicated that the main central lesions were "ring" haemorrhages. The haemorrhages were pericapillary, and there was no evidence of inflammation. These authors suggested, therefore, that the term "pericapillary encephalorrhagia" was more appropriate than "haemorrhagic encephalitis." In addition to these characteristic haemorrhages reactive gliosis was present in the neighbourhood of the affected blood vessels.

In our post-mortem reports these pathological findings have been confirmed. Pathologists agree, however, that such lesions as described are not peculiar to arsenical encephalorrhagia. They have been observed in association with many diseases.

Treatment

Since the majority of cases are rapidly fatal and are recognized only at necropsy, there is in the literature a paucity of information regarding the relative merits of suggested modes of treatment. In the one case of our series which did recover, repeated drainage of the theca was efficacious. This was instituted 5 hours after the occurrence of the initial convulsion and therefore, one may conclude, before the onset of any appreciable brain haemorrhage or necrosis. In addition this patient was kept under the influence of morphine. Other writers have suggested such procedures as venesection, the giving of large doses of adrenaline intramuscularly, repeated intravenous injections of sodium thiosulphate, calcium preparations, snake venom, and continuous inhalations of oxygen with intravenous injections of urotropin and caffeine.

Theories

The theories as to the cause of haemorrhagic encephalitis are numerous and, examined individually, are not altogether conclusive. As regards the toxicity of the drug administered, no trivalent arsenical is free from the risk of producing this condition. Sulpharsphenamine is stated to be associated with a higher incidence than the other members of the group. N.A.B. and mapharside, the drugs used in the cases reported, are considered to be less toxic than many, and, moreover, the N.A.B. was dissolved in 10 c.cm. of 10% sodium thiosulphate.

The dosage does not seem to play a prominent part in the aetiology, since the largest dose of N.A.B. given was 0.45 g. and of mapharside 0.06 g. Of the other causative factors cited by previous observers, none of our cases showed evidence of chronic arterial disease nor of liver or adrenal insufficiency.

It is reasonable to suppose that pregnancy must have some bearing on the aetiology, since, as already quoted, of women with haemorrhagic encephalitis 70% were pregnant. In one of our cases toxæmia of pregnancy was considered as a provisional diagnosis, and it is possible that an additional toxæmia due to pregnancy may be a predisposing factor. On the other hand, in our own experience a large number of women with ante-partum syphilis, many of them with marked general debility, have been treated with trivalent arsenicals without developing haemorrhagic encephalitis. Furthermore, during treatment a small proportion have presented definite signs of toxæmia of pregnancy. These did not become cases of haemorrhagic encephalitis.

Our post-mortem findings would appear to support the theory of direct toxic action on the brain capillaries. The

reason for this apparent selection is obscure, and our observations throw no new light on this aspect. From the study of the four cases reported one interesting feature emerges—namely, the interval between the first injection and the onset of the condition. It is not without significance that in three of them haemorrhagic encephalitis occurred about the tenth day after beginning treatment—a time when it is not uncommon to find other signs of intolerance to arsenic in the syphilitic patient. Indeed, one of our patients did manifest a concomitant morbilliform rash. Haemorrhagic encephalitis does occur in patients receiving arsenical therapy for non-syphilitic nervous disorders, but not with the same characteristic time interval. Therefore one may assume the syphilitic infection itself cannot be excluded as a factor in the aetiology.

Finally, two extraneous factors may be mentioned. It will be noted that these four cases occurred in winter-time, when as a general rule vitamin intake is at its lowest, especially vitamin C. Also they have been reported since the onset of the war. Conditions in wartime naturally impose greater mental stress and strain on the individual, and more so on the patient with syphilis.

Conclusion

Haemorrhagic encephalitis is a rare complication of treatment with arsenic in syphilis.

It is impossible to determine in advance the type of individual who will develop this complication, but the pregnant woman with syphilis should be regarded as a "potential reactor."

The clinical signs are those of cerebral irritation, and may be preceded by such symptoms as headache and dizziness.

The condition is rapidly fatal unless diagnosis is prompt and treatment immediate.

We wish to thank Dr. Ross and Dr. Sanderson for kindly allowing us access to their case.

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A CASE OF HAEMORRHAGIC ENCEPHALOPATHY FOLLOWING ARSENICAL THERAPY

BY

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The following case of arsenical encephalopathy is thought worthy of publication in view of the few references to this complication of arsenical therapy in recent British literature, and also because of the increasing incidence of syphilis at the present time.

Cases in the Literature

Serious cerebral complications following treatment with arsenical preparations are fortunately rare. Haemorrhagic encephalopathy or serous apoplexy is a complication of arsenical therapy which usually ensues within two or three days of the second or third injection of an arsenical preparation. The onset is characterized by drowsiness, irritability, and depression, followed by epileptiform convulsions and coma. The prognosis is bad unless cases are recognized early and prompt treatment is instituted. Lees (1937) mentions nine cases, five of which recovered. Winter (1940) describes a case of primary syphilis in a healthy young adult in which symptoms developed two days after the second injection of an arsenical preparation. The early symptoms in Winter's case were slight

nausea, headache, and feverishness. Examination revealed a scarlatiniform rash on the trunk, limbs, palms of the hands, and soles of the feet. The temperature rose to 104° F., the rash became more marked, and oedema of hands and arms developed. Vomiting was a feature, but mental and nervous symptoms were lacking. The rash became purpuric, and about 48 hours from the onset mild mental symptoms developed, followed by loss of consciousness and death. Necropsy revealed oedema of the brain and multiple haemorrhages throughout the brain substance. Friedman and Newman (1941) describe a case of encephalitis in a syphilitic subject aged 28; again the symptoms appeared shortly after a second dose of an arsenical preparation. These symptoms were epileptiform convulsions, projectile vomiting, and rectal and urinary incontinence. Examination revealed no abnormal neurological findings. The cerebrospinal fluid was not under pressure; it contained 15 cells per c.mm. and total protein 70 mg. per 100 c.cm. Their case recovered, after administration of adrenaline intramuscularly and glucose intravenously. Friedman and Shinefeld (1941) describe two cases in syphilitic children, both of whom died. In their cases symptoms occurred after several injections of arsenical preparations. The symptoms were irritability, convulsions, and coma. In one case cerebrospinal-fluid protein was 297 mg. per 100 c.cm. Russell (1937) describes the pathological findings in three cases. She found perivascular and ring haemorrhages, and also perivascular non-haemorrhagic areas of necrosis and demyelination in the central nervous system. All three were serologically positive cases of syphilis in young adults, the eldest being 31 years old. Symptoms in two of her cases appeared shortly after the second injection of an arsenical preparation; in the third case symptoms followed the third injection. All three patients died within four days of onset.

Case Report

Male aged 22. No previous history of ill-health. Treated for acute gonococcal infection from March 4 to 12, 1942, in V.D. hospital, and readmitted to the hospital on April 12 with multiple indurated ulcers on coronal sulcus. *Spirochaeta pallida* present on examination with dark-ground illumination. Treatment consisted of: April 11: novostab 0.45 g., chlorostab 1 c.cm. April 14: neo-kharsivan 0.3 g. April 18: novostab 0.45 g., chlorostab 1 c.cm. On April 21 the patient felt out of sorts, hot, and flushed; temperature 102° F. During the next two days temperature varied from 100° to 102° F. He was depressed, but made no special complaint. At 7 a.m. on April 23 he had an epileptiform convulsion and vomited bile-stained fluid; admitted to E.M.S. hospital.

Examination.—Temperature 98° F., pulse rate 78, respirations 20. Semi-comatose on admission; incontinent, with noisy moaning respirations; colour good. Pupils equal, circular, and contracted: reacted sluggishly to light. No neck rigidity, and Kernig's sign negative. All reflexes were exaggerated and ankle clonus was present; plantar responses doubtful flexor; abdominal reflexes present and normal. Other systems normal. Blood pressure 120/70. **Fundi:** Slight blurring of disk edges right side. Left side normal. **Urine:** S.G. 1030; no abnormal constituents; no red blood cells or casts. White cell count 12,000. Lumbar puncture at 11 a.m.: cerebrospinal fluid not under pressure; fluid contaminated with blood. **Blood:** Wassermann reaction ++, Kahn negative. Flocculation test, 1:16.

A few hours after admission plantar reflexes became extensor and respirations stertorous. By evening temperature had risen to 104° F. Pulse rate 118; respirations 40. Lumbar puncture repeated: cerebrospinal fluid clear; pressure 250 mm. water; cells 5 per c.mm.; Wassermann reaction negative; protein 230 mg. per 100 c.cm. By the following morning coma was deep, with marked venous congestion. Venesection performed and 14 oz. of blood withdrawn. Lumbar puncture repeated—10 c.cm. cerebrospinal fluid removed: pressure 260 mm. water; cells 5 per c.mm.; protein 270 mg. Kahn negative. By 2 p.m. on April 24 coma had deepened; temperature 104.8° F., pulse rate 108, respirations 32. Marked cyanosis, and at 6 p.m. patient had two epileptiform convulsions. Lumbar puncture repeated. Thereafter coma steadily deepened, and after two further epileptiform convulsions the patient died at 3 a.m. on April 25.

Necropsy

Apart from the central nervous system, all organs were normal except for punctate haemorrhages on the upper surface of lower lobe of right lung.

Brain: Macroscopic Appearance.—Considerable congestion of the pia-arachnoid all over the brain, with several irregular haemorrhages—one on the upper surface of the left half of the cerebellum, one on the contiguous lower surface of the corresponding occipital lobe, and