

with hypodermic injections of emetine hydrochloride in acute amœbic dysentery would seem to be beneficial, in that convalescence is established earlier and patients are less likely to become "carriers." It cannot be considered in the light of a substitute for emetine, as attempts to treat acute cases with it alone ended in failure, until emetine was used in addition.

In "carriers" and in those convalescents who continue to harbour cysts, emetine and bismuth iodide should prove superior to emetine, and it would seem a wise proceeding, from a public health point of view, to subject all cases of amœbic dysentery to a course of emetine and bismuth iodide during convalescence.

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NOTES ON THE TREATMENT OF SUBTERTIAN CEREBRAL MALARIA WITH QUININE AND GALYL.

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SALVARSAN and neosalvarsan have been used to a considerable extent during the last six or seven years in the treatment of malaria. Most observers are agreed that these drugs, especially when associated with quinine, are of value in infections with the benign tertian and quartan parasites, but are of little value against infections with the *Plasmodium laveraniae*. Although quinine alone may justly be termed a specific in the treatment of most types of malaria, the death-rate from malignant subtertian malaria is yet sufficiently high to stimulate further effort to find an even more efficient therapy.

The following six cases were treated with a combination of quinine and galyl:—

Case 1.—Pte. C., aged 31, admitted to base hospital on September 22, 1916. He had reported sick on September 18, complaining of headache, vomiting, and "the shivers." He stated that for the previous three months he had been having attacks of shivering and sweating at irregular intervals. On admission to hospital his general condition was good, his temperature was normal, and his spleen extended half an inch below his costal margin. He was treated with twenty grains of quinine sulphate three times a day by mouth. He felt quite well and his temperature remained normal until the morning of September 25. On that date his temperature rose to 100° F. and remained up all day. On the morning of the 26th it had fallen to normal, but rose again in the evening to 101° F., and the patient felt sick and vomited. An injection of twenty grains quinine bihydrochloride was administered intramuscularly. On the morning of the

27th another injection of twenty grains of quinine was given intramuscularly. His temperature was normal, and did not rise above normal throughout the day. At noon the patient refused his food, and looked strange; at 3 p.m. he was found to have complete paralysis of the muscles of both sides of the tongue, of the pterygoids and of the masseters. There also appeared to be some weakness of the external recti. There was no paralysis of the limbs, or alteration of the superficial or deep reflexes. The patient was quite conscious and could carry out directions as to the movements of his limbs; the fundi oculorum were normal. A blood-film showed the presence of numerous subtertian rings and crescents. He was given an intravenous injection of 0·8 gramme quinine bihydrochloride. At 8 p.m. the patient's condition was unchanged, except that he now appeared to have some difficulty in understanding what was said to him. There was a definite internal strabismus of the left eye; a further 0·8 gramme quinine was administered intravenously. On the morning of the 28th his condition was much improved. He could open his mouth, protrude his tongue, and articulate slowly. He had some difficulty in swallowing, as fluids tended to regurgitate through the nose. There was still defective movement of both eyes outwards. In the afternoon his temperature rose to 100° F. On this date he was given two intravenous injections of quinine bihydrochloride 0·8 gramme each. On the morning of the 29th his condition was much worse. There was complete paralysis of the tongue, the palate, and the muscles of mastication. There was also complete ophthalmoplegia, and it was doubtful whether the patient understood what was said to him. At 9 a.m. he received a further 0·8 gramme quinine bihydrochloride intravenously. At 11 a.m., as there was no improvement in his condition, he was given 0·3 gramme galyl intravenously. At 3 p.m. the patient was much improved. He could then protrude his tongue, move his jaw, talk slowly but quite intelligently, swallow slowly, and move his eyes. At 9 p.m. he was given a further 0·8 gramme quinine intravenously. On the 30th the patient's condition had continued to improve. There was still some dysarthria, but he was able to swallow without difficulty. He was put on 20 grains of quinine sulphate three times a day by mouth. The improvement steadily continued, but on October 1, as the temperature still rose to 100° F., he was given 0·2 gramme galyl intravenously. The temperature fell that night and remained subnormal during the rest of his stay in hospital. He showed no further symptoms and was transferred to hospital ship on October 18, when there was no evidence of organic nervous disease, and no malarial parasites could be found in the blood.

Case 2.—Sapper R., aged 33, admitted to base hospital on October 4, 1916. On admission the patient's general condition was bad, and the temperature was 103° F. He showed no evidence of any local lesion of the nervous system. A blood-film showed the presence of numerous subtertian malarial parasites. He was given 0·8 gramme quinine bihydrochloride intravenously. On the morning of the 5th his temperature was subnormal, but his general condition was very poor. He was again given 0·8 gramme quinine intravenously, and at 2 p.m. twenty grains of quinine sulphate by mouth. In the afternoon the patient developed marked dysarthria and difficulty in swallowing. The speech was quite unintelligible. The movements of the tongue and palate were present but much impaired. The patient's mental condition was not affected, and there was no paralysis of the limbs or alteration in the superficial or deep

reflexes. At 6 p.m. he received 0.4 gramme of galyl intravenously. On the 6th the patient's general condition was much improved, and beyond slight dysarthria, which rapidly passed off, he showed no evidence of local disease of the nervous system. He was then treated with quinine intramuscularly, and later by mouth, and rapidly became convalescent. He was transferred to hospital ship on October 21, without any evidence of organic nervous disease.

Case 3.—Pte. B., aged 48, admitted to base hospital on the night of October 7, complaining of headache and general weakness. On admission his temperature was 103° F., but fell to 99° F. on the morning of October 8. His general condition was fair, and his spleen extended about one inch below the costal margin. He was treated with twenty grains of quinine sulphate three times a day by mouth. He took his dinner at noon on the 8th without discomfort, but at 4 p.m. it was found that he was unable to swallow his tea, and he rapidly became unconscious. A blood-film showed the presence of numerous subtertian rings and crescents. When seen at 5 p.m. he was lying in a semi-conscious condition, and did not pay any attention to what was said to him. The conjunctival reflex was present and the superficial and deep reflexes were normal. The unconsciousness rapidly deepened, and he could not be roused by any stimulation. He received 0.8 gramme of quinine bihydrochloride at 5 p.m., 7 p.m., and 10 p.m. At 11 p.m. his condition was unchanged, except that his pulse was failing. He then received 0.4 gramme of galyl intravenously. When seen at 6 a.m. next morning he was quite conscious, able to answer questions slowly and intelligently, and swallow. His temperature was subnormal, and remained so for the remainder of his stay in hospital. A blood-film showed the presence of scanty subtertian crescents up to October 15, but he showed no further symptoms and was transferred to hospital ship on the 22nd.

Case 4.—Pte. C., aged 26, admitted to the base hospital on October 10. On admission the patient's general condition was poor, his temperature was 99° F. and his spleen extended about one inch below his costal margin. A blood-film showed the presence of rings and crescents. He tended to be drowsy, but answered questions quite intelligently, and had no complaints. He was given 0.8 gramme quinine bihydrochloride intravenously. On the morning of the 11th the patient's general condition was worse, he was more drowsy, and answered questions with difficulty. The pulse was 120 per minute and feeble. He received fifteen grains of quinine bihydrochloride intramuscularly. At 3.30 p.m. his condition suddenly became much worse; his breathing became stertorous, and his pulse imperceptible; he lay moaning incessantly, and rolling his head from side to side. There was no paralysis, and his superficial and deep reflexes were normal. His temperature was subnormal. At 4 p.m. he became violent, and lay on his left side in the typical attitude of cerebral irritation. He violently resisted any interference with this position. He received 0.4 gramme galyl intravenously. At 9 p.m. the patient's condition had definitely improved. He had slept for two hours and his pulse was better. At 1 a.m. on the 12th he again became rather excited, and was given $\frac{1}{16}$ grain hyoscine. After this he slept, and when he woke was rational, though weak. From this date he rapidly and steadily improved, and on the 22nd was transferred to hospital ship without presenting any further local symptoms.

Case 5.—Pte. L., aged 20, admitted to the base hospital on October 15, 1916, with a diagnosis of malaria. On admission his temperature was normal and he presented no local symptoms. His spleen extended half an inch below the costal margin. He had never suffered from fits nor had any of his family done so. On October 16, whilst in the latrine, he suddenly developed an epileptiform fit. After having been brought back to the ward, he was in a very confused condition, and paid no attention to any questions, but constantly attempted to get out of bed. The blood-film did not show any malarial parasites. His temperature had risen to 101·4° F. During the 16th he continued to have epileptiform fits, and in the twenty-four hours had some twelve in all. The clonic convulsions were general and did not appear to begin constantly in any particular part, but they were always associated with marked deviation of the head and eyes to the left. Between the fits he was either extremely drowsy or violently delirious. At 2 p.m. he received 0·8 gramme quinine bihydrochloride intravenously, and at 6 p.m. twenty grains intramuscularly. On the morning of the 17th his temperature was 101° F. and his pulse-rate 80 per minute. He was very drowsy and had passed no urine. He received twenty grains quinine intramuscularly. At 9 p.m. he developed another fit, and it was noted that the left plantar reflex was extensor; the right plantar reflex was flexor. He was given 0·4 gramme galyl intravenously, and a lumbar puncture was performed. The cerebrospinal fluid appeared to be under increased pressure, and two testtubefuls of clear fluid were drawn off. The cerebrospinal fluid showed no increase in cellular elements. At 8 p.m., as he had passed no urine for thirty-six hours, a catheter was passed, and less than an ounce of urine was obtained. It did not contain any albumin, sugar, or casts. On the morning of the 18th the temperature was normal, and the patient's general condition improved. He answered questions quite readily and was taking his nourishment well. The left plantar reflex was still extensor, and there were marked nystagmoid jerkings of the eyes on lateral movement to either side. The left leg was distinctly weaker than the right, but was capable of performing all movements with a fair amount of force, and there did not appear to be any ataxia of the limbs. Urine was being passed quite freely. He was given two doses of twenty grains quinine intramuscularly on this date. From this date onwards he was treated with quinine, at first intramuscularly, and later on by mouth. Convalescence was uninterrupted. The weakness of the left leg rapidly improved, but the plantar reflex remained extensor for four weeks. The nystagmoid jerkings of the eyes varied somewhat from time to time, but were still definitely present six weeks after the patient's admission to hospital. When able to get up he showed a pronounced reeling gait, and unless supported he tended to fall to the left. He stated that he felt as if his head were being pulled to the left. When made to walk holding his head down to his right shoulder with his right hand, the tendency to reel to the left was diminished, but was still present. There was no Rombergism and no ataxia. The optic disks were normal. He had no further fits after the 18th, and was transferred to hospital ship in February, 1917.

Case 6.—Dr. S., aged 22, admitted to hospital on September 29, 1916. He reported sick on the 21st, complaining of pain in the head and back, and diarrhoea. On admission to hospital, his general condition was fair, his temperature 103° F., his pulse 120 per minute, and his spleen two inches below the costal margin.

He was put on forty grains of quinine sulphate by mouth per day. On October 2, as the temperature was still raised he was given twenty grains of quinine bihydrochloride intramuscularly in addition. On the 4th his temperature did not rise above 99° F., and he appeared somewhat better. On the 5th the temperature again rose to 101.4° F., and he complained of some pain in the neck and a little difficulty in swallowing. No definite affection of the cranial nerves could be made out, but the right plantar reflex was definitely extensor. He was again put on quinine intramuscularly. On the 6th the temperature again rose; he still complained of pain in the neck, and the right plantar reflex was still extensor. The respirations had increased in frequency, and there was some dullness at the base of the right lung posteriorly. He was given two doses of 0.8 gramme quinine intravenously. On the 7th, as there was no improvement, he was given 0.4 gramme galyl intravenously. He died on the morning of the 8th.

Post-mortem.—The whole of the upper and lower lobes of the right lung were solid in a condition of grey hepatization. There was a considerable accumulation of cerebrospinal fluid below the tentorium and some œdema of the pia-arachnoid over the pons and medulla. The brain was hardened in formalin and then sectioned, but it did not show any macroscopic change.

In these six cases galyl was used in association with large doses of quinine. So far we have been able to make only a limited number of observations of the effect of galyl alone on the subtertian parasites in the peripheral blood-stream, but that galyl alone can cause the disappearance of the ring forms of parasite from the peripheral blood-stream is shown by the two following cases.

Case 7.—Sister S., aged 28, admitted to hospital on November 12, 1916, with pyrexia. Numerous subtertian rings were present in the blood. The patient was put on twenty grains quinine sulphate three times a day by mouth. This produced constant vomiting, headache, and very troublesome tinnitus aurium. The parasites persisted in the blood-stream and the pyrexia continued. On November 14 she was put on intramuscular injections of quinine bihydrochloride, twenty grains twice a day. The intramuscular injections were continued for four days, but the patient was extremely intolerant of quinine and complained of violent headache, and tinnitus aurium with occasional vomiting. The temperature was swinging between 97° and 101° F. Subtertian rings were constantly present in considerable numbers in the blood. She was again put on quinine by mouth, but, on account of vomiting, it was impossible to get her to take it regularly. An intermittent pyrexia continued up to November 27, and during this period subtertian rings were constantly present in the blood. On November 27 she received 0.2 gramme galyl intravenously. Her general condition definitely improved, but the blood still showed subtertian rings, although in diminished numbers, up to December 6, when she had a second dose of 0.4 gramme galyl. From this date onwards there was a marked general improvement in her condition, although she still continued to show an irregular pyrexia rising to 100° F. at night; her blood was examined every few days for malarial parasites until her discharge some two months later, but these were not again found. On December 10 typhoid bacilli were isolated from the stools, and on January 2, 1917, she developed a periostitis of the right humerus.

Case 8.—Pte. B., aged 26, elsewhere reported in detail, was admitted to hospital on the night of October 4, 1916. On October 5 his temperature rose

to 102° F.; his general condition was poor, his sclerotics icteric, and he presented gangrene of the toes of both feet. A blood-film showed the presence of rings and crescents, anisocytosis, poikilocytosis, and polychromatophilia. As it was considered possible that a vascular spasm aggravated by quinine might play a part in the condition of the feet, he was not put on quinine but given 0·3 gramme galyl intravenously. His temperature fell that night and remained subnormal throughout the rest of his stay in hospital. His general condition rapidly improved, and a blood-film taken on the 10th was reported negative to malarial parasites. Two other blood-films taken later were also reported negative. Before his discharge to hospital ship he was put on ten grains of quinine sulphate twice a day by mouth.

In this case it will be noted that the crescents also disappeared rapidly from the blood, but in most of our cases of combined quinine and galyl treatment the crescents have been much more persistent, as in the following case.

Case 9.—Pte. K., aged 25, admitted to hospital on December 23, 1916, with a diagnosis of bronchitis. The patient had been in hospital in May, 1916, with a diagnosis of P.U.O., and in October with malaria. He had not felt well since leaving hospital in October, and he stated that he had had frequent shivering fits since then. During September and October he had taken thirty grains quinine by mouth per day, but had only been taking it irregularly in November and December. On admission his general condition was poor. His temperature was 102° F. and rose to 103° F. next day, to fall to normal on the 25th. His blood showed numerous subtertian crescents and rings. From December 24 to 27 the number of crescents met with in counting 200 leucocytes was practically constant, the figures being 100 crescents to 200 leucocytes. On the 27th he was given 0·4 gramme galyl intravenously. On the 29th the crescents had fallen to 50, on the 30th to 36, for every 200 leucocytes. On the 30th he again received 0·4 gramme galyl. On December 2 the crescents had fallen to 24 in 200 leucocytes, on the 3rd to 14, and, on the 4th to 7 crescents for every 200 leucocytes. On the evening of the 11th he developed catarrhal symptoms with a temperature of 101° F., but without any rigor. A similar condition was at that time present in the ward and was almost certainly not malarial. The temperature was normal on the 6th, and on the 6th and 7th the crescents numbered respectively 11 and 10 to 200 leucocytes. He received another 0·4 gramme galyl on the 7th. On the 8th his temperature rose again and he had a malarial attack. Rings were found in the blood on the 9th. His temperature became normal again on the 11th and his blood showed no rings, but 23 crescents to 200 leucocytes. He was put on forty grains quinine bihydrochloride intramuscularly once a day, and twenty grains quinine sulphate twice a day by mouth. On the 13th, 14th and 15th his blood showed 8, 7 and 8 crescents respectively to 200 leucocytes. On the 23rd and 24th 1 crescent to 200 leucocytes was found, and on the 25th and 26th no crescents could be found in counting 300 leucocytes. On February 1, 1 crescent was found in counting 200 leucocytes, on the 2nd, 3 crescents to 200 leucocytes. On the 4th and 6th no crescents were found in counting 400 and 300 leucocytes respectively. His general condition was now excellent and he was transferred to hospital ship on February 7th.

With regard to the value of combining galyl with quinine in serious cases of malaria, our experience is yet too limited to permit of any dogmatic statements

as to its efficacy. It will be noted that, in the first six cases reported here, all were seriously ill with definite subtertian cerebral malaria. All the cases recovered, with the exception of one who died of a complicating croupous pneumonia. All had received quinine, several of them large doses by mouth, intramuscularly, and intravenously, without clinical improvement. In all of them, with the exception of the fatal case, the clinical improvement after the administration of galyl was striking and immediate. In none of the cases did the injection produce any unpleasant results, although several of the cases appeared almost moribund before the injection.

In the eighth case, in which it was considered inadvisable to give quinine, galyl alone caused the disappearance of the parasite from the peripheral blood and produced a striking improvement in the condition of the patient.

In Case 7 the patient took quinine in any form with great difficulty, and although she had taken a considerable amount of quinine by the mouth and intramuscularly, ring forms of the subtertian parasite were constantly present in the blood. After the first half-dose of galyl there was a notable clinical improvement, but the parasite could still be demonstrated in the blood. After the second dose the parasites at once disappeared from the blood. The typhoid ran a protracted course, and she developed a periostitis of the left humerus, but in spite of repeated examinations parasites were not again demonstrated in the blood during the rest of her stay in hospital.

In Case 9, subtertian crescents were present in large numbers. Under treatment by galyl alone they diminished from 100 per 200 leucocytes to seven or eight. The patient's general condition very greatly improved, but he still developed a malarial attack with the presence of rings in the blood. These rings disappeared under treatment by intramuscular quinine, and the crescents continued to diminish and were absent on February 7, when he was transferred to a hospital ship.

We consider that we are justified in concluding:—

(1) That the treatment in itself is free from danger.
(2) That, in subtertian malaria which is resisting adequate quinine treatment, or where the condition is sufficiently alarming, the results of the combined galyl and quinine treatment have been encouraging enough to justify a further trial. It must be thoroughly understood, however, that the addition of galyl in no way diminishes the necessity for quinine.

(3) That in cases where, on account of idiosyncrasy, quinine is impossible, a valuable substitute may be found in galyl.

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