

ARSENICAL TOXÆMIA: A SELECTION OF CASES.

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IN this paper is described a selection of cases of arsenical toxæmia among soldiers undergoing anti-syphilitic treatment which occurred in the Middle East.

Nearly thirty examples of this kind of toxæmia were treated within the space of a few months in this hospital and ample opportunity was afforded for bedside study but unfortunately laboratory facilities were meagre and only the simplest investigations could be carried out.

The drugs used were neosalvarsan, novostab, and sulphostab. Possibly some of the supply of sulphostab had deteriorated in condition because of exposure to tropical heat during transport from England and through the Middle East. Moreover it was administered by the intravenous route—a method which had been followed for some eighteen months previously without an undue incidence of reactions.

The manifestations of arsenical toxæmia are as protean as the remedies suggested are varied and even contradictory. The fundamental pathology of the condition is not clear although the feature common to all cases is acute capillary damage. In its mildest form this is shown by a dilatation of the surface vessels on the ball of the eye and of the external acoustic meatus, signs which were present in many of the cases described below. At the other extreme is the profuse hæmaturia illustrated in the case of toxic purpura which is included in this series. The severity of the capillary damage can be gauged roughly by a single capillary resistance test.

Two theories of the causation of this capillary toxæmia are commonly upheld. One supposes that arsenic or one of its products exerts a direct action on the capillaries. The other is based on the belief that the action is indirect; that the capillaries suffer as a result of toxic products which have been elaborated by the liver and distributed in the circulation, the hepatic cells being poisoned by arsenic. Early in the series of cases under review, insulin was used to enhance the therapeutic effect of glucose and it seemed to produce an early and striking improvement in the clinical condition of patients to whom it was administered. It was deduced, therefore, as a working hypothesis, that the liver should be the primary object of attention.

Accordingly treatment by intravenous sodium thiosulphate and sulphur by mouth were suspended and emphasis was put upon the three therapeutic agents, glucose, insulin and ascorbic acid.

Case 1.—Pte. T. Purpura hæmorrhagica toxica.

This man had been receiving anti-syphilitic treatment in the clinic regularly for seven months: he had not previously shown any signs of intolerance to arsenic.

31.12.41: Was given 0.6 g. sulphostab i/v.

4.1.42: Patient had been perfectly fit since receiving his injection and had returned to duty but suddenly developed profuse bleeding from the nose and gums. On the next day hæmaturia occurred in addition. He was put in a lorry and, after a journey of four days, arrived at this clinic on 8.1.42.

8.1.42: His condition was dreadful. He was extremely exsanguinated and here and there, over the whole surface of the body, were purple ecchymoses. He was bleeding profusely from the nose, mouth and kidney. The blood picture was: R.B.C. 2,080,000 per c.mm. Hb. unknown. W.B.C 11,450 per c.mm. Polymorphs 68.5 per cent, eosinophils 3.5 per cent, basophils 0.5 per cent, lymphocytes 23.0 per cent, monocytes 4.5 per cent.

The urine seemed to consist of pure blood and a cell count of the fresh unsedimented fluid read—R.B.C. 900,000 cells per c.mm.

It was impossible to carry out a blood platelet count. On auscultation of the heart the only abnormal sign discovered was a marked reduplication of the second pulmonary sound. The blood-pressure read as 130/80 mm. of mercury and the significance of this relatively high reading was not appreciated at the time. Subsequent events suggested that it may have been indicative of an incipient uræmia caused by blocking of the renal tubules by blood.

It is curious that, when palpated abdominally, the patient complained of no tenderness in the renal angles along the lines of the ureters or over the bladder—although discomfort in these areas developed some days later.

There were tiny petechial hæmorrhages on the surface of the eyeballs and subretinal hæmorrhages involving the macular regions of both eyes.

The immediate treatment was that for shock. In addition the patient was plied with glucose, fluids and ascorbic acid by mouth and given injections of horse serum and calcium gluconate.

9.1.42: He was much weaker and continued to lose a great deal of blood from the urinary tract and mouth. His temperature was 101° F. At 1100 hours he was transfused with $\frac{3}{4}$ pint of fresh citrated blood and one pint of glucose saline. He developed a rigor shortly afterwards and his temperature climbed still higher. Hæmorrhage seemed to have increased rather than diminished and his condition grew desperate.

10.1.42: The patient declared that he was feeling stronger but complained of pain in the renal angles and down the line of the ureters. The urine still contained great quantities of blood but without clots. Auscultation of the lungs showed no moist sounds of the bases. A small rectal washout was administered and shortly afterwards the patient vomited a copious quantity of blood but, since he was still bleeding profusely from the nose, this was possibly swallowed blood. Morphia was administered throughout the day but vomiting continued until 2200 hours. He had become too weak to raise his arms from the bed. Nevertheless, as a last

resort, he was given an intravenous drip saline with glucose late at night. He became delirious shortly afterwards.

11.1.42: The patient survived the night and it was a surprise to find that he had rallied somewhat. The amount of blood passed with the urine was much reduced but the gums and nose continued to bleed in spite of all efforts to arrest the hæmorrhage. He began, however, to take fluids by mouth and the vomiting became less severe.

Examination of the heart revealed a systolic murmur which could be heard all over the præcordia with a loud "click-clack" reduplicated second sound at the pulmonary area. The pulse-rate was 130 per minute and fever continued. There were no signs of right-sided cardiac failure.

Blood picture: R.B.C. 900,000 per c.mm. Hb. 15 per cent (Hæmoglobinometer unreliable). W.B.C. 15,000 per c.mm. Polymorphs 81 per cent, lymphocytes 18 per cent, monocytes 1 per cent.

Between 1500 and 1800 hours the patient was given $\frac{3}{4}$ pint of citrated blood and $\frac{1}{2}$ pint of glucose saline by slow intravenous drip. He seemed to improve in his general condition and the pulse became stronger at the wrist but the rate remained 130 per minute as before. The most heartening result of the transfusion was an increase in the urine output with noticeable decrease in the amount of blood contained. Bleeding from the nose had ceased completely. The patient slept well throughout the night and it was hoped that he had safely passed the crisis.

12.1.42: There was distinct colour in the lips and finger nails and the patient was cheerful. A curious feature was his drowsiness—he was continually falling asleep. The blood-pressure was now 90/40 mm. mercury and the R.B.C. count 1,562,000 cells per c.mm. Van den Bergh reaction was negative.

13.1.42: The temperature had fallen to 99.8° F., and the pulse-rate was 116 per minute. The blood urea was returned as 65 mgm. per cent. The patient received his third blood transfusion, $\frac{3}{4}$ pint of citrated blood being given by drip over a period of three hours. There resulted an unbelievable improvement in his condition. The temperature returned to normal.

14.1.42: Patient feeling very much better. The urine was only slightly blood-stained. By nightfall the pulse-rate had returned to 90 per minute.

17.1.42: Total R.B.C. 3,378,000 per c.mm. Hb. 55 per cent. W.B.C. 16,875 per c.mm. Polymorphs 58 per cent, lymphocytes 28 per cent, eosinophils 8 per cent, monocytes 6 per cent.

Convalescence was uneventful until 5.2.42, when the patient complained of dimness of vision. The visual acuity of the right eye was found to be 6/18 and that of the left 6/24. In the left eye a circular clot involved the entire macula and, in the right, the clot was half-moon shaped leaving the upper area of the macula intact. Both clots resolved during the course of the following seven weeks. In the case of the right eye the clot appeared to resolve into three smaller clots which eventually disappeared while, in the case of the left eye, the clot was vascularized before final resolution. The patient returned to duty.

Comment.—(1) A severe case of toxic purpura with massive hæmorrhage, saved by blood transfusion.

(2) The possibility that imminent renal failure and uræmia may have played a part in the pathology of the condition.

(3) The unusual complication of sub-retinal hæmorrhages occurring in the areas of the maculæ.

Case 2.—Flight-Lieutenant G., R.A.F. Severe jaundice following the second injection of arsenic.

This case is described because of its intimate relationship in symptomatology with Case 3 which follows.

The patient was admitted to hospital with a syphilitic chancre on 2.9.41. He was treated under best possible conditions, being confined to bed during the period of his first two injections. He was an apparently healthy young man. Glucose was given prior to each arsenical injection and weight and urine were watched.

6.9.41: Given neosalvarsan (Bayer) 0.3 g. i/v. Patient was not disturbed in the slightest degree by the injection.

9.9.41: Given 0.45 g. neosalvarsan and 0.2 g. bismostab. He exhibited no untoward symptoms and was discharged to out-patients on 10.9.41.

14.9.41: Patient was brought to hospital very ill. He had developed malaise three days after his last injection, followed by extreme nausea, rigors and vomiting.

On examination he displayed swelling of the eyelids and face; the fauces were congested and a white membrane covered both tonsils. The urine contained bile and already an icteric tinge could be made out on the sclera of the eye. On the chest there was a faint scarlatiniform rash. He complained of intense headache and was very restless. His temperature was high and of the remitting type. During the subsequent days jaundice developed but recovery was satisfactory and the patient was discharged from hospital some six weeks later. Initial treatment was on conventional lines and included five ounces of glucose daily but, later, insulin was given in addition to glucose and it was noticed that there followed a quite sudden improvement in the patient's general condition.

On going into his past medical history it was discovered that he had suffered a protracted attack of jaundice some six years previously at a time when he was engaged in work with high explosives.

Comment.—(1) The past attack of jaundice described by the patient may well have been due to subacute necrosis of the liver.

(2) An apparent improvement in the patient's condition when insulin was given in addition to glucose.

Case 3.—Pte. M. Sudden onset of œdema of the face and throat.

15.11.41: The patient was admitted to hospital with a primary syphilitic chancre of the lip. He was a healthy young man and there was no factor in his medical history to suggest that he would prove a bad subject for anti-syphilitic therapy.

Given 0.3 g. neosalvarsan i/v. After this injection the patient remained fit and well.

19.11.41: Given 0.45 g. neosalvarsan i/v. and bismostab 0.2 g. i/m. (The drug belonged to the same batch as that used in Case 2, Flight-Lieutenant G. It had been given to many other patients without noticeable toxic effects.) Within twelve hours of this last injection, Private M. began to develop symptoms and signs almost identical with those noticed in the case of Flight-Lieutenant G. The onset was characterized by intense headache followed by sore throat, rigors and fever.

22.11.41: Patient was extremely restless and ordinary sedatives were ineffective in producing sleep at night. His face was swollen and his eyelids were closed by œdema. The temperature was 103° F. In addition

to fluids and alkalis, the patient was given: Glucose—6 ounces during the course of the day; insulin—5 units t.i.d.; ascorbic acid tablets—(25 mgm.) three q.i.d.

24.11.41: Patient fit and well.

Comment.—An acute case of arsenical toxæmia which resolved rapidly under treatment with glucose, insulin and ascorbic acid.

Case 4.—Private W. Acute toxæmia occurring within two hours of an injection of arsenic.

This patient was an apparently healthy man. Examination of the urine and body weight were satisfactory prior to each injection.

24.12.41: Given 0.3 g. sulphostab i/v.

31.12.41: Given 0.3 g. sulphostab i/v.

4.1.42: Given 0.45 g. sulphostab i/v.

7.1.42: Given 0.3 g. sulphostab i/v.

This last injection was given personally by the Senior Medical Officer. Preparation of the solution and injection were alike carefully carried out and the dramatic results that followed were probably caused by the drug itself which proved to be one of the toxic batch.

Within two hours of the injection the patient was acutely ill and his temperature had reached 105° F. Vomiting was an outstanding clinical characteristic and the vomit contained both blood and bile. As a result of experience with previous cases, remedies in common use such as adrenaline and sodium thiosulphate were avoided but glucose and ascorbic acid were forced as far as vomiting would allow. Fever was controlled by tepid sponging. The blood-pressure was very low—95/?40 mm. mercury.

8.1.42: The patient was still very ill in the morning. Certain characteristic signs had developed overnight—signs dependent upon acute capillary toxæmia. There was marked congestion of the small vessels on the scleræ of the eyes and of the external acoustic meatus. There was likewise swelling of the eyelids and, to a less marked degree, of the face itself. Auscultation of the lungs revealed a mild degree of bronchitis. The retina and optic discs were normal. Over the chest, abdomen and back the skin was erythematous and a faint scarlatiniform mottling could be seen here and there. On this and succeeding days treatment was by: (1) Potassium bromide and belladonna; (2) glucose, 6 ounces; (3) insulin, 10 units m. et n.; (4) ascorbic acid, 15 tablets (each 25 mgm.), crushed in water; (5) fluids *ad lib*.

9.1.42: The patient's condition had improved very greatly. The temperature was now 99.6° F. and the pulse-rate 108 per minute. Treatment was continued much on the same line with ever decreasing doses of insulin until 14.1.42, when the pulse-rate finally stabilized and became normal in rate.

Comment.—(1) A severe toxæmia following with unusual suddenness upon a toxic dose of arsenic.

(2) The amelioration in the patient's condition which followed on treatment with insulin.

Case 5.—Sweeper P. S. Fatal case of serous apoplexy.

The patient was an apparently healthy individual and, as so often happens in such cases of hæmorrhagic encephalitis, the serious result of arsenical therapy was unpredictable.

10.11.41: Admitted to hospital with an indurated syphilitic chancre of the coronal sulcus. He had marked œdema of the prepuce, due to secondary infection of the sore, and balanitis. It was on this account that he was given a course of sulphonamide (30 g.) by mouth concurrently with his early arsenical injections.

13.11.41: Given neosalvarsan 0.3 g. i/v, bisiacol 1 c.c. i/m.

20.11.41: Given neosalvarsan 0.45 g. i/v, bisiacol 1 c.c. i/m.

27.11.41: Given neosalvarsan 0.60 g. i/v, bisiacol 1 c.c. i/m.

During the period of these injections, the patient appeared fit and well, there was no albuminuria and weight and appetite were maintained.

3.12.41: At 0500 hours he was found by the Medical Officer in epileptiform convulsions. The onset had been very sudden and without premonitory signs. He was frothing at the mouth, the pupils were widely dilated and he was incontinent of urine. By 1000 hours he was deeply unconscious and breathing stertorously. On examination of the fundi of the eyes the disc margins were found to be normal but the veins grossly congested. The pupils were non-reactive to light. All the limbs were spastic and twitching. Kernig's sign was not present but both plantar responses were extensor in type.

Blood picture: R.B.C. 5,375,000 per c.mm. Hb. 90 per cent. W.B.C. 20,625 per c.mm. Polymorphs 80 per cent, lymphocytes 15 per cent, monocytes 5 per cent. Lumbar puncture: Clear fluid under slightly increased pressure. Otherwise the cellular and chemical content of the C.S.F. was normal.

By 2100 hours the temperature had risen to 104° F. and the pulse-rate was 150 per minute. 2200 hours: Cheyne-Stokes respiration. 2300 hours: Pulse thready and uncountable; patient vomiting blood and mucus. Lumbar puncture was again performed to reduce the C.S.F. pressure but the patient died shortly afterwards.

An autopsy was performed by Captain Reynard Smith, I.M.S., and these excerpts are taken from his report.

"Circulatory System.—No evidence of disease was found in the myocardium, endocardium or pericardium, nor in the coronary arteries, aorta or larger vessels.

Cranium and its Contents.—The skull cap was of average thickness and broke normally. There were no adhesions between it and the dura mater nor were there any adhesions between this membrane and the underlying leptomeninges.

There was no excess of cerebrospinal fluid and the surface convolutions of the brain were not flattened nor was there any cerebellar pressure cone present.

The surface vessels of the brain were grossly congested. On sectioning the brain, numerous small punctate hæmorrhages were found; these were especially noticeable in the white matter.

Liver and Spleen.—Were normal in size and consistency. Some areas of the cut surface of the liver were paler in colour and more mottled than is usual.

Histological Report on Sections Removed at Autopsy.—Brain: This section does not demonstrate well the changes observed macroscopically. There is only dilatation of the vessels and some slight perivascular infiltration with lymphoid cells.

Liver: Distributed in a patchy manner through all the zones of the lobules is seen a granular and fatty degeneration of the hepatic cells with

coalescence, loss of discrete cell boundaries and, in some cases, loss of nuclei. There is a very marked round-cell infiltration of the biliary tracts and also a similar infiltration around the central veins of some of the lobules.

Hæmorrhage has occurred into many of the sinusoids which are seen filled with erythrocytes and hæmosiderin. Also, there is observed proliferation of the reticulo-endothelial cells of Kupffer.

In short, the outstanding features discovered post-mortem were the intense congestion of the blood-vessels on the surface of the brain, the widespread but minute petechial hæmorrhages in the brain substance itself and the histological picture of acute toxæmia in the liver."

Comment.—(1) The unpredictable nature of such a mishap occurring during the course of anti-syphilitic therapy.

(2) There may occur a latent period of days during which the patient shows no neurological abnormality until the onset of coma which may appear with catastrophic suddenness.

(3) The difficulty of arriving at a diagnosis, should there be no history of anti-syphilitic treatment, is increased by the lack of characteristic changes in the cerebrospinal fluid.

Arsenical Dermatitis.—There occurred in the clinic nine cases of dermatitis, all of which recovered. Four of these were of a mild type and four proceeded to complete exfoliation. One, which was initially severe, made an exceptionally rapid recovery; this last case is described in detail below as Case 6. It was the only one in the series of dermatitis cases in which insulin was used. With the exception of Case 6, the severe cases were treated on conventional lines with glucose, alkalis, ascorbic acid and sulphur orally and with injections of sodium thiosulphate. Contramine was given in some. It seemed that no great benefit accrued from the use of sodium thiosulphate. Toxic signs developed between the second and the sixth injection in the majority of cases and all occurred during the first unit courses.

A widely held view of the causation of arsenical dermatitis is that the skin becomes sensitized to the drug itself. One of the cases encountered lends support to this view. An Indian soldier, through a mishap in injection, received an infiltration of the tissues of the right arm. Subsequent injections had to be given in the left arm. But four weeks later, when he developed a papular dermatitis, the eruption made its first appearance on the back of the right arm and forearm. A mishap was anticipated in the case of another patient when, one month after recovery from exfoliative dermatitis, he was inadvertently given an injection of 0.45 g. novostab i/v. In this case, however, nothing untoward occurred, which tends to show that skin sensitization is not a factor in all cases of dermatitis. A further investigation two months later and the application of a solution of 3 per cent arsenic to his skin in the form of a "patch-test" produced a negative result.

Case 6.—Private H. H. Early arsenical dermatitis.

This case was unique in our series since it occurred at the end of a period of experience of many cases.

During this time many interesting examples of toxæmia had been insufficiently investigated and empirically treated. It had been decided that, if insulin were in reality of importance in the treatment of the later arsenical toxæmias, a severe case of early dermatitis would fully test its worth as a therapeutic agent; and this was such a case.

26.2.42: Patient admitted and after investigation was diagnosed as a case of sero-negative primary syphilis.

1.3.42: Given novostab 0.3 g. i/v.

4.3.42: Given novostab 0.3 g. i/v. He vomited following both these injections.

6.3.42: Patient fit and well, discharged to duty.

10.3.42: He was discovered in a medical ward. He had been taken ill suddenly on 8.3.42, two days after his second injection. On that day and the day following his temperature had reached 105° F.

When examined he was found to be covered with a morbilliform eruption; this rash was confluent here and there on the trunk but was absent on the face. The limbs showed the rash on both the flexor and extensor surfaces. The face was flushed and swollen. The capillaries on the surface of the eyeball and in the external ear were markedly congested as were the veins coursing over the retina.

A simple capillary resistance test was carried out on the left arm with a Baumanometer, the mercury being maintained at a level just above diastolic pressure. This produced a crop of petechiæ on the skin of the forearm within one and a half minutes. The blood-pressure was 115/70 mm. mercury. The blood urea was returned as 31.2 mgm. per cent and the urine contained albumin.

Treatment was initiated with fluids, glucose, ascorbic acid and alkalis and, since the case had been discovered late in the afternoon, the first injection of insulin (10 units) was not given until 1830 hours. A further 5 units was administered at 2330 hours.

11.3.42. The temperature had dropped to normal and the patient felt much improved. The morbilliform rash had become confluent over most of the body surface and on the left arm were scattered ecchymoses which had resulted from the test of the night before. Insulin was given thus: 1000 hours, 10 units; 1730 hours, 5 units. Glucose, six to seven ounces, was forced daily. The blood-pressure was 104/60 mm. mercury and the icteric index 10.

By 1800 hours the patient affirmed that he felt very much better and it appeared that the skin eruption was fading in colour.

12.3.42: In the morning he was afebrile and his pulse-rate was normal. The rash had vanished except for the petechiæ on the left forearm. One curious feature was his small urinary output. The intake of fluid had been large and the bladder seemed to be empty when percussed. The blood urea, however, remained at the reasonable figure of 30 mgm. per cent. The blood-pressure was 108/65 mm. mercury.

Insulin was given thus: 1130 hours, 5 units; 2200 hours, 5 units.

Fluid intake was 7 pints and output was 4 pints. This output began in the afternoon. In the morning the patient had passed only 6 c.c. urine; it was of a glue-like colour and was almost solid with glistening crystals which had the appearance of mica. Microscopic and biochemical examination failed to reveal their precise nature. The icteric index had fallen to 4.4 and the R.B.C. fragility test proved normal when tested against a control. The blood-picture was as follows: R.B.C. 5,140,000 per c.mm.

Hb. 80 per cent (Tallquist scale). W.B.C. 4,450 per c.mm. Polymorphs 55 per cent, eosinophils 2 per cent, lymphocytes 35 per cent, monocytes 8 per cent.

The patient showed a slight evening rise of temperature to 99.2° F. A rough test of capillary resistance, carried out as before, produced a few petechiæ only after a period of five minutes.

13.3.42: Patient was perfectly well and a capillary resistance test proved to be negative. A last dose of 10 units of insulin was administered before noon. The blood-pressure was 110/60 mm. mercury.

Convalescence was uneventful and the patient was discharged fit on 27.3.42.

This soldier was recalled to the clinic one month later for a "patch test." Within two hours of the application of arsenic to the skin of the arm, he experienced a burning sensation. The skin area was examined some twenty-four hours later and the patch removed. The area was swollen, hot and erythematous and covered with small papules and vesicles. The surrounding skin showed papules here and there. The patient said he felt slightly sick but his temperature and pulse remained normal during the period of seventy-two hours while he was under observation.

These cases are described merely because they are interesting in themselves and to emphasize that insulin may be used with great advantage in the treatment of the later toxæmias of arsenic. No reference has been made to other work on the subject because, in an isolated station such as this, there is no means of access to current medical literature.

Throughout these studies we were grateful for the guidance and co-operation of Major R. J. G. Morrison, R.A.M.C., and Captain W. R. Smith, I.M.S. Without their help this article would not have been written. And if the treatment of these cases was as successful as it is thought to have been, then the success was due to those who administered it—the R.A.M.C. orderlies of the unit.