

A PECULIAR NEUROLOGICAL SEQUEL
TO ADMINISTRATION OF 4 : 4'-DIAMI-
DINO-DIPHENYL-ETHYLENE (M.&B.
744)

By L. EVERARD NAPIER, F.R.C.P. (Lond.)

and

P. C. SEN GUPTA, M.B. (Cal.)

(From the School of Tropical Medicine, Calcutta)

4 : 4'-DIAMIDINO-DIPHENYL-ETHYLENE is one of the chemical compounds prepared by Dr. A. J. Ewins of Messrs. May and Baker that has been found very effective in the treatment of kala-azar by workers in different parts of the world. The drug was tried by Warrington Yorke (1940) on an Indian seaman suffering from kala-azar in Liverpool, by Napier and Sen (1940) in Calcutta, and by Kirk and Sati (1940) in the Sudan, in each instance with remarkable success. Other reports have followed and at present a report by the present writers and a colleague on the treatment of 98 cases of kala-azar is in preparation. Our total experience of the drug now amounts to over a hundred cases, as we have used it—with little success—in other forms of leishmaniasis.

Administration of this drug has not been absolutely free from unpleasant reactions; among these are a burning sensation all over the body, flushing of the face, transient difficulty in breathing, nausea, vomiting, epigastric distress, giddiness, palpitation, sweating and occasionally collapse.

The almost constant finding during and immediately after the first few injections of this drug has been a marked fall of blood pressure, both systolic and diastolic, the former to a greater extent than the latter. A drop of 20 to 40 mm. of mercury within a minute or two of the injection has been found in all cases showing the more severe symptoms, and the drop has been even greater in the patients who collapsed. The blood pressure rises to nearly the previous level in almost all cases within 5 to 10 minutes and with this rise most of the symptoms disappear. In the cases in which there are serious reactions, an injection of adrenaline raises the blood pressure almost immediately and the unpleasant symptoms subside. When in such cases an injection of adrenaline is given a few

minutes before a subsequent injection, little or no fall of blood pressure takes place and the symptoms may be entirely absent.

The symptoms, giddiness, faintness, palpitation, sweating, epigastric distress and collapse, can be readily explained in most cases by this fall of blood pressure that results from the injection. If we regard the drug as having a histamine-like effect, the sudden fall of blood pressure and the symptoms associated with it, the flushing of the face, the hot sensation, the occasional burning sensation in the different parts of the body, and the dyspnoea can all be explained. The fact that adrenaline relieves these symptoms, also supports this point of view.

During the period that we have used this drug, four of our patients, one Bengali, two Hungarians, and one Anglo-Indian, have developed a peculiar neurological symptom-complex subsequent to their treatment with this drug. Had the symptoms appeared in one patient only, we would probably have overlooked the possibility of any connexion with this drug, but the fact that four patients all showed very similar symptoms a few months after the administration of this drug, led us to carry out general neurological investigations in these cases, and to write this note.

Case 1.—Bengali business man, aged 34 years, was admitted on the 16th April, 1941. He said he had kala-azar in 1924 for which he was treated with organic antimonials intravenously. The patient came complaining of irregular attacks of fever for seven months and nodular eruptions over the face for 1½ years. On admission, the spleen was found to be enlarged down to 5½ inches below the costal margin, measured from the tip of the 9th rib, and the liver was enlarged 1½ inches below the costal margin. He had the nodular type of dermal leishmaniasis on his chin and nose. The aldehyde test was positive and the spleen puncture smear showed *Leishmania donovani*. Smears made from snippings from the dermal nodules also showed leishmania. The patient was treated with a course of 4 : 4'-diamidino-diphenyl-ethylene (M.&B. 744), 15 intravenous injections were given from 28th April to 12th May, 1941; the total dose was 1.535 grammes.

The patient was discharged from the hospital on 10th June, 1941, apparently cured of kala-azar. He was afebrile, the hæmoglobin had risen from 9.9 gm. per cent to 14.02 gm. per cent, the spleen was reducible under the costal margin, and he had put on 5 lb. in weight. The dermal lesions were unaffected and he was advised to attend the outpatient department for treatment of the dermal condition.

He was seen again in October 1941. He complained that since August 1941, he had been suffering from numbness and partial anaesthesia over his forehead, that exposure to the sun's rays for a time caused a burning sensation, that he had an intense sensation of cold when a slightly cold object came in contact with his forehead and cheek, and that shaving was quite painful (hyperaesthesia to temperature and touch). The trouble started as a sense of impairment of sensation over the upper lip, nose and forehead.

On examination.—He was found to be in good health, but the nodules of dermal leishmaniasis persisted unaltered on his chin and nose. The nose and the throat were apparently normal, the teeth and gums showed evidence of pyorrhoea, and there was tartar present. No abnormality was noticed in the heart or lungs. The liver was not palpable and the spleen was just palpable on deep inspiration.

(Continued from previous page)

5. The earlier in the disease the sulphapyridine treatment is started the quicker the response.

6. The period of hospitalization was 30 per cent less than that with the next most efficient form of treatment—i.e., serum.

7. It is relatively cheap: the most I spent on any one case was Rs. 3 as compared with Rs. 4 to Rs. 14 for serum treatment.

REFERENCES

- BRYANT, J., and FAIR- Trans. Roy. Soc. Trop. Med.
MAN, H. D. (1940). and Hyg., **34**, 117.
O'BRIEN, R. A. (1940). Ibid., **33**, 573.

There was no abnormality in the cranial nerves I, II, III, IV, VI, VII, VIII, IX, X, XI, XII, or in the motor part of V. There was a loss of sensation to light touch over the forehead, nose, and part of the cheek. Perception of deep pressure and pain were unimpaired. There was no tenderness of the branches of the Vth nerve on pressure. The motor functions were normal and there was no disturbance of sensory functions elsewhere. The visceral reflexes were unimpaired and there was no vasomotor disturbance or trophic change. Superficial and deep reflexes were equal and normal on both sides.

There are two other points of special interest in this case, namely, that it is one of the very few apparently authentic cases of re-infection, and that it is an instance, equally rare, of the co-existence of a visceral and a dermal infection with *Leishmania donovani*.

In a not inconsiderable experience, the senior writer has only encountered one other case in which there was any real evidence of a re-infection occurring—a child who had been treated a year previously in his own wards as a very early case of kala-azar, diagnosed by cultural

Subsequent to his discharge from the hospital he attended the outpatients' department on several occasions and the splenic enlargement steadily decreased and the general health improved.

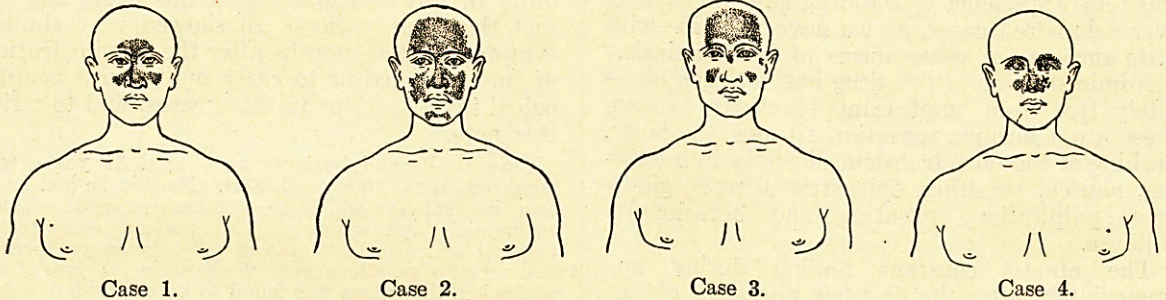
In May 1941, the patient experienced a sense of heaviness over the forehead and face, and this part seemed to be somewhat reddish in colour. Three weeks later he developed loss of sensation over this area. He was investigated at a general hospital and two of his teeth were removed; no abnormality was detected in his nose or sinuses. He had various treatments for this condition without benefit.

He was seen again in November 1941. He was complaining of a sense of heaviness over his forehead, face, eyelids and nose. His upper lip felt 'swollen'.

He could not keep his eyes shut tightly, there was a blinking movement of the eyelids, and occasionally a spontaneous twitching of some of his face muscles drawing up the angles of the mouth. He also complained of an erythematous rash developing over the chin and the tip of the nose.

He looked quite healthy. There was an erythema over the tip of the nose and the chin (the question of very early dermal leishmaniasis arose).

On examination.—No abnormality was detected in his nose and nasal sinuses, the remaining teeth were apparently healthy. The heart and lungs were quite normal. Neither spleen nor liver was palpable. There was no



Case 1. Case 2. Case 3. Case 4.
Anæsthesia to light touch with preservation of sensation to pain, temperature and pressure is shown by the stippled area.

An area of complete anæsthesia (case 4) is marked by a cross.

methods. In this case relapse was excluded by the clinical history and the serological tests. He has had many cases in which there was a history of treatment for kala-azar some years before, but the authenticity of the first diagnosis has always been in doubt.

Only one or two cases of the co-existence of a visceral and a dermal infection have been reported (these also must necessarily have been cases of re-infection or relapse of kala-azar).

Case 2.—A Hungarian business man, aged 40 years, was admitted on the 10th January, 1941, for repeated attacks of fever since May 1940. He was diagnosed as and treated for kala-azar in another hospital, where he had a full course of injections but without benefit. He was apparently a 'resistant case' of kala-azar. The spleen was enlarged down to 8 inches below the costal margin. The diagnosis was confirmed by a strongly positive aldehyde test and by the finding of numerous *Leishmania donovani* in the spleen puncture smear. The patient was treated with a course of M.&B. 744. Fifteen intravenous injections were given from the 13th January to 27th January; the initial dose was 0.03 gm., the maximum dose 0.18 gm. and the total dose 1.66 gm. No untoward reactions were noticed during the course of treatment. The patient left hospital on the 28th January; he was afebrile, the spleen was softer and now measured 6½ inches below the costal margin and the hæmoglobin had risen from 7.975 gm. per cent to 9.762 gm. per cent.

disturbance of function of the cranial nerves, I, II, III, IV, VI, VII (except for inability to keep the eyes shut tightly, the blinking movements, and twitching of some face muscles), VIII, IX, X, XI, XII, and motor part of the Vth cranial nerve. There was loss of sensation to light touch over the forehead, nose, upper eyelids, cheek, and part of the chin. There was perception of deep touch and pain as tested by a pin-point. There was no tenderness of any of the branches of the trigeminal nerve. Motor functions were normal all over and there was no impairment of sensation in any other part of the body. Superficial and deep reflexes were quite normal on both sides and there was no impairment of visceral reflexes or disturbance of the vasomotor system.

The neurological condition has shown little or no change in eight months since it was first noticed by the patient.

Case 3.—An Anglo-Indian engineer, aged 26 years, was admitted on the 9th January, 1941, for fever for two months. He had been a patient in the hospital in August 1940, suffering from kala-azar and had been treated with a course of injections of neostibosan. After discharge from the hospital he remained afebrile for a month or so and then the present attack of fever commenced. At first, the attacks came on at irregular intervals, but at about the time of admission to the hospital it came on daily with chill and rigor. On examination, he was found to have an enlargement of the spleen 6 inches below the costal margin. No other abnormality was detected. The diagnosis of 'resistant' kala-azar was confirmed by demonstration of numerous *Leishmania donovani* in a sternal puncture smear.

He was given a course of 15 injections of M.&B. 744, intravenously, from the 9th January, 1941. The total dose was 1.36 gm. He was discharged from the hospital on 3rd February, 1941, apparently doing well: he was afebrile, the spleen had gone down considerably (2½ inches below the costal margin), and the hæmoglobin had risen from 6.325 gm. per cent to 8.662 gm. per cent.

In May 1941, the patient experienced a sensation like cramp in his upper lip. After about 3 weeks this symptom disappeared. Soon after, he felt a numbness first over the eyebrows, then it spread to the forehead and part of the face. Occasionally, he felt as if there was ice-cold water running down his neck. Since June 1941, he has often felt 'as if there were some worms running down the skin of his forehead' (formication) and this gave rise to itching, and was very disturbing. He had all his teeth extracted, and the nasal sinuses were attended to by a specialist.

He had injections of vitamin B₁ and some other treatments to no effect.

On examination.—The patient was apparently quite healthy. There was no detectable abnormality in his nose or throat. He had a complete set of false teeth. There was no abnormality in the heart or the lungs. Neither liver nor spleen was palpable. There was no disturbance of function of the cranial nerves, I, II, III, IV, VI, VII, VIII, IX, X, XI, and XII, or of the motor part of the Vth nerve. There was a loss of sensation to light touch over the forehead and anterior one-third of the head (a light touch to the hair over this was not felt), root of the nose, part of the cheek and right upper eyelid. There was some impairment of sensation to heat but not to cold over the forehead. The sensation of pain and deep touch were unimpaired. There was no tenderness of any of the branches of the Vth nerve. Motor functions were normal all over the body and there was no impairment of sensory functions over other parts of the body. Superficial and deep reflexes were equal and normal on both sides and there was no impairment of visceral reflexes or of the vasomotor system.

There has been little change in the symptoms during the last six months.

Case 4.—A Hungarian student, aged 15 years, was admitted on the 11th August, 1941, for intermittent fever for one month. On admission, the patient had an enlargement of the spleen 5½ inches below the tip of the 9th costal cartilage and the liver was palpable on inspiration. There was no other obvious abnormality. On investigation the aldehyde test was positive, and *Leishmania donovani* were found in the sternal puncture smear. The patient was treated with a course of 10 injections of M.&B. 744, from 12th to 21st August. The total dose was 0.96 gm. and the maximum single dose was 0.12 gm. The temperature came down to normal during the course of the injections. The patient was given a course of crinodora (atebrin-like compound), 1 tablet *t.d.s.* for five days, for giardia infection, and was discharged on 1st September, 1941. The spleen was greatly reduced, being just palpable on inspiration, at the time he left hospital.

He was seen again on 27th December, 1941. He complained of impairment of sensation and a sense of numbness over his face, a symptom he noticed whilst washing his face about a month before. He also complained of anaesthesia over his nose for about 3 or 4 weeks.

On examination the patient was found to be otherwise healthy. The throat was slightly congested, the tonsils had been removed two years previously and there was one 'filled' tooth, the rest being healthy. He had an attack of common cold, and the nasal mucous membrane looked congested. The heart and the lungs were quite normal. The liver and the spleen were not palpable. The left palpebral fissure was slightly wider than the right, but this condition had been present since childhood.

Neurological examination failed to reveal any abnormality in the cranial nerves I, II, III, IV, VI, VII, VIII, IX, X, XI, XII, and the motor part of V. There was anaesthesia to light touch over the areas indicated in case 4, with preservation of sensation of pain, pressure and temperature. In one small area (marked x) there was complete anaesthesia. There was some impairment of sensation over the scalp corresponding to the distribution of the ophthalmic division of the trigeminal nerve. He could feel similar light touch better over other areas of the scalp than over this part. There was no marked tenderness of the main branches of the trigeminal nerve on pressure. The motor function was unimpaired and the superficial and deep reflexes equal and normal on the two sides. The sensory function, visceral reflexes and vasomotor system were quite normal.

Discussion.—The salient features of the above four cases are: (1) Subjective disturbance of sensation over various parts of the trigeminal area, paræsthesia, anaesthesia, formication, and hyperæsthesia. (2) Loss of sensation of light touch over this area, with the preservation of sense of pressure and pain (dissociated anaesthesia). (3) No evidence of other neurological or any systemic disorder.

The fact that there is evidence of loss of function of the sensory part of the nerve rules out the possibility of trigeminal neuralgia. The affected areas do not coincide with the whole of the distribution of any of the branches of the 5th nerve and the dissociated anaesthesia and lack of trophic changes preclude the lesion being of the nature of peripheral neuritis.

Syringobulbia and thrombosis of the posterior inferior cerebellar artery give rise to lesions involving the medulla and the upper cervical segments of the spinal cord, and these by injuring the spinal tract and its nucleus will cause analgesia and thermo-anaesthesia, with preservation of sensibility to light touch. But in our cases, the conditions were exactly the opposite.

The following quotation from Russell Brain (1933) would appear relevant: 'Owing to the divergence of the sensory fibres of the trigeminal nerve within the brain stem, dissociation of sensibility over the face commonly results from central lesions. A lesion of the pons which involves the principal sensory nucleus will cause anaesthesia to light touch over the trigeminal distribution, with preservation of appreciation of pain, heat and cold'.

It would thus appear that the site of the lesion in these cases is in the pons, affecting the chief sensory nucleus. It is not possible to be dogmatic as to the nature of this lesion; it is possibly a toxic degenerative condition.

The slight weakness of the orbicularis oculi and occasional twitching of face muscles in case 2 are possibly due to irritation of the nucleus of the VIIth nerve which is situated in the pons.

The next question that arises is whether diamidino-diphenyl-ethylene can be regarded as the cause of this lesion. In this connexion, we must emphasize that there has been a complete absence of similar symptoms following any other

form of treatment for kala-azar, or in untreated cases of kala-azar, in the senior writer's experience of the disease in India.

The symptoms appeared a short period (3 to 4 months) after the cessation of treatment with this drug, in no case could any other cause be found, and the syndrome is entirely unlike any of the recognized diseases of the nervous system; the drug is, therefore, undoubtedly incriminated as the toxic agent causing this neuropathy.

This appears to be a particularly good example of the selective action of a drug on one particular part of the central nervous system. There are other examples of this selective action, e.g., wrist drop in lead poisoning, though in this case the action is less specific. Trichlorethylene inhalation in industry is reported to produce bi-lateral loss of sensation confined to the distribution of the trigeminal nerve, a condition which is suggestively similar to the one we are describing.

The facts that the symptoms were noticed by the more intelligent patients and that these four cases constitute a considerable proportion of the patients we have examined subsequent to the course of treatment by this drug, suggest that this neuropathy may have been more frequent than this report on only four cases would appear to indicate, and careful enquiries should be undertaken to ascertain whether similar symptoms have occurred in patients treated in other parts of the world.

On the other hand, three out of four were 'resistant' cases and therefore a larger total dose was given than would be given to a previously untreated patient.

Prognosis.—Two of these four patients (cases 2 and 3) were under observation for some months and the condition did not seem to progress during this time. On the other hand, some of the patients suggested that the area involved was greater when they first noticed the condition than at the time of examination. We are probably justified in inferring that the condition is not progressive and that there is a tendency to spontaneous cure.

Summary

1. Four cases of kala-azar, treated with 4:4'-diamidino-diphenyl-ethylene, developed anaesthesia to light touch over the trigeminal area with preservation of sensation of pain, temperature and pressure.

2. The lesion is apparently in the pons, involving the principal sensory nucleus of the trigeminal nerve, and is possibly a toxic degenerative condition.

3. 4:4'-diamidino-diphenyl-ethylene is probably the toxic factor responsible.

4. The lesion is not progressive and its symptoms do not cause much physical discomfort. It would appear that the condition

(Concluded at foot of next column)

USES OF TESTOSTERONE PROPIONATE : A REVIEW TOGETHER WITH SHORT REPORTS ON ITS USE IN SENILE PRURITUS AND SENILE ARTHRITIS IN MALES

By M. L. GUJRAL, M.B., M.R.C.P. (Lond.)

1, Curzon Road, New Delhi

TESTOSTERONE PROPIONATE, the synthetic male sex hormone, is a potent therapeutic agent in the treatment of certain male and female disorders. It was first isolated from bulls' testes and later synthetically from cholesterol. It has been used clinically with marked success by many workers. In spite, however, of the fact that much has been written about it in recent years, the literature on male sex hormone as applied to various clinical conditions is still far from complete. Thus far, no clear-cut understanding as to the indications for therapeutic use of the hormone has been established. What is more important, the dangers of its indiscriminate use are apparently not realized by those who use it.

The following indications for the use of testosterone propionate are briefly considered :—

A. In males

1. Eunuchism, Eunuchoidism, Hypogonadism.
2. Cryptorchidism.
3. Male climacteric.
4. Premature senility.
5. Senile pruritus in males.

(Continued from previous column)

improves with time, as is the case in many other toxic affections.

5. One of the cases reported was incidentally a rare instance of the co-existence of dermal and visceral lesions of leishmania infection.

REFERENCES

- BRAIN, W. R. (1933) .. *Diseases of the Nervous System*. Oxford University Press, London.
- KIRK, R., and SATI, M. *Ann. Trop. Med. and Parasit.*, **H.** (1940). **34**, 83, 181.
- NAPIER, L. E., and SEN, *Indian Med. Gaz.*, **75**, 720. G. N. (1940).
- YORKE, W. (1940) .. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **33**, 463.

Postscript.—We have since seen three more patients, two Bengalee males and one Anglo-Indian female, who have developed similar dissociated anaesthesia over the trigeminal area. In the Anglo-Indian female patient there was dissociated anaesthesia also over both sides of the neck corresponding to areas supplied by the cutaneous branches of the posterior roots of the third cervical nerves of the spinal cord. It is probable that in this case the lesion had spread to some fibres of the lemniscus which are situated close to the sensory nucleus of the trigeminal nerve in the pons.

The observation of these further cases adds weight to our suggestion that this sequel to the use of diamidino-stilbene may be much more common than we first believed.