LIVER DAMAGE DURING TREATMENT WITH DIAMINODIPHENYLSULPHONE

J. BARNES AND E. J. BARNES

We think the case described below might be of interest as it shows that fatal subacute necrosis of the liver may occur on a diaminodiphenylsulphone dosage of 200 mgm. a day after a total of only 7.8 gms. has been administered.

Njenbo, a woman of about 30, was admitted to Obudu Leprosy Segregation Village on 16.10.50 with mild maculo-anaesthetic leprosy consisting only of small flat depigmented macules, one on the abdomen, forehead, right thigh and arm. There was peripheral anaesthesia of the feet. Her general condition was very good.

Treatment was started with chaulmoogra oil, 3 cc. rising to 5 cc. intradermally twice weekly, and diaminodiphenylsulphone starting at 100 m.m. for six days, rising to 200 mgm. daily for 6 days a week thereafter. She was quite well until Wednesday, December 6th, when she was seen complaining of swelling of the feet and ankles, and irritation of the skin. The sclerae were noticeably jaundiced, but she did not complain of this. On questioning she said that she had been ill for three days. The first day of the illness was marked by malaise, headache, pain in the neck and generalised vague pains. On the second day swelling of the feet was noticed, and an irritating rash appeared on the thighs, abdomen and forearms. The jaundice was last to appear, not being accompanied by nausea, anorexia, vomiting and subcostal pain.

On examination the patient looked ill and lethargic, and was markedly jaundiced. She had a low fever of 99.4 degrees, respiration and pulse were normal. A micropapular eruption (reminiscent of morbilli in the dark skinned African) was present on abdomen, thighs and forearms, and was mildly irritating. No koplick spots or enlarged lymph glands were found. The tongue was clean and normal. No abnormality of respiratory or cardiovascular systems was found; pitting oedema of feet and ankles was marked. Abdominal examination revealed the uterus enlarged with a four-month pregnancy. There was no pain or tenderness, but the liver was smooth and not hard.

The urine was a dark brown, small in amount and rather viscuous; it was obviously loaded with bile, although no reagents were obtainable to check the presence of bile salts. There was a faint trace of albumen. The faeces were of normal colour and consistency throughout the illness.

She was transferred to Ogoja, where she was treated with rest, salt free boiled yam and just sufficient water by mouth to prevent thirst—about 2 pints a day. Mag.Sulph. was given and Phenergan 25 mgm. bid. Her condition remained stationary for a week, neither the jaundice nor the odoema subsiding. The rash gradually subsided but remained for a while confined to a macule on the abdomen. She did not appear so lethargic as when first seen, ate with relish her salt-free boiled yam, and had no complaints at all except that the swelling was not subsiding.

For the last five days of her life her condition gradually declined, the oedema becoming more marked and spreading to the hands and face. The liver was noted to be only just palpable. Two days before her death she suddenly became much worse, sleeping heavily, not answering questions, and finally refusing food. There was a brisk diuresis following the intramuscular injection of a mercurial diuretic, but her mental deterioration continued and she died in coma on the 16th day of her illness.

A post mortem Caesarian Section was performed immediately, but the foetus was dead. The liquor amii was heavily bile stained, but the foetus was not jaundiced. Necropsy was carried out immediately. The body was that of a well built young woman, with oedema of the extremities and right side. All the organs, except the liver, appeared normal, although heavily bile stained. The liver was small, lying high up under the diaphragm, and weighing 23 oz. There were no adhesions, the gall bladder was flacid and contained a little blackish bile. All the ducts were patent, there being no signs of stones, inflammation or any other obstruction. The pancreas was normal. There were three lymph glands about the size of hazel or almond nuts in the porta hepatis. The liver was smooth, pale and flabby, with no irregularity. On cross section it was pale and bile stained, the lobular pattern being ill defined. The kidneys too were pale and bile stained, but no other abnormality was noted.

Our diagnosis before death was acute yellow atrophy of the liver, probably due to diaminodiphenylsulphone. The illness in no way resembled infectious hepatitis or yellow fever, and on post mortem we found no signs of obstruction to the billiary tract. A

piece of liver, kidney, and lymph from the porta hepatis were sent to Dr. Winston, who kindly made his report on the histology. "The lymph node and kidney sections from this patient may be disposed of quickly. The former shows an inflammatory reaction, and the latter no abnormalities which cannot be assigned to post mortem changes. The liver shows extensive necrosis which varies in extent in different parts of a section. Where it is least it is in the central and midzonal parts of a lobule. There is some fatty degeneration, but it is not extensive. At the periphery of many lobules, bile duct proliferation is very marked and there is a round-cell infiltration of the portal tracts. There is very little fibrous tissue. The liver therefore, shows much evidence of a severe necrosis, but attempts at regeneration are marked. Hence the histological evidence favours a diagnosis of subacute rather than acute necrosis of the liver. There is no evidence that this is yellow fever."

DISCUSSION.

Of 153 cases treated with diaminodiphenylsulphone from 2 to 6 months, 5 other cases of hepatitis were seen, all with exfoliative dermatitis.* The worst case was heavily jaundiced, and the liver was not palpable, suggesting a subacute necrotic condition; the other 4 cases had enlarged and tender livers. All cases were on the same dosage, being strong adults, and although the full dose of 200 mgm. was reached at the end of a fortnight, no toxic manifestations have been noted until about the 6th week; we had in fact come to look on that as the "danger period."

Tropical sub-clinical cirrhosis of the liver due to malnutrition, and recurrent malaria does not appear to be more common here than elsewhere in Eastern Nigeria, but probably renders the liver more susceptible to damage by a toxic agent.

In addition to these cases of liver damage, we have seen all the other toxic manifestations mentioned in the literature; dermatitis, anaemia, erythema nodosum and lepra reactions. We have come to the conclusion that a dose of 200 mgm. daily is too toxic for general use, and are now waiting to see whether lower doses varying from 50 to 130 mgm. daily will be effective and non-toxic.

(* Barnes reports (**Lancet**, Sept. 29, 1951—Correspondence) that the sulphone syndrome was seen in 7 out of the 153 cases treated with DADPS, and 1 out of the 657 treated by parenteral sulphetrone.—Ed.)