1969 was 151 cm tall, weighed 35 kg, and the epiphyses at the knee were just beginning to close. Growth hormone response to insulin-induced hypoglycaemia became normal, growth hormone levels fasting and at 30-minute intervals after the administration of insulin 0.1 unit/kg being 1.4, 9.7, 50, 21, and 18.8 ng/ml. The corresponding blood sugars were 80, 30, 44, 53, and 58 mg/100 ml. The asthma was well controlled on disodium cromoglycate, though there was still evidence of airways obstruction ($FEV_1/FVC=0.75/1.4$).

Comment

This patient developed undoubted clinical hypothyroidism as a result of the long-continued administration of Felsol Powders. Possible explanations for the inappropriately normal level of serum protein-bound iodine and high radioactive iodine uptake were discussed by Begg and Hall (1963). The increase in iodine uptake strongly suggests that the patient's thyrotrophin response was normal.

Five months after discontinuing Felsol he was euthyroid but had a low gonadotrophin output and probable impairment of ACTH response. Lessof *et al.* (1969) reported a deficiency of ACTH output in some hypothyroid patients which usually improved with correction of the hypothyroidism. This patient's growth of 23 cm between the ages of 24 and 28, after the correction of hypothyroidism, accompanied by recovery of

the growth hormone response to hypoglycaemia, suggests that the dwarfism might have been mediated at least partly through growth hormone deficiency. Deficiency of thyroxine alone, however, lessens linear growth, growth hormone output being normal in some cases of juvenile hypothyroidism with dwarfism (Root *et al.*, 1967).

This case illustrates the difficulty of diagnosing primary hypopituitarism in the presence of hypothyroidism. The presence of circulating autoantibodies to thyroid is often useful in identifying patients with primary thyroid disease (Vallotton *et al.*, 1967), but they were not present in this case.

References

- Begg, T. B., and Hall, R. (1963). *Quarterly Journal of Medicine*, 128, 351.
 Greulich, W. W., and Pyle, S. I. (1959). *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, 2nd edn. Stanford, California, Stanford University Press.
 Harrison, M. R., Fierro-Benitez, R., Ramirez, I., Refetoff, S., and Stanbury, J. B. (1968). *Lancet*, 1, 936.
 Hartog, M., Gaafar, M. A., and Fraser, R. (1964). *Lancet*, 2, 376.
 Lessof, M. H., Lyne, C., Maisey, M. B., and Sturge, R. A. (1969). *Lancet*, 1, 642.
 Root, A. W., Rosenfield, R. L., Bangiovonni, A. M., and Everlein, W. R. (1967). *Pediatrics*, 39, 844.
 Utiger, R. D., Parker, M. L., and Daughaday, W. H. (1962). *Journal of Clinical Investigation*, 41, 254.
 Vallotton, M. B., Pretell, J. Y., and Forbes, A. P. (1967). *Journal of Endocrinology and Metabolism*, 27, 1.

Hepatotoxicity After Treatment of Schistosomiasis with Hycanthone

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A new drug, hycanthone methanesulphonate, has recently been introduced for the treatment of urinary and intestinal schistosomiasis. It is usually given as a single intramuscular injection at a dose of 3 mg/kg body weight (Clarke *et al.*, 1969). A transient rise in serum transaminase levels (SGOT and SGPT) has been observed after treatment with hycanthone and a case of jaundice has been reported (Cook and Jordan, 1971).

We report here a pronounced rise in bromsulphalein (BSP) retention and serum transaminase levels after hycanthone therapy in two young boys (in a series of eight patients) treated for *Schistosoma haematobium* infestation. In one of

the patients liver biopsies before and after treatment confirmed the development of acute hepatic cell necrosis.

Case 1

A 14-year-old boy was admitted to hospital complaining of dysuria and terminal haematuria of two years' duration. His general physical condition was excellent (weight 34 kg). The liver and spleen were not palpable.

Haemoglobin was 12.1 g/100 ml. Urine contained live eggs of *S. haematobium*, mean daily urinary egg excretion 46,000 (Bell, 1963). Repeated stool examinations were negative for *S. mansoni* eggs. Kidney function tests including phenosulphonphthalein excretion, creatinine clearance, blood urea nitrogen, and intravenous pyelography were normal. Pretreatment liver function tests showed no abnormality (see Table).

Two weeks after admission he was given a single intramuscular injection of hycanthone at a dose of 3 mg/kg (102 mg). One hour later he complained of severe headache and nausea and began vomiting. The vomiting was severe and repeated. Three days after the injection the serum transaminase levels had risen to the upper limits of normal. Because he continued to feel poorly and complain of anorexia and nausea the liver function tests were repeated seven days later. BSP dye retention had risen to 20%, SGOT to 325 units, and SGPT to 455 units. It took three weeks for the BSP and transaminase levels to return to normal. At that time he had recovered his appetite and felt much better.

Two months after treatment he again complained of dysuria and terminal haematuria. A mean urine egg count performed three months after the injection showed an egg reduction of only 60%. The hatching test was positive. He refused any additional treatment.

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Liver Function Tests

	Total Bilirubin (mg/100 ml)	BSP Retention (%) at 45 min (5 mg/kg)	SGOT (Sigma-Frankel Units)	SGPT (Sigma-Frankel Units)	Alkaline Phosphatase (Sigma Units)	Thymol Turbidity (Units)
Case 1:						
Before hycanthone	0.3	4	31	29	6.7	2.8
Three days after injection	40		40	35		
Ten days after injection	0.3	20	325	455	6.8	3.5
Case 2:						
Before hycanthone	0.3	5	26	28	5	1.6
Second day after injection	1.6	58	2,150	1,840	5.8	2.8

Case 2

A 14-year-old boy was admitted to hospital complaining of severe dysuria, frequency, and terminal haematuria of three years' duration. His general condition was good (weight 31 kg). The liver and spleen were not palpable.

Haemoglobin was 14.8 g/100 ml. Urine contained live eggs of *S. haematobium*, mean daily urinary egg excretion 57,000. Stools were negative for *S. mansoni* eggs. Kidney functions including phenolsulphonphthalein excretion, creatinine clearance, blood urea nitrogen, and intravenous pyelography were normal. Liver function tests showed no abnormality (see Table). Needle biopsy of the liver disclosed normal lobular architecture, some schistosome pigment in Kupffer cells and portal areas, and moderate infiltration of some portal areas by lymphocytes. Parenchymal cells were normal (Fig. 1).

One week after obtaining the liver biopsy specimen the patient was given a single intramuscular injection of hycanthone at a dose of 3 mg/kg (93 mg). A few hours later he started vomiting and during the next 48 hours vomited 13 times. Results of liver function tests performed 24 hours after the injection were severely abnormal. Serum bilirubin had risen to 1.6 mg/100 ml, BSP retention to 58%, SGOT to 2,150 units, and SGPT to 1,840 units. During the next few days he continued to complain of nausea and ate little. Six days after the injection a repeat liver biopsy showed slightly disturbed lobular architecture, the same irregular portal lymphocytic infiltrates, and pronounced parenchymal cell changes consisting of small and medium-sized droplet fatty metamorphosis and occasional acidophilic degeneration (Fig. 2). These degenerative changes were principally midzonal. There were also prominent regenerative changes consisting of anisocytosis, anisonucleosis, and amitotic and mitotic division. Three weeks after the injection results of liver function tests had returned to normal and a third liver biopsy showed some residual fatty metamorphosis, rare acidophile bodies, and moderate regenerative changes. By now the boy had recovered his appetite and appeared well. Four weeks after the injection he had stopped excreting eggs of *S. haematobium* in the urine.

Comment

Non-specific changes in serum transaminase levels have been described after the use of many drugs (Sherlock, 1968). They have occurred after treatment of schistosomiasis with niridazole (Kanani *et al.*, 1970) as well as after hycanthone (Cook and Jordan, 1971). But because there have been few reports describing the histological appearance of the liver during these serum enzyme changes clinicians have tended to ignore their significance.

In the present cases the clinical picture and pronounced biochemical changes after the injection of hycanthone resembled those of acute hepatitis, and serial liver biopsy specimens obtained from one of the patients confirmed acute hepatocellular injury. The histological pattern is *not* consistent with viral hepatitis or hypersensitivity to a drug and appears to be an acute toxic hepatitis.

Until further experience is gained with the use of this drug we recommend caution in its use in mass therapy of schistosomiasis.

FIG. 1—Pretreatment biopsy specimen. Parenchymal cells show no degenerative or regenerative changes. (Haematoxylin and eosin. $\times 935$.)

FIG. 2.—Six days after treatment: parenchymal cells have numerous small and medium-sized fat droplets. Note the acidophilic degenerated cell (arrowed). ($\times 935$.)

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References

- Bell, D. R. (1963). *Bulletin of the World Health Organization*, 29, 525.
- Clarke, V. De V., Blair, D. M., and Weber, M. C. (1969). *Central African Journal of Medicine*, 15, 1.
- Cook, J. A., and Jordan, P. (1971). *American Journal of Tropical Medicine and Hygiene*, 20, 84.
- Kanani, S. R., Knight, R., and Woodruff, A. W. (1970). *Journal of Tropical Medicine and Hygiene*, 73, 162.
- Sherlock, S. (1968). *British Medical Journal*, 1, 227.