THE INDICATIONS FOR GLOBIN INSULIN

BY

DAVID W. PUGH, D.S.C., M.D., M.R.C.P.*Physician, Bath Clinical Area; Late Senior Registrar,
the London Hospital*

When globin insulin was introduced over six years ago it was hoped that a single daily injection of this type of insulin would control most diabetics. Mosenthal (1944) reported on a series of 50 ambulant diabetics treated with globin insulin (G.I.) and showed that as a rule G.I. produces a fall in blood sugar within two hours of injection. This effect is intermediate between that of soluble insulin (S.I.) and zinc protamine insulin (Z.P.I.). The action lasts for 12 to 16 hours and sometimes 24 hours, depending on the size of dose and other factors.

Eaton (1944) reported on a series of 41 diabetics treated with G.I. who had failed to do well on other types of insulin. He showed that a combination of Z.P.I. and S.I. produces a lower fasting blood sugar than G.I., but that in suitable cases G.I. gave results more nearly physiological than did any other single type of insulin, and that its action closely resembled that of mixed doses of Z.P.I. and S.I. containing over 50% of the latter.

These favourable reports encouraged other clinicians to use G.I. Wauchope (1948) reported enthusiastically on a series of 366 diabetics treated with G.I. as out-patients thus: "All types of patient do as well on a single dose of globin insulin each day as on other kinds of insulin, singly or in combination." This has not been quite the experience at the diabetic clinics of the London Hospital, and I was prompted, therefore, to review the records of diabetic patients who had been treated with G.I. since its introduction in 1943. In that year a large number of patients attending the London Hospital were changed from a twice-daily dose of S.I., or a single combined dose of S.I. and Z.P.I., to a single daily dose of G.I. This dose was usually two-thirds of the previous total dose of other insulins. In addition, a small number of new diabetics were treated with G.I. from the start. Out of a total of approximately 1,800 diabetics treated between 1943 and 1948, 360 were given G.I. In 55 of these, control of the diabetes proved unsatisfactory, so that a change to some other kind of insulin had to be made.

It is of interest to note at this point that during the same period over 750 patients were being maintained satisfactorily on a twice-daily dose of S.I. or a combined daily dose of Z.P.I. and S.I.

The methods of control were those in general use at diabetic clinics. Some patients attended weekly or fortnightly, others at monthly or three-monthly intervals. The urine examined was the early morning specimen, unless otherwise stated, using Benedict's reagent. Control was mainly by the result of urine examination, blood sugars being estimated in difficult cases. The diet employed during the period was the calorie-control type of Crooke and Scott (1943); usually of 2,000 calorie value, but higher in adolescent subjects and lower in the overweight and more elderly.

Of the 305 cases successfully treated by G.I. the majority were elderly patients with diabetes of no more than moderate severity. Only 36 (12%) were under 40 years of age, and 79% received a single daily dose of G.I. of less than 40 units. Thus the cases successfully treated by G.I. were usually not severe and they belonged to the older age groups. Such cases are usually easy to control on any regime.

Of the 55 cases who failed on G.I., 22 were males and 33 females. The majority were young (18 were below the age of 40—i.e., 35%). The 55 cases were made up of (a) 17 new diabetics who began treatment on G.I.; and (b) 38 old diabetics who had previously been treated with either twice-daily S.I. or a once-daily injection of Z.P.I. and S.I. Of this latter group all except one were receiving more than 30 units of insulin per day.

The patient who is poorly controlled on G.I. often shows a characteristic picture. He is usually under middle age, and his diabetes is of moderate or greater severity. He complains of nocturnal thirst and polyuria, and an early morning specimen of urine will show heavy glycosuria (more than 2% sugar, Benedict's test brick red precipitate). There is usually steady loss of weight (7 patients lost over a stone (6.3 kg.) in weight, and 13 patients over 10 lb. (4.5 kg.) in weight, in periods varying from three to nine months). Female patients complain of troublesome pruritus vulvae. If the dose of G.I. is increased to overcome these symptoms midday reactions usually occur, as happened in 18 of these cases.

The reactions tended to occur about four to six hours after taking the insulin. Ten patients suffered reactions at midday, eight in the late morning, and two in the late afternoon. Those patients who had experienced reactions from S.I. or Z.P.I. usually complained that G.I. produced more severe reactions. The feature that particularly worries the patient is the suddenness of the reaction. Patients on a single daily morning dose of G.I. should therefore have their main meal of the day at midday.

I believe that this combination of nocturnal thirst and polyuria, with midday or afternoon reactions if the dose of insulin is increased, along with heavy morning glycosuria, loss of weight, and pruritus vulvae in women, constitutes a clinical picture which might be called the "failed-globin syndrome," and it is not uncommon when globin insulin is used in unsuitable cases. When it appears, a different insulin arrangement is obviously necessary. This may be either a twice-daily dose of S.I., or often more conveniently a combined daily morning dose of Z.P.I. and S.I.

As would be expected, if a patient continues with a heavy glycosuria, the risk of ketosis is increased. Ten of these patients had episodes of ketosis while taking G.I. Since changing back to S.I. twice daily or S.I. and Z.P.I. there has been only one incident of ketosis, in a patient with cellulitis of the leg, among the 55 cases.

All of the 55 patients have subsequently been adequately controlled on a twice-daily dose of S.I. or on a combination of Z.P.I. and S.I. Over 80% of them have now been under observation for a further two years. The glycosuria has been stemmed, with gain in weight and relief from nocturnal thirst and polyuria. The troublesome nocturnal pruritus vulvae has disappeared in nine out of ten women affected.

Conclusions

(1) Globin insulin is often successful in the treatment of diabetes of older persons when the total daily dose of insulin does not exceed 40 units.

(2) Young and severe diabetics, when treated with a single daily injection of globin insulin, may show heavy morning glycosuria and suffer from nocturnal polyuria, thirst, and loss of weight.

(3) An increase in the dose of globin insulin in such patients usually produces midday reactions without relief of these symptoms.

(4) Such patients can be better controlled by a twice-daily dose of soluble insulin, or a combination of soluble insulin and zinc protamine insulin.

It is a pleasure to acknowledge the help and criticism of Dr. R. R. Bomford and Professor Clifford Wilson in preparing these notes, and the permission to use the case histories of their patients.

REFERENCES

- Crooke, A. C., and Scott, E. (1943). *British Medical Journal*, 1, 64.
Eaton, J. C. (1944). *Lancet*, 2, 269.
Mosenthal, H. O. (1944). *J. Amer. med. Ass.*, 125, 483.
Wauchope, G. M. (1948). *British Medical Journal*, 2, 191.

SOME ASPECTS OF SCHISTOSOMA MANSONI INFECTION

BY

DAWOOD MUSTAFA, D.K.S.M.

Medical Registrar, Khartum Civil Hospital

Extensive subperitoneal miliary infiltration of the small intestine by *Schistosoma mansoni* and enlargement and heavy invasion of the mesenteric and retroperitoneal lymph nodes by ova of the same schistosome are rare enough to warrant being recorded. The post-mortem findings of three cases are therefore given.

Case Reports

Case 1. "Miliary Schistosomiasis" of Subserous Surface of Small Intestine.—A man aged 35 was admitted to hospital on September 14, 1949, with acute dysenteric symptoms. *Sch. mansoni* ova were found in his stools. He died five days later. On post-mortem examination the outer surface of the whole length of the small intestine was found to be studded with tiny nodules which were macroscopically indistinguishable from miliary tubercles. Only a few such tubercle-like lesions were seen on the surface of the lowermost portion of the large bowel. The mesenteric and retroperitoneal lymph nodes were moderately but universally enlarged. Some were haemorrhagic. The outer surface of most of the large bowel as well as the parietal peritoneum were devoid of nodules. The inner lining of the small intestine was congested and showed some minute submucous haemorrhages, but no ulceration or overgrowth. Ulcers and polypoid growths were, however, seen on the mucous surface of the whole length of the large bowel. The liver was cirrhotic. Scrapings from the miliary nodules on the surface of the small intestine revealed large numbers of ova of *Sch. mansoni*, while digested sections (with sodium hydroxide) of the mesenteric and retroperitoneal lymph nodes were simply clumps of such ova. They were negative for tuberculosis.

Case 2. Heavy Adult Infection; Enlargement and Heavy Invasion of Mesenteric and Retroperitoneal Lymph Nodes by Ova.—A man aged 30 was admitted on September 11, 1949, with acute watery diarrhoea. On admission he was extremely toxic, dehydrated, and anaemic. Stools were positive for *Sch. mansoni* ova. He died ten days later. At necropsy a very heavy adult infection of the portal vein and of its intrahepatic tributaries was found. Most were present in the portal vein. The cut surface of the liver, which was soft and dark red, showed many adult worms as well as ova. The mesenteric and retroperitoneal lymph glands were all enlarged and were teeming with ova. The transverse and descending colon showed extensive submucous polypoid growths and ulcers.

Case 3. Minimal Intestinal Lesions; Enlargement of Mesenteric Lymph Nodes.—A man aged about 40 was admitted on August 8, 1949, for fever. He had no intestinal symptoms or signs on admission. Blood culture was positive for *Salmonella paratyphi A*. He went downhill and became more and more toxic and anaemic. A terminal diarrhoea developed and he

died on September 26. Stool examination was negative for schistosoma ova. On post-mortem examination the mesenteric lymph nodes were slightly enlarged. Sections showed the presence of many ova. The mucous membrane of the small intestine was slightly congested, while that of the large bowel was a trifle thickened. There were no overgrowths or ulcers. The liver was slightly enlarged but otherwise normal.

Comments

The points of interest in these cases are:—Case 1: the miliary lesions, their simulation of miliary tuberculosis, and the heavy infection of the mesenteric and retroperitoneal lymph nodes. Case 2: the heavy adult infection of the portal system and enlargement of the lymph nodes. Case 3: the paucity of intestinal lesions while the lymph-node infection was the predominant feature.

Subserous miliary schistosomal infiltration of the small intestine is an abnormal feature in *Sch. mansoni* infection, which could easily have been mistaken for miliary tuberculosis, while enlargement of the mesenteric and retroperitoneal lymph nodes is rare. Small-intestinal and lymph-node lesions are, however, the usual findings in Asiatic schistosomiasis.

The most interesting feature of these cases is therefore that their pathology resembles in some respects that of *Sch. japonicum* infection.

In *Sch. mansoni* infection the organs and tissues most seriously involved are the colon and rectum, though eggs carried in the mesenteric current into the portal vessels may filter out in the liver and lead to cirrhosis.

The essential difference in *Sch. japonicum* infection is the location of the adult worms and the discharge of ova primarily in the mesenteric vessels draining the small intestine. Thus the organs and tissues most seriously involved are jejunum, ileum, appendix, and mesentery. But the relatively short distance for transportation of eggs in the mesenteric current into the intrahepatic portion of the portal vessels and the large numbers of eggs discharged by *Sch. japonicum* females combine to set up periportal fibrosis and other visceral lesions—for example, lymph nodes—as more important in this disease than intestinal lesions.

It is stated that the same schistosome may present different pathological features in different parts of the world. It may therefore be that lymph-node involvement is not an uncommon feature in Sudan schistosomiasis (*mansoni*). Many post-mortem examinations are required to prove this.

I am indebted to the Director of Health Services for permission to publish these cases, and to Dr. R. Kirk, assistant director of research, for his kind criticism and comments.

A report on the British Legion Village covering the years 1947–9 has recently been issued. It pays tribute to the work of Professor F. R. G. Heaf, consulting physician to the Village, whose methods are used in the training schemes. Over 10,000 tuberculous ex-Service men and women of the 1914–18 war have benefited from the services provided by the Village, and many of the second world war are now doing so. The hospital section of the Village has been transferred to the Ministry of Health, but the settlement will still be considered as a unit. Throughout the organization national scales of salaries and wages are paid, and men undertaking full hours of occupational therapy receive increases in wages in accordance with their technical skill. This arrangement benefits morale, since the disabled men know that they are working under conditions like those of their fellows in the outside world.