Subsequent inquiries revealed that the patient had been to an ordinary school, and, although considered backward, had attended a junior technical college for a year, leaving at the age of 15. He had been employed as a factory hand and later as a storeman before his national service. On entering the Army at the age of 18, he had been regarded as rather dull and mentally immature, but no physical abnormalities were found. Three months before the illness here reported he had "collapsed" during a battle course done as part of his Army training, and a weakness of the right hand had been noted in examination. This had cleared in a few days, and he had been returned to duty but excused further battle courses.

His father, mother, and only sister each proved to have a positive W.R.

Discussion

The rarity of juvenile G.P.I. was emphasized by Worster-Drought (1940). This case also showed several uncommon features. The clinical onset was abrupt, and, although some degree of dementia may have been present for a time before the acute breakdown, it was not sufficient to prevent his wage-earning employment or his acceptance for national service. The presentation with focal neurological signs is unusual. However, such a syndrome in G.P.I. was recognized by Lissauer and Storch (1901), and these cases are sometimes referred to as "Lissauer's paralysis." Lissauer himself explained them as being due to an intense localized atrophy of a group of convolutions, but of the same pathogenesis as the more diffuse cerebral atrophy of G.P.I. More recently, however, Stewart (1933), in reviewing the pathology of juvenile cases, could find little to differentiate histologically between ordinary G.P.I. and Lissauer's type, as localized atrophy with status spongiosus occurred in both. In our case the abrupt onset of hemiparesis, the focal clonic movements, the localized electroencephalographic abnormality, and the rapid improvement with potassium iodide and penicillin, with slight residual focal signs, all suggest that a meningovascular process with gumma formation may have been present in addition to the G.P.I.; and, indeed, this may be the explanation for other cases of "Lissauer's paralysis."

A predominantly manic psychiatric picture is also unusual, though recorded in this condition. This patient's initial response to penicillin was very striking. His subsequent improvement has continued, though more slowly, and it can certainly be said that already, during the course of a year since the diagnosis was made, progress has been much better than with older remedies such as malaria, arsenic, and bismuth. Worster-Drought (1951) has used a combination of penicillin and malaria in treating 10 cases of juvenile G.P.I., with improvement in all cases. However, it is still a matter of debate whether such a combination has any advantages over penicillin alone, used, as in the acquired form of G.P.I., in large and repeated doses until the serology shows a definite response. Either way, treatment should be continued until such a response does occur.

We should like to thank Professor P. C. Cloake for the follow-up notes of the case, and the Director-General, Army Medical Services, for permission to publish.

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Spastic and other disabled children in hospitals and special schools are finding the use of magnetic letters both entertaining and instructive. Clinging to the surface of special blackboards, which can be held in any position, these letters are particularly helpful in the education of children who have to lie on their backs.

ANAPHYLACTIC SHOCK AS A COMPLICATION OF INSULIN COMA THERAPY

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Changes in insulin sensitivity are fairly common during insulin coma therapy and are shown by changes in the time and depth of coma, usually in the direction of increased sensitivity, requiring reduction of the original coma-producing dose. Insulin hypersensitivity (or allergy) is far less common and actual anaphylactic shock is extremely rare.

Case Report

A 40-year-old male paranoid schizophrenic was admitted to hospital on October 15, 1953. He had been in hospital in 1950 (when he had a three-weeks course of modified insulin) and in 1952. There was no personal or family history of allergy. He was in satisfactory physical health, and routine blood investigations were normal. After preliminary electroplexy, modified by relaxants, he began deep insulin therapy on October 22. This was administered by the routine technique modified by the use of intravenous insulin. Daily injections of insulin were given for six days a week, at first intramuscularly, beginning with 10 units, then 20 units, then increasing daily by 20 units, changing to intravenous injection at 60 units. Various brands of soluble insulin of 20 units per ml. strength were used in the treatment unit, but only one batch was in use at any particular time.

November 1 was a rest day, and on the 2nd an intravenous injection of 160 units of soluble insulin was given at the usual slow speed at 7.50 a.m. This was the tenth treatment, and the dose was the same as that administered on October 31, when only sweating had resulted, with termination of the hypoglycaemia by oral glucose at 10.30 a.m. No untoward reactions had previously been noted. On this occasion, however, five minutes after injection coughing and retching occurred. The manifestation of anaphylaxis was immediately suspected, and during the preparation of an adrenaline injection severe bronchospasm occurred with startling rapidity and severity, and the patient became pallid and cold. Intravenous adrenaline tartrate, 2 ml. of 1 in 1,000 solution, was given, and general treatment for shock was begun. Bronchospasm and vasomotor collapse remained very pronounced, and consecutive intravenous injections of 60 ml. of 33½% dextrose solution and 2 ml. of nikethamide were given, accompanied by continuous insufflation of oxygen (later changed to oxygen with 5% carbon dioxide). Slow intermittent intravenous injection of adrenaline was maintained, and between 8 and 8.35 a.m. 8 ml. of 1 in 1,000 solution was administered. The case proceeded as follows.

At 8.40 a.m. he was given atropine sulphate, 0.6 mg. (1/100 gr.), and aminophylline, 0.5 g., intramuscularly and 33½% dextrose, 60 ml., intravenously. He was now sufficiently recovered to ingest chlorcyclizine hydrochloride tablets ("histanin"), 100 mg., crushed in a little glucose solution. 9.5 a.m.: Blood sugar, 143 mg. per 100 ml. 9.10 a.m.: I.V. 33½% dextrose 60 ml., and normal saline 40 ml. 9.30 a.m.: B.P. 114/76; pulse rate, 130 a minute. 10.5 a.m.: B.P. 94/62; I.M. nikethamide 2 ml., and I.V. injection aminophylline 0.25 g.; general condition unchanged. 11 a.m.: B.P. 80/50; pulse rate, 80 a minute; blood sugar, 43 mg. per 100 ml. 11.15 a.m.: Patient suddenly became very collapsed, with dyspnoea and very weak pulse volume; I.V.

nikethamide 2 ml., I.V. 33½% dextrose 60 ml., and I.M. aminophylline 0.5 g. administered, with rapid improvement. 11.30 a.m.: B.P. 84/60; pulse rate, 90 a minute. 12 noon: Renewed collapse, with dyspnoea, weak pulse, and cold extremities; I.V. adrenaline 2 ml., I.M. methylamphetamine hydrochloride 10 mg., and I.V. 33½% dextrose 110 ml. were injected, with consequent improvement. 2 p.m.: B.P. 114/76; blood sugar, 212 mg. per 100 ml.; I.V. 33½% dextrose 60 ml., and I.M. methylamphetamine hydrochloride 10 mg. At 2.10 p.m. the urine contained 2% sugar. The patient was now taking frequent sips of fluids and was maintaining his general condition. 4 p.m.: Blood sugar, 132 mg. per 100 ml.; B.P. 88/58, but general condition fairly good. Conversation was rambling at times, probably due to methylamphetamine abreaction.

The systolic blood pressure remained consistently below 100 mm. despite the general improvement. Another intramuscular injection of methylamphetamine produced further abreaction, and this drug was then discontinued to avert possible exhaustion. Intramuscular nikethamide, 2 ml., was continued two-hourly throughout the night and then four-hourly; chlorcyclizine hydrochloride tablets, 100 mg., were also given four-hourly from the next morning (November 3), when the patient's improvement was well maintained, although his conversation was noted to be rambling.

On November 4 he was still rambling and confused, although accessible mentally. Nikethamide and chlorcyclizine were discontinued, and paraldehyde, 2 fl. dr. (7 ml.), was prescribed as a nocturnal sedative. Next day he was more rational and quite normal physically. Clinical psychological examination on November 14 showed no significant mental change resulting from the anaphylaxis.

Follow-up Allergy Studies

An intradermal technique was adopted, using 0.01 ml. of test solution injected from a tuberculin syringe with a fine needle. The batch of insulin in use at the time of the anaphylactic incident ("AB" insulin, 20 units per ml.) gave a strong positive reaction. Similarly strong positive skin reactions were given by all other types of insulin tested, both unmodified (Novo insulin 20-unit solution, and Boots insulin 20-unit solution) and modified (Wellcome P.Z.I. 40-unit solution, Boots I.Z.S. 40-unit solution, and Boots I.Z.S. (amorphous) 40-unit solution). Control solutions used were normal saline and 0.3% cresol (since this latter was the preservative added to the original insulin solution): these gave consistently negative results, as also did Bencard intradermal solutions of pig, beef, and mutton proteins.

At the beginning of December passive transfer of sensitivity was attempted, using four healthy non-allergic subjects: three gave positive reactions and one gave a slight positive reaction. Sensitized skin areas were prepared by the injection of 0.1 ml. of the patient's serum.

In January, 1954, when his intradermal response to soluble insulin was still strongly positive, experiments with antihistamines were carried out, and it was found that oral dosage (chlorcyclizine hydrochloride tablets, 100 mg., an hour before the injection) diminished the reaction considerably; but this remained positive, whereas coincident injection with the insulin solution, using 0.01 ml. of a 2.5% solution of mepyramine maleate (0.25 mg. of salt) with 0.01 ml. of soluble insulin (0.2 unit) achieved almost complete neutralization.

In April, intradermal testing revealed the continued presence of a strongly positive allergic reaction to insulin. It is proposed to keep this patient under observation, so that the expected waning of his allergic state may be detected by repeated tests for skin allergy and circulating skin-sensitizing antibodies (reagins).

Discussion

The occurrence of a true anaphylactic reaction was confirmed by the presence of an incubation period, the positive

intradermal tests, and the detection of circulating antibodies. These features are absent in the so-called anaphylactoid response to intravenous injections (Sollmann, 1942).

Earlier literature on the allergenic properties of insulin has been well summarized by Harten and Walzer (1940) and by Yasuna (1941). The above case is an unusually severe example of the generalized reaction regarded as occurring in about 1 in 1,000 insulin users, although Ulrich *et al.* (1939) suggested that insulin allergy was relatively more frequent in the non-diabetic patient. Harten and Walzer criticized the paucity of skin-test recording in these cases and pointed out that even less often was the possible presence of circulating reagins investigated, although neither of these reactions necessarily parallels the presence or severity of clinical symptoms.

Of particular interest in the described case was the presence of the "latent period" prior to the anaphylactic incident that occurred 11 days after the first injection of the insulin course—which was itself begun two and half years after a previous course. The increased frequency of allergy (particularly generalized) when insulin therapy had been interrupted and the resemblance of the "latent period" to the incubation period of serum sickness were emphasized in the reviews by Tuft (1928), Harten and Walzer, and others. A further feature was the occurrence of the episode immediately following an insulin-free "rest day"; this can be compared with the cases of Hinko *et al.* (1941) and of Sherman *et al.* (1941). Non-diabetics are far more likely to suffer interruptions of insulin administration, and this may account for their reported greater liability to allergic reactions.

Allergy studies in the above case confirmed the activity of a specific antigen. Despite the improved purification of insulin, some authorities maintain that its apparent allergenic properties are due to minute amounts of contaminating protein material, or even to an alteration of insulin in the isolation process, rendering it a "foreign protein" (Waters and Best, 1941).

Jorpes (1949) claimed that repeated recrystallization of insulin reduced the incidence of allergenic reactions, and suggested that these were usually, if not always, due to impurities.

The antihistamine experiments demonstrated the efficacy of these drugs in neutralizing insulin allergic effects: this has been confirmed by therapeutic experience, sometimes combined with desensitization, spontaneous or induced (Hunter and Hill, 1947; Leavitt and Gastineau, 1947; Armstrong and Lloyd, 1954). In the treatment of the above case an oral antihistamine was used, but it may be that early administration of an injectable compound, unfortunately not available at the time, might have shortened the emergency period.

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