Discussion

No adverse effects of nitrazepam on the haemopoietic system or renal and hepatic function has been noted (Jordan, 1965). Nor has this drug shown any incompatibility when used with other drugs in the treatment of epilepsy (Kryspin-Exner, 1966), thyrotoxicosis, cardiac failure, hypertension (Maibach, 1965), and diabetes mellitus (Wyss and Mäder, 1965). Dependence on, or addiction to, nitrazepam has not been observed (Franke, 1965 ; Bethune *et al.*, 1966), nor has there been any report of delirium or epileptic seizures on withdrawal of the drug such as may complicate the withdrawal of other hypnotics (Glatt, 1968).

Few reports of overdosage with nitrazepam have been recorded. Hirsch (1968) reported a 15-year-old girl who suffered from liver disease and ingested 26 tablets, Liske and Forster (1963) a 27-year-old woman who took between 24 and 30 tablets, Franke (1965) a man aged 40 who took 18 tablets, and Bethune *et al.* (1966) a boy aged 6 years who ingested 16 tablets and an obese woman who took 70 tablets. With one exception no effect of the overdose other than profound but rousable sleep was noted. The exception (the patient who took 70 tablets) did not even fall asleep. No depressant effect on the respiratory or the cardiovascular system was observed.

To these isolated instances we add the findings in 27 patients. Despite careful observation we could determine no significant effect of overdosage with nitrazepam other than minimal disturbance of consciousness, even in a patient who took 80 tablets. We have been unable to find an authenticated record of death due to poisoning by this hypnotic ; the lethal dose for man remains unknown.

It is therefore evident that nitrazepam is a hypnotic which, tablet for tablet, is unsurpassed as yet in safety. This element of safety would, however, be valueless if it were not also shown that the drug had a hypnotic effect as adequate as a barbiturate.

Many methods, including use of activity beds and continuous E.E.G. monitoring, are available for the assessment of hypnotic drugs. Nevertheless, as insomnia is a subjective state, a feeling beyond the observation of mere indicants, the paradigm should surely be the personal report of the patient. The language offered to the patients in this trial for communication of their feelings is known to be reliable and valid (Aitken, 1969).

The clinical trial clearly showed that nitrazepam was superior to a placebo as a hypnotic drug, and that it was as effective as butobarbitone. There was consistency between the patients' reports on the quality of sleep and the nurses' assessments of the duration of sleep. The results are similar to those of another trial with a similar method of analysis comparing nitrazepam and sodium amylobarbitone in psychiatric patients (Davies and Levine, 1967).

We conclude that nitrazepam is an effective hypnotic which is safe in overdosage.

We are grateful to Dr. S. L. Tompsett, who undertook the chemical estimations of nitrazepam ; to Dr. D. L. Scott, of Roche Products Ltd., who supplied the tablets for the sleep trial ; and to Mrs. D. White, who assisted with the statistical analysis of the sleep trial.

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Growth Hormone Secretion in Growth-retarded Asthmatic Children

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Summary: The serum growth hormone response to Bovril was studied in 12 growth-retarded children with severe asthma, and was found to be normal. Eight children who were receiving corticosteroids had been small for their age before starting steroid treatment. It is concluded that there is no case for treating growth-retarded asthmatic children with growth hormone.

Introduction

Growth retardation which occurs in severely affected asthmatic children (Falliers *et al.*, 1963, and Norman, 1965) can be accentuated by the use of corticosteroid drugs (Kerrebijn and De Kroon, 1965). Now that a simple and reliable method of evaluating growth hormone secretion is available in the Bovril test (Jackson *et al.*, 1968) we decided to study the human growth hormone (H.G.H.) responses of severely growth-retarded asthmatic children.

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Materials and Methods

Twelve patients who were attending the asthma clinic at the Hospital for Sick Children, Great Ormond Street, London, and showed growth retardation were studied (see Table). At the time of H.G.H. assay the heights of eight patients were below the third percentile, those of three were on the third percentile, and that of one on the fifth percentile, while all showed retardation of skeletal maturation. Two of the 12 patients were girls and 10 were boys ; their ages ranged from 7·3 to 16·5 years (mean 12·6 years). All of them were severely asthmatic, but 10 also had had or were suffering from eczema and six from hay-fever. Corticosteroids, in doses of prednisone ranging

Details of Results

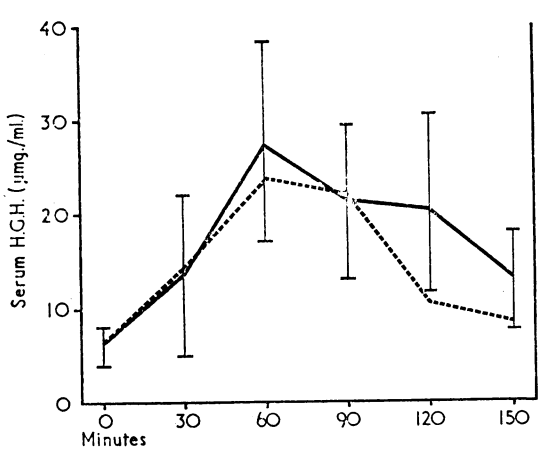
Case No.	Date of Birth	Sex	Asthma	Eczema	Hay-fever	Age at Test (Years)	Height (Percentile) at Test	Weight (Percentile) at Test	Duration on Steroids (Years)	Height (Percentile) Before Steroids	Serum H.G.H. (mμg ml.) Minutes after Bovril 0	30	60	90	120	150
80	26/11/51	M	+	+	+	16·51	<3	<3	3·35	10	7·2	20·0	14·2	9·8	7·8	7·2
82	1/1/53	M	+	+	+	15·44	<3	3	3·04	20	1·1	11·2	4·9	9·2	5·4	2·1
76	11/3/61	M	+	+	+	7·27	3	<3	Not on steroids		12·6	12·9	16·6	9·5	3·4	6·0
64	24/2/57	F	+	+	+	11·37	<3	<3	3·95	3	3·1	15·3	24·4	6·3	15·4	32·0
40	8/7/55	M	+	+		13·09	<3	<3	4·95	3	1·4	2·0	32·0	32·0	14·2	10·6
75	6/7/53	M	+			15·20	3	5	5·90	35	2·2	2·4	2·8	25·1	2·8	2·9
17	24/1/55	M	+	+	+	13·65	<3	3	7·46	?	4·7	4·1	32·0	32·0	32·0	7·7
36	11/1/55	M	+	+		14·00	<3	<3	5·19	3	12·3	5·2	64·0	64·0	64·0	23·7
38	23/9/57	M	+			11·30	<3	<3	4·64	3	15·3	64·0	49·0	15·2	14·1	18·2
88	12/8/55	M	+	+		13·43	5	<3	Not on steroids		5·3	12·0	64·0	7·2	37·8	26·6
02	2/1/59	M	+	+		10·03	3	5	Not on steroids		4·9	4·9	6·8	31·2	28·6	11·1
89	26/10/58	F	+	+	+	10·23	<3	<3	Not on steroids		8·1	9·2	23·0	19·1	19·2	17·3
					Mean	12·63				Means	6·52	13·60	27·80	21·71	20·39	12·95

from 5 to 10 mg. a day, had been given to eight of the patients, who were all receiving them at the time of testing. In all but one of these the height was known before corticosteroid therapy was begun; while, of the remaining seven, four already showed severe growth-retardation—that is, were on the third percentile for height—and three moderate growth-retardation. The height percentiles of all eight had fallen after they had been receiving corticosteroids for periods ranging from 3·0 to 7·4 years (mean 4·9 years), and when tested for H.G.H. all had heights which fell on or below the third percentile. Of the remaining four patients who had not been treated with corticosteroids all showed severe growth retardation. The heights were plotted on charts devised by Tanner *et al.* (1966).

The Bovril test was performed on the patients according to the method described by Jackson *et al.* (1968). Capillary blood specimens were taken before the Bovril was administered and thereafter at 30-minute intervals for two-and-a-half hours, Serum growth hormone was determined by a double-antibody technique (Jackson *et al.*, 1968).

Results

All the patients had a normal H.G.H. response to Bovril (see Table). Nevertheless, the quantitative H.G.H. results cannot be correlated with the patients' growth status.



Mean serum H.G.H. results (with standard deviations) (——) compared with normal results (- - - -) reported by Jackson *et al.* (1968).

The Chart, which shows the mean serum H.G.H. results (with standard deviations) plotted in comparison with the normal results previously reported by Jackson *et al.* (1968), demonstrates that the two curves are similar in contour.

Discussion

The depression of growth which follows corticosteroid therapy in asthmatic children is not necessarily due to lack of H.G.H. Furthermore, our findings confirm the work of Morris *et al.* (1968a), who showed (Morris *et al.*, 1968b) that treatment of their patients with H.G.H. over a period of four to eight months did not increase the rate of growth. Moreover, in those children whose growth is depressed as a result of persistent asthma alone satisfactory secretion of H.G.H. does occur. It has been suggested in another context—that is, African pygmies—that there is either an abnormality in the H.G.H. molecule (Rimoin *et al.*, 1968) or a tissue subresponsiveness to H.G.H. (Merimee *et al.*, 1968). No prima facie case for administering H.G.H. to growth-retarded asthmatic children can therefore be made at present.

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