TREATMENT OF MONGOLISM WITH PITUITARY EXTRACT

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WHEN mongolism was first described, it was considered by some authors to be a form of cretinism (Seguin, 1866), and with the discovery of the effect of thyroid treatment in cretinism, this was tried in mongolism also. The disappointing results diverted attention to other endocrines. Tredgold, in 1929, was recommending a mixture of thyroid, pituitary, thymus, suprarenal and pineal glands, though he did not believe that such treatment was curative.

Many observers have considered that there is a disturbance of pituitary function in mongolism and some that pituitary therapy is beneficial. In particular Benda (1947), stated that "mongolism is the congenital type of hypopituitarism". His views, however, largely depend on his own somewhat unorthodox interpretation of the histological findings in the pituitary in mongolism. In reference to 100 children treated with a small dose of thyroid and a calf pituitary powder (Armour) given orally, Benda (1953) claimed that "it is possible nowadays to influence the physical growth of the mongoloid child to such an extent that he remains within the average range of height and weight" and that, in regard to mental development, "some of the children made amazing progress". After 10 years' experience of this form of treatment, Benda (1956) observed that some children "lose their 'mongoloid' appearance almost completely" and that the influence on mental development is "less striking but appears definite" if many untreated children are compared with his group of over 100 treated cases. Carter (1958), in a preliminary report on the use of an oral preparation of young calf pituitary extract in mongolism, also claimed some excellent results both in terms of physical and mental development. Blumberg (1959), using an oral preparation of pituitary extract, in this case from adult animals, plus thyroid, claimed good physical development in 11 cases of mongolism during the 2-year treatment period. An influence on mental growth could not, however, be established.

Some of these claims are unconvincing because of inadequate data on methods for selection of patients, criteria for assessing progress and/or absence

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of controls. Nevertheless, they arouse considerable interest among parents of children with mongolism who may feel that, if their children are not given what is asserted to be effective treatment, an opportunity is being missed. It was therefore decided to attempt to assess the value, if any, of pituitary administration.

Since there is uncertainty about the effectiveness of *oral* preparations of pituitary, as they may be destroyed by the gastric juices (Benda, 1956; Carter, 1958), we tried to obtain for our trial an active preparation which could be given by injection. Through the courtesy of Dr. F. Paulsen, a quantity of "Somacton" (Ferring AB) sufficient to treat 3 children daily for 6 months was made available to us. "Somacton" is a growth hormone preparation extracted from hog pituitary glands as a by-product of A.C.T.H. production. The makers state that it is certain that this preparation is active in humans and differs from other preparations in that it is more soluble, purer, and free from A.C.T.H. contamination.

Method

Three pairs of mongols, all in-patients in the Fountain Hospital, were matched as closely as possible for age, sex, weight, height and mental level. The youngest patients available were chosen, since it has been suggested by Benda and others that such children derive most benefit from pituitary therapy. All six children appeared free from intercurrent illness when selected for the trial and none had specific motor defects. All were transferred to the same small ward prior to commencement of the trial and remained there throughout, thus ensuring as constant an environment and diet as possible.

Before the trial, intelligence tests were carried out; weights, heights and head circumferences recorded; serum calcium and phosphate values determined; neutrophil lobe, neutrophil and lymphocyte counts done; and skull radiography and electro-encephalography undertaken. All the investigations were repeated at the end of the trial and the leucocyte studies also during it.

One of each of the 3 pairs of mongols, chosen at random, was given 100 tibia units of "Somacton" subcutaneously, daily (this dose corresponding to 2 international units), the other having a like amount of a control injection consisting of 0·5 ml. normal saline. Daily pituitary extract and control injections were given for a period of 6 months from August, 1958 to February, 1959. There were 2 breaks of 6 and 8 days due to delayed arrival of supplies. Also, the special pituitary preparation in the form of ampoules containing 5 mg. of lyophilized powder ("Somacton") was replaced during the last month of the trial, because of termination of supplies, by the ordinary commercial preparation of "Somacton" containing 500 tibia units per ampoule; the same dose was, however, maintained. Throughout the trial, the powder was made up freshly daily with 0·5 ml. of solvent for each child. The key to the identity of the injections was kept by the Chief Pharmacist and none of the observers taking part in the trial was informed which child was having which injection.

Results

The results of mental, physical and biochemical measurements are shown in Table I and of leucocyte counts in Table II. In these tables, 1, 2 and 3 indicate the three matched pairs of mongols, A those who received pituitary extract injections and B those who received placebo injections.

TABLE I

Mental, Physical and Biochemical Measurements Before and After Trial

Case	Sex	Before							After						
		Age	I.Q.	Weight	Height	Head Circum-ference	Serum Calcium	Serum Phos-phate	Age	I.Q.	Weight	Height	Head Circum-ference	Serum Calcium	Serum Phos-phate
1 A ..	F	16	54	7·77	72·0	41·2	8·9	4·9	22	44	9·68	74·5	42·2	8·8	4·5
1 B ..	F	16	48	7·03	69·5	42·3	8·9	4·8	22	31	8·45	72·0	43·0	8·9	5·0
2 A ..	M	25	23	7·51	73·5	44·8	9·2	4·6	31	16	8·90	75·5	45·3	8·2	4·4
2 B ..	M	27	32	11·28	80·0	47·0	9·5	5·2	33	30	13·47	82·5	47·6	9·2	4·5
3 A ..	M	48	40	15·54	93·5	46·5	9·2	4·5	54	38	16·53	94·5	46·7	8·8	4·5
3 B ..	M	48	30	13·83	87·5	47·5	8·9	4·4	54	31	14·26	89·0	47·7	9·4	4·3

I.Q. assessed on Griffiths Mental Development Scale.

Age expressed in months, weight in kg., linear measurements in cm., and serum calcium and phosphate levels in mg. per 100 ml.

TABLE II

Neutrophil Lobe, Neutrophil and Lymphocyte Counts Before, During and After Trial

Counts	Case	Before Trial	During Trial	After Trial	Difference During–Before Trial	t	P
Mean neutrophil lobe counts	1 A	1·41	1·57	1·61	0·16	2·640	0·060
	2 A	1·32	1·59	1·52	0·27		
	3 A	1·54	1·67	1·51	0·13		
	1 B	1·80	1·83	1·62	0·03		
	2 B	1·63	1·60	1·70	−0·03		
Average neutrophil counts	1 A	4,780	7,990	5,126	1,496	2·927	0·044
	2 A	3,433	7,369	5,349	3,210		
	3 A	3,578	5,074	4,256	3,936		
	1 B	5,763	4,903	5,071	−860		
	2 B	2,795	2,394	4,133	−401		
Average lymphocyte counts	1 A	4,546	3,228	4,739	937	0·223	0·85
	2 A	1,943	2,873	3,692	−1,318		
	3 A	2,325	3,262	2,233	930		
	1 B	2,693	5,455	3,163	2,762		
	2 B	1,234	2,104	1,607	1,607		

Each entry in the columns headed before, during and after trial represents the average of 3 determinations.

No differences between the two groups before and after the course of injections were apparent in terms of mental development and physical measurements (Table I). Likewise, X-ray examination of the skulls and electroencephalograms revealed no changes which could be attributed to the pituitary extract. Clinically, observation of the children by medical and nursing staff throughout and after the trial produced no evidence of differences between the two groups. In children with mongolism the serum calcium tends to be low and the serum inorganic phosphate slightly raised (Stern and Lewis, 1958). There was no indication in this trial that the pituitary injections tended to raise the serum calcium or lower the serum phosphate levels (Table I).

The leucocytes in mongolism show two peculiarities: (*a*) a reduction in the average number of lobes of the neutrophils and (*b*) a higher neutrophil count and lower lymphocyte count than in other children of the same age group (Mittwoch, 1958). In view of this, mean lobe counts of the neutrophils and total neutrophil and lymphocyte counts were done on the patients taking part in the trial on 3 occasions before, 3 occasions during and 3 occasions after the course of injections, so as to see whether these variables were affected by the treatment. Counts were performed without knowledge of the origin of the slides. One of the patients (Case 3B) developed glandular fever (?) before injections commenced, with a lymphocyte count of 32,000 per c.mm. and a neutrophil count of 11,000 per c.mm. As a count of this magnitude would have swamped all comparisons, this patient was excluded for the purpose of evaluating leucocyte counts. Since he received the placebo, the present results are based on 3 patients receiving the pituitary extract and 2 controls (Table II). With regard to the mean neutrophil lobe counts, there was a slight increase during treatment in the 3 patients receiving pituitary injections and no increase

in the 2 patients receiving placebo injections. However, the mean lobe counts of the latter patients was altogether higher than those of the former ones. With regard to the neutrophil counts, the 3 patients receiving pituitary injections showed an increase in neutrophils during treatment and a fall thereafter; no such effect occurred in the 2 patients on placebo injections. As for the lymphocyte counts, there were no consistent changes in either group. Bearing in mind the extreme caution required in interpreting results based on 3 cases, the present data suggest that the pituitary extract produced an increase in the neutrophil counts. As there was no increase in lymphocyte counts, the ratio of neutrophils to lymphocytes, which in any case tends to be elevated in children with mongolism, became even higher in the patients having pituitary injections.

Discussion

It is now generally considered that there is a considerable degree of species specificity in growth hormone preparations. Wilhelmi (1955) and Knobil (1955) failed to demonstrate any consistent effect of bovine hormone in monkeys, and suggested that the ineffectiveness of this preparation in man and monkey was due to species difference in hormone composition. Raben (1959) has reviewed the subject and concludes that "the available bovine and porcine growth hormones are not suitable for clinical use. There is also reasonable doubt that the anabolic effects seen in man were more than artefactual. Alternatively, it is necessary to believe that these preparations are only erratically and sporadically active in man."

Critical as we are of the claims made for pituitary therapy in mongolism in other reports, we are also conscious of the limitations of the present trial. We were unable to check independently the activity of our preparation in humans. Further, it could be argued that our conclusions would be more tenable if based on a larger and younger series and a longer trial. For practical reasons, this was not possible. Despite these limitations, however, we thought it worth recording this study since it adds to the weight of evidence which now suggests that, even when given by injection, bovine and porcine extracts are virtually ineffective in humans and consequently of no value in the treatment of mongolism.

There is now adequate evidence that human and monkey pituitary growth hormones are active in man (Beck, 1959; Beck *et al.*, 1957 and 1958). Though there is no *a priori* reason to suppose that an effective pituitary growth hormone will remedy the developmental abnormality in mongolism, it would seem worth while to try the human and monkey hormones in this condition in the hope of producing some amelioration. If such treatment is to be beneficial, it would probably be necessary to give it to very young infants, but a preliminary trial might be made on older patients to assess the effect on metabolism.

Summary

One of each of three matched pairs of mongols, aged 16 to 48 months, was given 100 tibia units of "Somacton" (a growth hormone preparation extracted from hog pituitary glands) subcutaneously, daily, for 6 months, the other receiving a daily control injection of 0·5 ml. normal saline. No significant differences were noted between the 2 groups after the trial in terms of intelligence, weight, height, head circumference and serum calcium and phosphate levels. Nor were there apparent differences in appearance, behaviour, skull X-ray and electroencephalographic findings. Those receiving pituitary

extract showed, during treatment, an increase in neutrophil counts; these changes did not occur in those receiving placebo. There was no consistent change in lymphocyte counts in either group.

This small study lends support to the view that porcine and similar pituitary growth hormones are of no value in mongolism. It is suggested that human and monkey preparations should be tried.

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