was the cause of the bone-marrow aplasia in the patient under discussion. On the other hand, the patient was perfectly well (apart from arthritis) until treatment with phenylbutazone was begun; within one week she had developed epistaxis and a purpuric rash; and within two weeks a fulminating aplastic anaemia had led to death. It seems, on the whole, more reasonable to incriminate phenylbutazone, though it might be that in some way the patient had become sensitized to phenylbutazone by the previous course of gold.

Two further possibilities should be mentioned: that hypothyroidism or rheumatoid arthritis may have influenced the structure of the bone marrow in this patient. In hypothyroidism, hypoplasia of the bone marrow occurs, but the anaemia is not usually severe. As this patient had been adequately treated with thyroid extract for four years there is no reason to suppose that her myxoedema would affect the bone marrow. As regards rheumatoid arthritis, Leitner (1949) states that "in all our cases of rheumatoid arthritis we have observed plasma-cell proliferation" in the bone marrow. He cites Mester (1938), who "collected 75 cases and found an increase of plasma and reticulum cells in acute and chronic rheumatoid arthritis." Some relative proliferation of plasma cells is sometimes seen in idiopathic aplastic anaemia, but not to the same extent as in this patient. Infiltration of the bone marrow with plasma cells is, of course, a feature of multiple myelomatosis, of which there was no clinical or pathological evidence here. The relationship, if any, between plasma-cell proliferation and phenylbutazone remains to be determined.

Are the toxic effects of phenylbutazone due mainly to overdosage or to idiosyncrasy? With this question in mind, an attempt has been made to correlate the frequency of toxic reactions with the dosage of the drug administered. It seems, however, that no such broad correlation can be established, and this may indicate that idiosyncrasy to the drug is the predominant factor. Thus, on a dosage of 1 g. daily, Cudkowicz and Jacobs (1953) reported toxic effects in 26 out of 50 patients, whereas Currie (1952) reported no toxic effects in 81 patients. Loxton *et al.* gave doses varying from 0.4 to 0.8 g. daily, and reported toxic effects at each level. Of the patients with agranulocytosis, three had never received more than 0.8 g. daily, whereas two had received 1.2 g. daily. Of the present cases, Case 1 received 0.6 g. daily, a dosage normally regarded as safe, and Case 2 received 1.6 g. daily for the first week and 0.8 g. thereafter. It thus appears from these cases that the administration of small doses of phenylbutazone does not eliminate the possibility of developing serious blood dyscrasias. The possible dangers of phenylbutazone therapy are increased by its effectiveness, which encourages its employment in general practice. It would seem that its use should be closely controlled by frequent blood counts, and that it should be confined at present to patients in hospital.

Summary

Details of 356 toxic effects occurring in 1,526 patients treated with phenylbutazone have been collected from the literature (an average incidence of 22%).

A fatal case of aplastic anaemia is reported. Though the patient had also been treated with gold, it is contended that phenylbutazone was probably responsible for the anaemia.

A case of agranulocytosis due to phenylbutazone is also described.

The incidence of toxic effects does not seem to be related to the dosage of phenylbutazone, as reactions commonly develop in patients treated with small doses. It is suggested that the use of the drug should be confined at present to patients in hospital.

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ETHOPROPAZINE HYDROCHLORIDE IN TREATMENT OF CEREBRAL PALSY

BY

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The use of drugs plays only a small part in the treatment of cerebral palsy, and so varied are the conditions grouped under this comprehensive term that a single agent is unlikely to be of value in every case. Barbiturates, anticonvulsants, and the belladonna alkaloids are the only drugs in regular use, but reports on recently developed synthetic drugs hold out hope of more effective agents in the future. Jersild (1950) reported encouraging results in congenital spastic paralysis with the synthetic spasmolytic substance caramiphen hydrochloride ("parpanit"), while improvement has been noted in cerebral palsy treated with muscle-relaxants. Some of these, such as mephenesin, may establish a place in treatment (Berger and Schwartz, 1948), while the value of others, such as neostigmine, has not been confirmed (Perlstein and Barnett, 1950).

The beneficial effect of antihistaminic and related drugs in parkinsonism (Sigwald, 1949; Palmer and Gallagher, 1950) suggests their possible value in cerebral palsy, especially in cases in which extrapyramidal signs predominate. Opinions vary on the relative merits of these agents in the treatment of parkinsonism; Garai (1951) found that improvement with benzhexol hydrochloride ("artane") was greater than with ethopropazine ("lysivane"), whereas Gillhespy (1951) considered that ethopropazine was superior to all other drugs of this series.

Effron and Schultz (1951) reported that benzhexol hydrochloride was relatively ineffective in the treatment of eight patients with cerebral palsy. In the present investigation, ethopropazine was chosen because of the favourable impression created by the treatment of a few selected out-patients with this drug.

Details of the Investigation

The trial of ethopropazine was carried out at a residential school for children with cerebral palsy. The school is equipped with physiotherapy, occupational therapy, and speech therapy departments, all of which took part in the investigation.

The 19 children at the school comprised 6 with spastic tetraplegia, 4 with spastic paraplegia, 7 athetoid, and 2 ataxic, their ages ranging from 5 to 14 years. None of them was mentally retarded and all were moderately to severely handicapped. The children were arranged in pairs of approximately the same age and type of palsy, and were then divided into two groups without further selection. The groups were therefore comparable in age distribution and in type and degree of disability; one group was given ethopropazine and the other constituted a control group.

The trial was confined to school terms, since in the holidays the children return to their homes, making supervision impossible. When the children return to school after the holidays some are usually found to have regressed slightly, so that the trial was not begun until three weeks after the beginning of term, to allow for the expected improvement. This left a period of about seven weeks for the trial, and it was decided to give the drug for four weeks in order to assess the child's performance before treatment and to ensure supervision for a week after stopping the drug, in case of possible withdrawal effects. Although four weeks is not a long period, it was thought to be long enough for any improvement to be evident.

The trial was divided into two parts, the 10 spastic children being tested in the first term and the 9 athetoid and ataxic children in the second term. This division was necessary because of the time involved in carrying out accurate tests, which imposed considerable extra demands on the staff of the school.

Dosage of Ethopropazine.—The ethopropazine was supplied in 10-mg. sugar-coated tablets, and the control tablets were identical in appearance but contained lactose. The tablets were administered in four divided doses during the day, each child in the control group receiving the same number of tablets as his equal in the trial group. In the first half of the trial the starting dose was 20 to 30 mg. daily, depending on age, and the dose was increased by 10 to 20 mg. a day at intervals of four days, until a maximum of 100 to 150 mg. daily was reached. In the second half of the trial the starting dose was 30 to 50 mg. daily, and the dose was increased by 20 to 30 mg. a day at intervals of four days, to a maximum of 200 to 250 mg. daily.

Methods of Assessment

Once a week, on the same day each week, the children's progress was assessed, using a number of tests designed to measure different activities. The time taken for each test was measured in seconds with a stop-watch, the final figure being the mean of at least three attempts. The tests used were as follows:

A tests measured ability to relax—for example, the time for which the child could maintain his lips together or could lie still without moving.

B tests measured balance—for example, the time for which the child could hold his head steady or could stand on one leg.

C tests measured active movement—for example, the speed of rising from supine to sitting or standing positions, or the time taken to flex and extend the elbow a given number of times.

D tests measured manual dexterity—for example, the time taken to transfer articles from one container to another, or to take out and replace pegs on a board.

E tests measured speed of rolling—for example, the time taken to roll a measured distance on the floor.

Every child was tested in at least three activities, and, although the tests were adapted to suit the individual child, each performed the same tests each week and did not carry them out at other times during the week.

Speech records were made before the beginning of the trial and again when the children were receiving the maximum dose. The school teachers were also asked to note any changes in ability in the class-room, and the children were under constant supervision by the resident nursing sister. The sister was the only person in the school who knew which children were receiving ethopropazine and which the control tablets.

Results

The results of the trial are presented in the accompanying table. A child's performance for each activity in which he was tested was recorded as having improved or as showing no change. An improvement was regarded as having taken place if either of two criteria was satisfied: (1) if progressive and uninterrupted improvement occurred while the child was receiving the tablets; or (2) if the mean performance during the trial period was at least 100% better than the mean performance when no tablets were being given.

Only one child, No. 3 in the table, improved in all tests. This was a girl of 13 years with severe spastic tetraplegia, and the improvement was maintained permanently after completion of the trial, so that it is difficult to attribute it to the ethopropazine. An assessment of improvement based on the total number of tests performed shows that 23.3% improvement occurred in the trial group and 22.2% improvement in the control group. When the different

Results of Trial

Type of Cerebral Palsy	Case No.	Improved	No Change
<i>Group Receiving Ethopropazine</i>			
Spastic	1	—	C D E
	2	—	C D E
	3	C E D	—
	4	—	C D E
	5	—	C D E
Athetoid	6	—	A B D
	7	A	C D
	8	A D	B
	9	B	A D
Ataxic	10	—	B C D
Totals of 30 tests on 10 patients		7 (23.3%)	23 (76.7%)
<i>Group Receiving Control Tablets</i>			
Spastic	11	D E	C
	12	—	C D E
	13	—	C D E
	14	C D	E
	15	—	C D E
Athetoid	16	—	A C D
	17	D	B C
	18	D	A B
Ataxic	19	—	B C D
Totals of 27 tests on 9 patients		6 (22.2%)	21 (77.8%)

types of cerebral palsy are considered, no consistent improvement in one type or in one activity is found, though the numbers in each group are too small for definite conclusions to be drawn.

The speech records made before and during the trial were carefully compared; two of the ethopropazine group and three of the control group were regarded as having improved slightly. The school teachers noted no unusual improvement in ability in any of the children.

Toxic Effects of Ethopropazine.—In the first half of the trial no toxic effects were noted. In the second half three children, aged 8½, 8, and 7 years, became rather drowsy and listless when a daily dosage of 140, 120, and 140 mg. respectively was reached. In none of these children were the symptoms severe enough to necessitate withdrawal of the drug. Total and differential leucocyte counts were carried out before and at intervals during the administration of the tablets. In no case did a significant reduction in the number of leucocytes occur. On completion of the trial, administration of the drug was stopped abruptly. None of the children showed symptoms of withdrawal except for one boy who developed severe constipation, which might possibly have been due to withdrawal. The three children who showed toxic symptoms became normally alert within 48 hours of stopping the drug.

Summary and Conclusions

The results of a trial of ethopropazine in the treatment of cerebral palsy are recorded. Ten children with various types of cerebral palsy were given ethopropazine and a comparable group of nine children received lactose control tablets.

There was an improvement of 23.3% in the children treated with ethopropazine, but a similar improvement occurred in those who received only lactose tablets. No evidence of a special effect of ethopropazine on any type of cerebral palsy or on any specific ability was obtained. It is therefore concluded that ethopropazine is of no value in the treatment of cerebral palsy.

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ADRENALINE NECROSIS

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Tissue necrosis due to adrenaline injections is a rare occurrence when it is considered how often the drug is administered.

Urbach (1936) reported a case in which multiple areas of skin necrosis followed the self-administration of adrenaline by a female patient who suffered from severe bronchial asthma. To gain relief she often gave herself as many as three injections a night. Urbach observed insistent "intention tremor" at the time of injection, which often took as long as fifteen minutes to complete. When the injection was given to the patient he was unable to get the slightest reaction in the skin. Again, when the patient herself administered an injection of normal saline there were no visible changes in the skin. In this way it was shown that the damage produced by the adrenaline injections was not due solely to mechanical irritation. Urbach concluded that the trauma caused by the "intention tremor" combined with the constriction of the blood vessels, due to the adrenaline, produced a necrosis of the superficial skin.

Necrosis of the tips of two fingers of the hand of a patient operated upon for Dupuytren's contracture was noted by Hanke (1936). The local analgesic used was a 1% procaine-adrenaline solution, the adrenaline being added in the correct dosage just before the injection. He thought that the explanation of this was that the anaesthetizing fluid had acted over a prolonged period on tissue devitalized by the gradual contraction of the palmar aponeurosis which is a feature of the disease.

The most recent case of tissue damage due to the self-administration of adrenaline was reported by Robertson (1951). In his case the tissue reaction was that of keloid formation, which was presumably a personal skin characteristic and due to trauma with a hypodermic needle.

Delaunay *et al.* (1948) conducted a series of experiments, injecting adrenaline in various strengths (1,000 μ g., 200 μ g., 100 μ g., 50 μ g., 33 μ g., 25 μ g., 20 μ g., and 10 μ g.) under the skin of the abdomen of guinea-pigs. The stronger solutions (1,000–25 μ g.) produced changes in the skin visible to the naked eye. With the weaker solutions reactions were noted microscopically. These workers think that adrenaline is not directly toxic to tissues, but that adrenaline necrosis arises rather from various vascular disturbances. They suggest that both vasomotor upsets and disturbance of the permeability of the vessels play a part by interfering with the oxygen supply to the tissues and by inhibiting the diapedesis of polymorphs.

Because of the seeming rarity of skin reactions to the repeated use of adrenaline, and because trauma has apparently played some part in the causation of the cases reported, it was thought that the following case was worth recording.

Case Report

A joiner aged 35 developed asthma at the age of 14, and, after prolonged treatment with various remedies, he obtained relief only from injections of adrenaline. About five years ago his attacks became more frequent and severe, totally incapacitating him, and he found it necessary to give himself adrenaline by injection (1 ml. of 1/1,000 three or four times daily). He became so dependent upon the adrenaline that he administered it as a routine in anticipation of an asthmatic attack. These injections continued for two and a half years without any noticeable cutaneous reaction, the dose remaining the same. He first noticed, at the site of injection, a small red swelling which was painless and did not itch. The surface of the swelling then broke down and a necrotic central patch developed. A black eschar was eventually sloughed and a shallow ulcer remained. This sequence of events took seven to ten days. The ulcer healed slowly, leaving a foveated scar, which later became livid.

Photograph showing active, healing, and healed necrotic areas.

In spite of these reactions he continued to give himself the injections, in the same dose, for a further period of two and a half years, at which time he was seen by one of us (D. McP.).

On examination his appearance was startling. His buttocks, thighs, arms, and shoulders were covered by a multitude of active, healing, and healed necrotic areas of almost uniform size and shape. He was beginning to run short of accessible parts on the limbs and was encroaching on the chest (see Fig.). Until the onset of the skin reactions the right and left arms had been used alternately for the injection.