APPEARANCE OF PARKINSONISM IN MENTALLY DEFECTIVE PATIENTS TREATED WITH "DARTALAN"

WITH THE OCCURRENCE OF OCULOGYRIC
CRISES IN IDENTICAL TWINS

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"Dartalan" is a phenothiazine derivative and is therefore related chemically to chlorpromazine. The manufacturers claim for dartalan qualitatively similar effects on the central nervous system of dogs to those of chlorpromazine. They further claim, however, that its tranquillizing and anti-emetic potency is approximately five to ten times greater by both oral and parenteral administration.

In discussing possible side-effects on human subjects the manufacturers state that signs suggesting involvement of the extrapyramidal system will appear in about one-third of *psychotic* patients receiving daily dosages of 80 mg. or more, that they have not been reported to occur in *non-psychotic* patients, and that they are rare even in *psychotic* patients who are receiving less than 50 mg. daily.

The present paper is concerned with our own findings only in so far as they concern the appearance of extrapyramidal signs in mentally defective patients who were given dartalan in an attempt to control their behaviour disorders.

The Investigation

Of the 31 patients 19 were female and 12 male. Their chronological ages ranged from 16 to 44 in the females and from 13 to 45 in the males and their I.Q.s from approximately 20 to approximately 70 in both females and males. In no case was there any history of a preceding encephalitis, nor were there any signs of extrapyramidal involvement before treatment.

One of the female patients suffered from major epilepsy and three from myoclonic epilepsy; three of the male patients suffered from major epilepsy.

Dosage.—Nineteen of the patients were given 10 mg. of dartalan t.d.s., five were given 10 mg. b.d., two were given 20 mg. b.d., four were given 20 mg. t.d.s., and one was given 30 mg. t.d.s.

Incidence of Parkinsonism.—Signs of Parkinsonism developed in 11 (57.9%) of the female patients and in four (33.3%) of the male patients. Their earliest appearance was on the fourth day in a male patient who was receiving 10 mg. of dartalan t.d.s. Six of the female patients who were receiving 10 mg. t.d.s., including a pair of identical twins, developed signs within seven days, one within 10 days on this dosage, one within eight days on a dosage of 20 mg. b.d., and one within nine days on a dosage of 20 mg. t.d.s.; one did not develop signs until the 25th day, and one not until the second month of treatment with 10 mg. t.d.s.

In the other three male patients, signs appeared in one case on the sixth day on a dosage of 10 mg. t.d.s., in another during the fifth week on a dosage of 10 mg. b.d. throughout, and in the third on a dosage of 10 mg. t.d.s. for 14 days and 20 mg. t.d.s. for 19 days. The smallest total quantity of dartalan which produced signs of Parkinsonism was 100 mg., which a female patient had received in a dosage of 10 mg. b.d. for five days.

Of the female patients who did not develop signs of Parkinsonism one was receiving 10 mg. b.d., five (including a pair of identical twins suffering from myoclonic epilepsy) were receiving 10 mg. t.d.s., one was receiving 20 mg. t.d.s., and one 30 mg. t.d.s. The last was reported as showing excessive salivation one afternoon, but in the absence of any other conclusive signs of Parkinsonism she was not included in the affected group. Of the male patients who were unaffected, two were receiving 10 mg. b.d., one was receiving 20 mg. b.d., and five were receiving 10 mg. t.d.s.

None of the epileptic patients developed signs of Parkinsonism.

Development of Signs of Parkinsonism.—The earliest sign observed of the development of Parkinsonism was the loss of the associated movements of the arms, which were held semi-flexed at the elbow. Cog-wheel rigidity occurred early and was more marked in the arms than in the legs. Other early signs were the fixed mask-like or anxious facies and monotonous voice, the stooping attitude, and gliding steps. Tremor of the limbs appeared later as pronation and supination movements of the forearm, later developing into pill-rolling tremor of forefinger and thumb. Less frequently occurring signs were oculogyric crises (two females, two males), excessive salivation (one female, one male), and pseudocatatonia (one female). One patient complained early in treatment of pain of a dull aching character in the shoulder girdle and upper limbs. Of particular interest was the development of oculogyric crises in a pair of identical twin female patients with a chronological age of 20 and I.Q.s below 25. Both were receiving 10 mg. of dartalan t.d.s. In one the oculogyric crises appeared on the fifth day of treatment and in the other on the sixth day.

E.E.G. Findings.—It was possible to arrange E.E.G. examinations while signs of Parkinsonism were present in only three cases (two female, one male). In each, low-amplitude slow components were recorded from all areas of the brain. In one of the female cases it was thought that the amplitude, distribution, and wave form of the slow components suggested the possibility of a deep-seated abnormality.

Reversal of Symptoms.—When conclusive signs of Parkinsonism appeared the same dosage of dartalan was continued and treatment with "disipal" (brand of orphenadrine) 50 mg. t.d.s. was started in all but one male who was given tab. bellad. $\frac{1}{4}$ gr. (16 mg.) b.d. In all but three cases the signs began to disappear within five days on this treatment, but in these three cases (two female, one male) it was necessary to increase the dose of disipal to 100 mg. t.d.s. before this occurred.

Discussion

In this small series of cases the incidence of Parkinsonism was much greater and occurred on a much lower and less prolonged dosage of dartalan than in any previously reported series. We consider it possibly significant, however, that, whereas all previous reports

have concerned patients of normal intelligence, all our patients were mentally defective. We suggest that in the genetically determined cases of mental defect, developmental abnormalities of and, in the environmentally determined cases, damage to the basal ganglia, insufficient in itself to produce signs of Parkinsonism, may considerably lower the threshold dosage of dartalan that can cause these signs to appear.

As we have stated, none of these patients had previously shown any signs of Parkinsonism, nor were any of them known to have suffered from encephalitis. It is well known, however, that a clear history of encephalitis in patients developing post-encephalitic Parkinsonism is frequently absent, and it seems probable that it would be absent in our cases if, as we suggest, the resulting damage was insufficient to produce post-encephalitic Parkinsonism of its own accord.

Summary

An account is given of the development of signs of Parkinsonism in 15 of 31 male and female mentally defective patients who were under treatment with dartalan, a phenothiazine derivative, in an attempt to control their behaviour disorders.

Attention is drawn to the occurrence of oculogyric crises in a pair of identical twins.

A possible explanation is suggested for the very much higher incidence of this complication of treatment with dartalan in this series than in any previously reported.

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INCIDENCE OF INTUSSUSCEPTION IN NEWCASTLE CHILDREN

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There are only two published estimates of the incidence of acute intussusception in this country. The first (Spence and Court, 1950) gave an estimated incidence of 3.8 per 1,000 live births in Newcastle upon Tyne in the years 1944 to 1949. The second (MacMahon, 1955) estimated that Birmingham children between 1945 and 1954 had an attack rate of only 1.49 per 1,000 live births. Both studies found evidence of variations in the attack rate from year to year.

It is a common impression that intussusception occurs more often in the North of England than in the Midlands and the South, and that it is more frequent in this country than in North America. The aetiology of intussusception is still unknown, but a difference of

incidence as great as that described above is important enough for this impression to be tested and if possible brought to proof. For this reason it seemed worth while measuring the incidence in Newcastle again to see whether the previous high incidence, compared with Birmingham, was the result of two or three exceptional years or a persistent feature of the local scene.

Method

The method is identical with that used on other occasions (Davison, 1946; Spence and Court, 1950)—the enumeration of all children admitted to all Newcastle hospitals and giving a Newcastle address. The years chosen were 1950 to 1957. Reasons have been given in the papers referred to above why this can be regarded as a quantitative ascertainment for Newcastle. Only cases confirmed by operation (the majority) or by barium enema have been included, and suspected intussusceptions undergoing spontaneous reduction were not counted. When intussusception recurred, only the first illness was included.

This method of enumeration has the further advantage of being formally equivalent to MacMahon's. Like us, he counted all cases with a Birmingham address treated in any Birmingham hospital, included only cases where the diagnosis was confirmed, and excluded "instances of supposed spontaneous reduction without laparotomy."

Findings

In the eight years 1950 to 1957 there were 168 affected children and a steady rate of admission, none of the annual totals departing markedly from the yearly average of 21 (see Table). In the years 1950 to 1957 there were 39,100 live births to Newcastle residents. This may be taken as a sufficiently accurate denominator and gives an incidence of 4.3 per 1,000 live births.

Intussusception in Newcastle Children Between 1950 and 1957

	1950	1951	1952	1953	1954	1955	1956	1957	Total
Children affected	23	20	22	21	22	26	17	17	168

This figure confirms the previous findings in Newcastle and strengthens it, as the estimated incidence between 1944 and 1957—more than 4 per 1,000 live births—is based upon 295 cases (168 presented now, and 127 by Spence and Court, 1950). The estimate in Birmingham, 1.49 per 1,000 live births, was based upon 296 cases (MacMahon, 1955). With these figures there can be no doubt that the incidence in Newcastle is more than twice as high as that reported in Birmingham. This difference is the more remarkable because of the general similarity of the two cities in the occupations of the inhabitants, in the density of population, and in climatic conditions. Both the Newcastle and Birmingham studies depend, however, upon the supposition that not many children with intussusception and belonging to the two cities received treatment outside. Since the north-western border of Birmingham is an arbitrary rather than a natural boundary and merges with an extensive urban area containing a number of hospitals, is it possible that the observed difference could be an artifact?

There is some evidence tending to discount this possibility, derived from the measurement by the same method of the incidence of congenital pyloric stenosis in