THE NIRVANOL TREATMENT OF CHOREA

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Since the introduction of nirvanol in the treatment of chorea by Roeder¹ in 1919, it has been used by many workers, particularly in Germany, and it was introduced into this country in 1929 by Poynton and Schlesinger².

Details of its composition and general use may be found in many papers, notably those of Lesigang³ in German and Poynton and Schlesinger in English, and it is the intention in the present paper to discuss those points in which there may be difference from papers already published, thus to some extent avoiding unnecessary recapitulation.

During 1929 a number of cases were treated at the East London Hospital for Children, and of these eleven have been already published by Whitaker⁴, but, by arrangement with him, they have been included in the present series, as the present writer was able to follow them from the beginning and to see them as out-patients later, thus being able to present a more complete picture.

Nirvanol sickness.—This consists of the following phenomena, which occur despite the cessation of nirvanol administration on the first appearance of symptoms.

RASH. After a time, varying usually from 7 to 12 days after the start of the treatment, a rash appears on the body. It usually occurs first on the elbows and buttocks—possibly as being points of pressure in bed—and spreads over the body. Poynton and Schlesinger have found it starting most often on the chest, abdomen, and elbows, and Lesigang thinks there is no definite order of onset.

It is a macular eruption, morbilliform in type, and usually discrete, though it may become confluent in parts. Scarlatiniform and urticarial rashes have been seen. It may affect any part of the body, including the hands and feet and the mucous membranes, and the face may show a rash or an erythema with circumoral pallor. The extent of the rash varies considerably, being sometimes extremely slight or very well marked. Ashby⁵ finds that the rash varies in

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intensity within a short time, and gives a coloured plate showing the appearance. The deeper colour round the edge, as shown in his plate, was not observed in this series. Following a well marked rash there is sometimes desquamation.

PYREXIA. A febrile reaction is usually also present. This most commonly accompanies the rash, but may occur before or after it. The temperature usually ranges between 100° and 102° , but may vary from normal to 104° . The pulse rate is correspondingly raised, but the respiration rate remains unchanged. This fever lasts from two to four days, after which the temperature drops and remains normal.

OTHER SYMPTOMS. Accompanying the reaction are found, though not invariably, headache, malaise and conjunctivitis, all of which are fairly common, while more rarely there are vomiting, adenitis, œdema of the eyelids, and diplopia. The urine in practically all cases remains unaffected, only one case showing a transient albuminuria of one day.

BLOOD-PICTURE. During the reaction the blood picture is altered. The most obvious fact is that a true eosinophilia frequently occurs, apart from the slight eosinophilia sometimes found in chorea.

The eosinophil count ranges from 1 per cent., or 108 per c.mm., to 21 per cent., or 2,310 per c.mm., and may vary considerably. It comes on at the same time as the rash, but often lasts for some time after this has faded. There is also, though less frequently, a leucopenia, and this may be a point of some importance in considering the risks of the treatment. Poynton and Schlesinger report a relative lymphocytosis, and Lesigang says there is no change. In the present series there was a lymphocytosis in 16 per cent., and some lymphopenia in 44 per cent. of cases. The polymorphonuclear count is sometimes diminished.

In two cases with marked previous eosinophilia, the effect of the reaction was to produce a comparatively low count, which rose again later. There appeared to be no relation between the grade of eosinophilia and the degree of reaction, for one of them had an extremely severe reaction, while the other had a very slight one. In four other cases the eosinophil count was lowered at the time of reaction.

The eosinophil count is of importance, for it may be the only evidence of a reaction to be found, as occurred in six of the cases considered.

The degree of eosinophilia at the time of reaction does not appear to influence either the severity of the reaction or the speed of recovery from chorea, as one case with only 108 eosinophils per c.mm. recovered quickly, while one with 1,230 per c.mm. took a long time.

The red-cell count and hæmoglobin are not particularly affected. Lesigang states that the coagulation-time and blood-platelet count were unaltered. Lichtentritt, Lengsfeld and Silberberg⁶ find that there is a thrombocytopenia.

Effect on chorea.—The effect of nirvanol on the choreic movements is first to produce an increase of chorea, which is most marked during the reaction, and then to cause a diminution, which may be very rapid or slow, but which

usually takes place in about a week (see Fig. 1). At the same time the child becomes drowsy about three days previous to and during the reaction, but becomes alert soon after it ceases. In cases where the mental state is already excitable, the increase of mental stimulation may result in temporary instability, as seen in one of this series, and as reported by Schlesinger⁷. In general the mental condition of the child during the reaction is one like that of slight inebriation.

Secondary reaction.—Two mild secondary reactions were seen in this series. Keller⁸ reports a case in which the second reaction was extremely severe, and the patient nearly died. He believes that this may have been due to an exposure to sunlight, and as other cases have been described in which ultra-violet light caused a reaction, some authors consider it unwise to expose cases to strong sun. This was investigated in this series, and, after careful

FIG. 1. Reproduction of hand-writing of a boy with chorea treated with nirvanol.

previous experiments, two children were exposed to strong sunlight, with the result that one had no reaction, while the other had a faint rash on his neck. The latter was then exposed to ultra-violet light with no effect, and the same was done to five other cases, each being given a maximal dose of carbon-arc light with no effect. One child was sent to a convalescent home after recovery from chorea, where she spent a great deal of time in the sun, but with no reaction.

Single dose reaction.—Several authors have commented on the fact that, after the ordinary reaction has subsided, it is sometimes possible to provoke another reaction by a single dose of nirvanol given at any time up to some months later. In this series it occurred in seven patients, while in five it did not occur. In one case the rash was morbilliform in the first reaction, and scarlatiniform in the second.

Reaction in adults.—The effect of nirvanol on adults is sometimes more alarming. Majerus⁸ reports a case in which hæmorrhagic nephritis and death followed the use of nirvanol ; but, as Lesigang reasonably points out, the patient had a streptococcal empyema of four weeks duration, which may have been largely responsible. Majerus⁹ recommends that it should not be given to cases with arterio-sclerosis. Three cases of toxic poisoning have been reported, and one of suppurative conjunctivitis. Meissner¹⁰ reports two cases in which, after only one dose of nirvanol, amnesia developed, together with the signs of nirvanol sickness. The patients both recovered completely.

Other uses of nirvanol.—Schlesinger has been trying the effect of nirvanol on rheumatic nodules, and states that his results so far have been encouraging, though he does not yet claim a cure. He is under the impression that the accompanying carditis is favourably influenced, but in this series the improvement did not seem to be more than that commensurate with rest in bed.

Lesigang tried nirvanol on cases of pertussis, but the results were poor. He and others have found a substantial diminution in the number of attacks in epilepsy.

Dosage.—The drug is given orally in tablet or powder form, the dose being 0.3 gm. daily. It is recommended by Keller and by Poynton and Schlesinger and others that this dose should not be exceeded, for fear of over-dosage. In this series seven cases had their dose increased after a while to 0.45 gm. daily with no ill-effects, and de Rudder⁴ has given 0.6 gm. daily for a few days. It is given until the reaction appears, or until it is decided that it will not appear.

Huber¹² and Mautner¹³ consider that if there is no rash or pyrexia there will be no improvement, but this is not borne out by the present series. De Rudder, Huber, and others say that, if the rash does not appear by the fourteenth day, it is useless and possibly dangerous to continue. A rash has been seen, however, in this series on the seventeenth day, and one child was treated for 29 days with no apparent ill-effects. The latter was given a total of 8.7 gm., and the highest total dosage given was 9.3 gm.

Dangers.—There are definite risks to be encountered in the use of nirvanol, and it is undoubtedly a drug which should be used with caution, and under careful supervision. All cases under treatment should be confined to bed. It may be considered by some that any drug which entails danger should not be used for treating chorea, which is of itself a disease of no danger and of limited duration. One must, however, consider the carditis which frequently accompanies it, and any drug which holds out hope of cutting short an attack should at least be investigated.

Lichtentritt, Lengsfeld, and Silberberg, working with rabbits, found that the long continued administration by mouth produced a leucopenia, and eventually an aleukæmia with destruction of the bone-marrow, similar to that of X-ray or benzol poisoning. It is essential, therefore, to watch the leucocyte count during treatment, and stop at once if it falls unduly. In this series only one patient developed a marked leucopenia (3,300 per c.mm.), and she showed no untoward symptoms. Two cases were treated for 28 and 29 days respectively, and showed no marked leucopenia.

The effect of sunlight, as already mentioned, was negligible in the cases under consideration, but whether it has any bad influence is a moot point.

The cases mentioned under adult reactions, the case resembling bronchopneumonia (Pilz¹⁴), and the temporary mental upsets recorded by Schlesinger and by Meissner, merit consideration. As no instance of a permanent change in the motor system has yet been reported, it may be assumed that the mental changes are also temporary.

Curschmann¹⁵ recommends that nirvanol should not be given in conjunction with other sedatives, such as bromide.

Results in present series.

Many workers have reported on the use of nirvanol in chorea since its introduction in 1919, and their comments on the whole have been favourable. Practically all those who consider it of value say that it is of most use in well marked cases, and they all emphasize the need for care in its administration.

In a disease which may show such marked changes in its course, and which is more or less self-limiting, it is difficult to establish a definition of cure. Accordingly, it was decided to take a purely arbitrary figure of six weeks, and to call all those completely free of chorea in less than that time 'cures' and those not free 'non-cures.' Six weeks was chosen because there is a belief that chorea is self-limited in that time, though this is not always true. Included in the 'non-cures' are those left with a residual chorea, for it was felt to be difficult to prove that they were truly residual. The steadiness of the grip was usually the final sign of absence of chorea.

In the series of cases treated by the writer, twenty-nine children were given nirvanol. Of these, fifteen were considered good results, five were definitely failures, and nine were markedly improved, though left with a mild degree of chorea.

No controls were used, as it was felt that, with the vast number of cases previously reported with other treatments, and with the comparatively limited space available for the cases here described, it was better to treat all those possible with nirvanol. No other form of treatment was given, other than rest, and septic tonsils and teeth were left untreated till after the course of nirvanol.

A summary of the results is given in the Appendix.

While it is difficult to produce convincing figures, the personal impression formed is that the immediate results are good, especially in the severe cases. It may be said that a treatment which only modifies the chorea without curing it, as happened in nearly 50 per cent. of the cases, is not of much value in a disease where the mild form may have just as damaging an effect on the heart as the severe one. If, however, it is true that there is some degree of organic change in the brain in chorea, it may be that the chorea left after the reaction is due to the continuance of these lesions, and that it only disappears as they heal, a contention difficult to prove either way.

The brand of nirvanol used may perhaps make a difference. The first fourteen cases were treated with that made by Meister Lucius & Bruning;

this became unobtainable, so the remainder were given the v. Heyden brand. The proportion of cures with the former was 10 : 4, and with the latter it was 5 : 10.

Two normal cases, one a convalescent jaundice, the other a case of constipation, were given a course of nirvanol to compare their reaction. Both had an ordinary reaction and recovery, but the former returned to the hospital six months later showing, somewhat disconcertingly, symptoms of chorea, while the latter, shortly after the reaction, had a slight degree of polycythæmia which soon passed off. These are probably only coincidences, but it is as well to record them.

The permanent effects of nirvanol appear disappointing. Of the fifteen cases classified as 'cures,' six have relapsed within five months of the end of the series, while nine have remained free, i.e. 31 per cent. of the total cases remain free. It appears, therefore, that the use of nirvanol as a permanent cure for chorea is unsatisfactory, but, as a treatment for acute chorea, the results are encouraging. From this one is led to believe that nirvanol does not attack the root-cause of chorea, but only affects the central nervous condition, so a cure for chorea has yet to be found.

Summary and conclusions.

1. There are described twenty-nine cases of chorea treated with nirvanol, and no other treatment except rest : also two cases given nirvanol as control.
2. The use, dosage, and dangers of nirvanol are discussed, and an appendix is given, showing comparative figures and results in tabulated form.
3. The heart remains unaffected by the use of the drug.
4. Exposure to sunlight and artificial sunlight produced no reaction, unlike the dangerous results reported by other investigators.
5. The blood count is altered. Eosinophilia is an almost constant phenomenon, and leucopenia is fairly common.
6. Prolonged treatment—up to twenty-nine days—does not necessarily produce marked leucopenia.
7. Of twenty-nine cases treated, fifteen were quite free of chorea in less than six weeks. Of these, six relapsed in six months or less.
8. The results of treatment with nirvanol are considered to be good in a proportion of cases, but it is not a specific cure for chorea, and steps should be taken to deal with any underlying cause if this can be found.

The treatment of these cases was carried out during 1929 at the East London Hospital for Children, to the honorary staff of which I am much indebted for permission to publish the results.

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Appendix.

Total cases treated with nirvanol	..	..	..	29
Cured ..	..	..	..	15
Markedly improved	..	..	..	9
Not improved ..	..	..	..	5

Cases markedly improved :

Case No.	Improved in :	Chorea gone in :
1	3 days	9½ weeks.
3	5 „	9 „
4	7 „	Over 4½ weeks.
13	17 „	6 weeks.
14	10 „	7 „
19	10 „	Over 4½ weeks.
26	10 „	12 weeks.
28	15 „	Over 6 weeks.
29	5 „	„ „

Cases treated with nirvanol from Meister Lucius & Bruning 14

Cured ..	..	..	..	..	10
Not cured	..	..	..	..	4

Cases treated with nirvanol from v. Heyden .. 15

Cured ..	..	..	..	..	5
Not cured	..	..	..	..	10

Cases which reacted without cure .. 12

Cases with no reaction except eosinophilia .. 6

Cases given U-V. light without marked reaction .. 6

Cases given single dose after first course	..	..	..	12
Reacted	..	..	..	7
Did not react	..	..	..	5
Highest dosage given	..	..	..	9.3 gm.
Longest period of treatment	..	..	..	29 days.
Blood picture at time of reaction of all cases :—				
leucocytosis	..	6	lymphocytosis	.. 5
leucopenia	..	17	lymphopenia	.. 14
indefinite	..	9	indefinite	.. 13
Cases with eosinophilia at time of reaction	..	..	24	
,, ,, no ,, ,, ,,	..	..	6	
,, ,, eosinophilia (over 4 per cent.) before treatment	..	..	7	

The degree of eosinophilia had no relation to the severity of the reaction. Previous eosinophilia (2 cases) had no relation to the severity of the reaction.