cardiac pain and enlargement and electrocardiographic changes may persist and be almost identical to the signs of organic heart disease. Thus in chronic anaemia, even when the heart appears normal, ischaemic changes may already have occurred. This, however, seems unlikely to be the case in children.

Summary and Conclusions

A method is described of rapid intravenous transfusions to children. The procedure is regarded as safe in children with clinically normal hearts. It may be particularly indicated where regular transfusions are required during the child's life.

In children with chronic anaemia the blood volume does not fall as in adults. The relative volume increase after transfusion is thus small.

More blood can be given and at a faster rate owing to a reduced blood volume resulting directly from ether anaesthesia, and probably a release of venous vasomotor tone.

The young chronically anaemic heart can withstand fast transfusions better than adult hearts. In selected children transfusions can be given with safety two to four times faster than the rate causing a falling cardiac output in chronically anaemic adults.

The blood volume soon after transfusions is greater than can be accounted for by the volume of blood given; the extra volume may come from the splanchnic or hepatic pools.

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GREAT AURICULAR NEUROTOMY FOR TIC DOULOUREUX

A CONTROLLED CLINICAL TRIAL

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Tic douloureux can at present be cured by any of several methods, all of which depend on interruption of those pain-conducting nerve fibres which pass from the ganglion of the trigeminus to the nucleus of its descending tract. All therefore cause some lifelong trigeminal sensory loss, which in most cases entails lifelong facial dysaesthesiae, and each has at least one of these further drawbacks: a more than negligible death rate, an insufficiently high success rate, and a risk of neuromyolytic keratitis or of lesions of other cranial nerves besides the fifth. For many years there has been a search for a cure—or even a means of prolonged relief—without such drawbacks, the two latest operations, which are both still unproved, being trigeminal “decompression” and compression.

Wyburn-Mason (1953) reported that he had treated about 56 patients suffering from tic douloureux by interruption of the great auricular nerve. Each of them first received an alcohol block of that nerve, and about half were completely relieved, “provided the tongue was not involved. . . . The treatment does not relieve the pain in the tongue.” Regarding the periods of complete relief thus obtained, he wrote: “In cases treated by alcohol block alone the pain may return after 6 to 18 months.” When the pain had returned, or if it had not been initially relieved, he treated it in some cases by a further alcohol block and in others by surgical section of the nerve.

Twenty-five of his patients received this surgical treatment, of whom two, at the time when he wrote, had had some return of pain, one two and a half years and the other three and a half years after nerve section. His follow-up was for as long as five years, which presumably means that five years was the maximum, but he did not state the minimum period.

Here, one might think, is the long-sought remedy without serious drawbacks, except for its failure to relieve pain in the tongue. Of the two ways of interrupting the great auricular nerve, Wyburn-Mason evidently prefers surgical section, and we agree with him, for with only a little more trouble than alcohol injection it produces a more certain interruption and a permanent one. Anything which it fails to do, injection likewise will fail to do. We have therefore subjected great auricular neurotomy to a controlled clinical trial on the lines recommended by Hill (1951).

Present Trial

Definitions.—Throughout the remainder of this paper neurotomy means great auricular neurotomy, and injection means alcohol injection of the trigeminal sensory root. Entry-injection interval means the interval between the date of a given patient's entry into the trial and the date of his injection.

Purpose of Trial.—The trial was primarily designed to answer the following question. Suppose that a patient with tic douloureux (1) after hearing the pros and cons of injec-

tion, decides for himself when to undergo it, and (2) agrees to try neurotomy while awaiting or considering injection. What difference will neurotomy make to the entry-injection interval?

Collection of Patients

Out-patients with "trigeminal neuralgia" were referred to one of us (J.P.) for injection, but only those who fulfilled five diagnostic criteria (Penman, 1950) were accepted as having tic douloureux. To each of them an explanation of injection and its results was given, with emphasis on three points: that permanent cure was probable, that it would mean permanent and uncomfortable numbness of the affected side of the face, and that there would be a small risk of temporary trouble with the eye on that side. Each patient was then asked: "At present, are you sure you want injection, or sure you don't want it, or not sure either way?" Not infrequently he tried to make the doctor, or the relative or friend whom he had with him, decide this question for him, but he was told that he must decide for himself, since no one else could judge how severe his pain was. His answer having been recorded, he was asked: "Suppose you were suitable for another, milder treatment, which is certainly harmless, but which is still unproved and may turn out to be useless; would you be interested in that?" If he answered yes, an explanation of neurotomy was given to him, but it was stressed that this treatment, being unproved, could not be given to everyone who wanted it. If he said that he would be willing to try it he thereby entered the clinical trial. Whether in fact he was to be neurotized or not was determined randomly, by the method described below under the headings "classification" and "treatment groups," and he was immediately told the result of this random determination.

Fifty-one patients were thus collected, and eight more in the following different way. At the beginning of the trial there were eight patients who had previously been given the same explanation of injection, had said that they definitely wanted it, and were already waiting for it. To be brought into strict conformity with the other 51 they would have had to be interviewed again and specifically offered the opportunity of entering the trial; instead, their acceptance of it was assumed, and a date soon after the beginning of the trial was taken as the date of entry for all eight. When their treatment was randomly determined, five proved to be for neurotomy, were offered it in the same terms as the other 51, accepted it, and underwent it; the remaining three were not neurotized.

To this second method of collection it can be objected that any of the three unneurotized patients, if specifically

offered entry into the trial, might perhaps have declined it. However, these eight cases gave results so similar to the rest that we think it justifiable to include them.

During the period of collection one patient was seen who had tic douloureux limited to the tongue, and was therefore excluded. Eighteen patients were included who had pain in the tongue as well as in other structures.

Classification

One of these 59 patients had bilateral tic douloureux which was almost equally severe on the two sides, and each side of his face was regarded as a separate case. In many places, therefore, we shall refer to our 60 cases instead of our 59 patients.

The cases were analysed at entry into the trial with regard to six features which might be held to influence the course of the disease (see Table I, part 1).

Severity of Pain at Time of Entry.—By their responses to the offer of injection the patients divided themselves into three classes, which finally contained the following numbers: class 1, certainly wanting injection (38 patients, 39 cases; class 2A, uncertain (18 patients); class 2B, certainly not wanting injection (3 patients). In randomly allocating treatment by neurotomy we preserved this division into three classes, but for all other purposes we have combined class 2B, since it was so small, with class 2A to make a single class 2.

Sex.—There were 34 women and 25 men.

Age on Date of Entry.—The patients were divided into those below the age of 60 years, who numbered 25, and those aged 60 years or over, who numbered 34.

Side of Face Needing Treatment.—Forty patients needed treatment on the right side, 18 on the left, and 1, already mentioned, on both.

Duration of Tic Douloureux at Time of Entry.—The cases were divided into those of less than four years' duration, which numbered 28, and those of four years' duration or more, which numbered 32.

Previous Attempts at Radical Treatment.—The cases were divided into those in which one or more attempts at injection, trigeminal sensory rhizotomy, or other forms of trigeminal surgery had already been made, which numbered 12, and those in which none had been made, which numbered 48.

In Table I, part 2, the features of patients in more severe pain (class 1) are compared with the features of those in less severe pain (class 2). Even with these small numbers it

TABLE I.—Classification, Treatment Groups, and Results

Features Possibly Influencing Results	Primary Groups	Part 1	Part 2		Part 3		Part 4				Part 5. Results							
		All Cases	Distribution of Other Features in Classes 1 and 2		Treatment Groups		Classes 1 and 2 Subdivided into Treatment Groups				Class 1				Class 2			
							Class 1		Class 2		Neuro-tomized		Unneuro-tomized		Neuro-tomized		Unneuro-tomized	
			Class 1	Class 2	Neuro-tomized	Unneuro-tomized	Neuro-tomized	Unneuro-tomized	Neuro-tomized	Unneuro-tomized	Injected	Not Injected	Injected	Not Injected	Injected	Not Injected	Injected	Not Injected
Severity of pain (see text)	Class 1 ..	39			23	16												
	" 2A ..	18			11	7												
	" 2B ..	3			1	2												
Sex ..	Female ..	34	20	14	19	15	11	9	8	6	10	1	9	0	4	4	2	4
	Male ..	26	19	7	16	10	12	7	4	3	12	0	5	2	3	1	1	2
Age at entry	60 or more ..	35	23	12	20	15	13	10	7	5	13	0	9	1	4	3	2	3
	Under 60 ..	25	16	9	15	10	10	6	5	4	9	1	5	1	3	2	1	3
Side of face	Right ..	41	27	14	23	18	16	11	7	7	15	1	10	1	6	1	2	5
	Left ..	19	12	7	12	7	7	5	5	2	7	0	4	1	1	4	1	1
Duration of illness	4 years or more ..	32	19	13	18	14	10	9	8	5	10	0	8	1	6	2	1	4
	Under 4 years ..	28	20	8	17	11	13	7	4	4	12	1	6	1	1	3	2	2
Previous radical treatment	Not attempted ..	48	31	17	25	23	17	14	8	9	16	1	12	2	4	4	3	6
	Attempted ..	12	8	4	10	2	6	2	4	0	6	0	2	0	3	1	0	0
	Total ..	60	39	21	35	25	23	16	12	9	22	1	14	2	7	5	3	6

is worth noting that of the patients who were sure that they wanted injection, practically one-half were men, but of those who were uncertain or against injection only one-third were men. Also the shorter histories of tic douloureux were associated with a *greater* tendency to want injection. (The men did not tend to have shorter histories than the women.) In other respects the two classes did not differ.

Treatment Groups

Classification of the cases in relation to all the six features listed in Table I leads to 96 subgroups. Though some of these subgroups were bound to remain empty, 96 lists were prepared, each with spaces for ten names. Opposite each space, before the trial began, was written either A, signifying treatment, or C for control, the order of A's and C's on each list being determined by random sampling numbers. As soon as each case had been classified, the patient's name was written in the first vacant space on the appropriate list, and the presence of A or C opposite it determined whether neurotomy should be carried out or not. The resulting distribution of cases is shown in Table I, part 3. The aim of this method of determination of treatment was to obtain neurotized and unneurotized groups that were equivalent in their main features, and it was achieved except as regards previous treatment (and as regards the very small class 2B). Even for classes 1 and 2 separately there was a reasonable equivalence between the neurotized and unneurotized groups (see Table I, part 4). In order simultaneously to achieve equal numbers of neurotized and unneurotized cases, a larger total than 60 would have been needed.

The patient needing bilateral treatment proved to have his right side among the neurotized cases and his left among the unneurotized.

Of the 18 patients with pain in the tongue as well as in other structures, 12 were neurotized and 6 unneurotized.

Neurotomy

As soon as it had been determined that a given patient was to be neurotized, his name was put on a list, and the neurotomies were carried out in the order in which the names had been listed. The names of all patients in class 1 and of some in class 2 had on the day of entry into the trial been put also on a second waiting-list, for admission to hospital and injection. Whenever this second list was short—and it was seldom long—there was a danger that a patient's injection might have to be delayed in order to find time for his neurotomy. To reduce this danger, most neurotomies were carried out within five days of entry, some one day after it, and a few on the day of entry; but, even so, there were some cases in which injection was thus delayed for a short while. Such delays could only weight the results slightly in favour of neurotomy.

Just before each neurotomy we applied pressure, as recommended by Wyburn-Mason, to the great auricular nerve of the affected side through the intact skin. A few patients, all of whom had been having paroxysms of tic douloureux just before this pressure, had them also just after it, but none was relieved of pain by it.

All 35 neurotomies were carried out by one of us (L. S. W.) and nearly all were witnessed throughout by the other. Only local analgesia was used, and Wyburn-Mason's directions were strictly followed. The great auricular nerve was identified where it crossed the posterior border of the sternomastoid muscle, freed from neighbouring structures, and traced as far centrally as possible. In 31 cases the most central portion of the nerve that could be reached was squeezed and tugged with a forceps; 4 of these 31 patients felt nothing, doubtless because of the preliminary infiltration of the operative field with local analgesic; 25 felt painful or other sensations in the ear; two felt them only in the neck; but none felt any sensation in the trigeminal area. (In the remaining four cases of neurotomy we inadvertently did not record whether this stimulation of the nerve was carried out or not.)

A length of at least 1 cm. of the nerve was excised and sent for microscopy, which in each of the 35 cases confirmed that it was a portion of a peripheral nerve. A few patients felt the same sensations during the cutting of the nerve as they had felt during the squeezing and tugging of it, and in the same areas. One patient, when re-examined just before injection, had no sensory loss on the ear; presumably the great auricular nerve was either exceptionally small and had a correspondingly small territory, or else proximally to the site of operation it had already divided into two or more branches, of which only one was found and cut. In all other cases there was permanent analgesia or anaesthesia in the lobe of the ear and in immediately adjacent areas, but in none was there any sensory loss within the trigeminal area.

Thus the great auricular nerve was stimulated in 31 cases and completely cut in either 34 or 35 cases, but no support was found for Wyburn-Mason's view that it must partly innervate the trigeminal area.

Follow-up

Patients whose names were on the waiting-list for injection were told that if by the time they were sent for they no longer wanted it they would be welcome to postpone it. Those whose names were not on the waiting-list were told that whenever they wanted injection they might send word, and their names would at once go on the list. Both these instructions were given whether neurotomy had been carried out or not, but in addition the neurotized patients were told that if they really wanted injection they should not postpone it because of the neurotomy. However, the inclination to wait a little longer and give the neurotomy "time to work" must have been strong in some cases, and it is doubtful whether our instruction entirely counteracted it. One patient to our knowledge was persuaded by his general practitioner to postpone injection for that reason, and others may have been similarly persuaded. This is a second inevitable factor which tended to weight results somewhat in favour of neurotomy, especially in class 2.

Injections were carried out in the order of the waiting-list. So far as was possible, all uninjected patients were followed up every two calendar months from the date of entry, on the first two occasions by interview and thenceforth by letter. On five occasions we had to be content with a letter instead of an interview, and on three with a telephone message instead of either. Twice we lost touch with patients temporarily, but none defaulted entirely, and a few had extra interviews at their own request. The first entry was on August 16, 1954, the last on May 4, 1955, and the follow-up was closed on August 16, 1955.

Results

One criterion of failure or success with the 35 neurotomies is the subsequent need or absence of need for injection, as compared with the same need or absence of it in the 25 unneurotized cases. In injected cases another criterion is the entry-injection interval, and in uninjected cases the period for which each patient was followed up without needing injection.

Injection had to be carried out in 36 of 39 cases, or 92.3%, in class 1, but in only 10 of 21 cases, or 47.6%, in class 2, and all results must therefore be considered separately for these two classes.

In class 1 there were 23 neurotized cases, 22 of which had to be injected, and 16 unneurotized cases, 14 of which had to be injected. In class 2 there were 12 neurotized patients, seven of whom had to be injected, and nine unneurotized patients, three of whom had to be injected. For details see Table I, part 5. The maximum, average, and minimum entry-injection intervals are given in Table II, which shows that in class 1 the average intervals for neurotized and unneurotized cases differed by less than one day. In class 2 the average entry-injection interval was 75 days longer for the neurotized than for

TABLE II.—*Injected Cases: Number of Days Elapsing Between Entry into Trial and Injection*

		Class 1		Class 2	
		Neuro- tomized	Unneuro- tomized	Neuro- tomized	Unneuro- tomized
No. of cases Entry- injection interval (days)	Maximum	22	14	7	3
	Average	85	148	204	25
	Interval	21.4	22.1	93	18
	Minimum	4	0	12	16

the unneurotomized, but here the total of 21 patients, injected and uninjected, was too small for this comparison to be very significant.

Uninjected cases numbered 14. In class 1 they represent one "success" out of a possible 23 for neurotomy and two "successes" out of a possible 16 for doing nothing; in class 2, five "successes" out of a possible 12 for neurotomy and six out of a possible nine for doing nothing. The follow-up periods, for what little they are worth with so few cases, can be compared in Table III; the three

TABLE III.—*Uninjected Cases: Length of Follow-up*

		Class 1		Class 2	
		Neuro- tomized	Unneuro- tomized	Neuro- tomized	Unneuro- tomized
No. of cases Length of follow-up (days)	Individuals	1	2	5	6
	Maximum	250	321	—	—
	Average	—	322	314	271
	Minimum	—	—	189	125

patients in class 1 all happened to enter the trial before any of the 11 in class 2, which is the only reason why they were followed up longer.

The patient needing bilateral treatment said when first interviewed, and again on the day of his right-sided neurotomy, that the left side needed treatment rather more than the right, so that it was for left-sided injection, as we thought, that he was admitted to hospital. He then said, however, that the right-sided pain had become worse than the left, and asked for a right-sided injection, which was given. About three and a half months later he began to have a bout of severe left-sided pain, which continued for two to three weeks and then abated. During that bout he asked for left-sided injection, but changed his mind before it could be given. Thereafter until his latest follow-up, 322 days after entry, his left-sided pain was not severe enough to make him want injection.

In all of those 12 cases in which the pain had both affected the tongue and been treated by neurotomy, it continued not only in the tongue but also in other structures, and in 10 out of the 12 cases injection was carried out.

A few neurotomized patients found the numbness in and round the ear unpleasant, especially when lying in bed with the affected area in contact with a pillow. The 29 neurotomized patients who required injection nearly all said in effect that neurotomy had been worth trying, but had made no difference whatever to their pain.

Comment

Controls apart, it would be hard to praise any treatment for tic douloureux which in 22 out of 23 severe cases left the patient in need of injection within 85 days.

The search for a cure without trigeminal sensory loss must continue, but each proposed new remedy ought, in the very first cases in which it is used, to be subjected to a controlled clinical trial. This precaution is especially necessary in any disease which is so chronic and remittent as tic douloureux. The two features of the present inquiry which we have found most valuable are (1) preliminary classification of the severity of each case by the patient himself, through his response to a standard offer of radical treatment, and (2) assessment of the efficacy of the method

under trial by the patient himself, through his decision when to undergo radical treatment. By these means, and with an adequate supply of patients; reliable results can be obtained within 12 months.

Summary

Between August, 1954, and May, 1955, 23 severe cases of tic douloureux, strictly diagnosed, were treated by great auricular neurotomy, and 16 other severe cases, comparable in all essentials with the first 23, were left untreated. In each of these 39 severe cases the patient when first interviewed had his name put on a waiting-list for trigeminal injection, which he was left free to postpone if his pain had abated enough. In 22 of the 23 neurotomized cases (95.7%) trigeminal injection had to be carried out at most 85 days later, and in 14 of the 16 unneurotomized (87.5%) it had to be carried out at most 148 days later. The average interval between entry into this clinical trial and injection was 21.4 days in the 22 neurotomized and 22.1 days in the 14 unneurotomized cases. One severe neurotomized case and one equally severe unneurotomized case, instructively, were on the right and left sides of a single patient. Twenty-one other patients with milder tic douloureux were similarly divided into 12 neurotomized and 9 unneurotomized and left to decide when they must undergo trigeminal injection, with similar results. Great auricular neurotomy, to judge from this trial, has no effect on tic douloureux.

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HAEMOGLOBIN C DISEASE AND TRAIT REPORT OF A FAMILY IN ENGLAND WITH HAEMOGLOBIN C

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Abnormal, genetically determined haemoglobins are being recognized with increasing frequency as the cause of certain anaemias, generally of the haemolytic type. Their discovery has followed the application of electrophoretic techniques to the study of sickle-cell haemoglobin (S) by Pauling, Itano, Singer, and Wells (1949). The other human haemoglobins so far described are A (adult), C, D, E, F (foetal), G, H, I, and J; and the list is doubtless incomplete. The hereditary haemoglobinopathies occur almost exclusively in people of non-European descent, and principally in negroes.

Haemoglobin C was described by Itano and Neel (1950). Their cases were North American negroes, and the haemoglobin C was in the heterozygous state, with A or S. Homozygous haemoglobin C (haemoglobin C disease) was reported, again in North American negroes,