A STUDY OF THE TREATMENT OF DYSTROPHIA MUSCULORUM PROGRESSIVA WITH AN ANABOLIC STEROID: NOR-ANDROSTENOLONE DECANOATE *

by

K. Pateisky, H. Schinko & H. Haberler

Introduction

Dystrophia musculorum progressiva has been treated at different times variously with vitamins (especially vitamin E), with various types of sugars (particularly inosit) with amino-acids (glycocol, glutamic acid etc.), with enzymes (such as cytochrome C, ATP, and others) and with organ extracts - particularly from the pancreas and the gastro-intestinal tract; in addition such treatment as adrena-line-pilocarpine courses, induction of malaria, colchicine and dietetic therapy (Milborat 1954) have been employed. None of these therapeutic measures has produced satisfactory results. On the other hand one finds a series of publications on the favourable therapeutic effect of treatment with anabolic substances related to testosterone (Hesser et al. 1940, Franceschetti & Mach 1940, Waring et al. 1940, Hoagland et al. 1945, Perlstein & Guttermann 1950, Quinn & Worcester 1951, Bekeny et al. 1955a, 1955b, 1957a, 1957b, 1959, 1960, Taselaar 1955, Horanyi et al. 1957, de Toni 1959, Stur 1960, Kaeser 1961).

This therapeutic approach is based on the proven ability of these substances to stimulate nitrogen retention, presumably with a resultant build-up of body protein, the muscle protein benefitting most markedly. Animal experiments have proved that testosterone leads to the incorporation of glycogen in the skeletal musculature, and that in cardiac muscle the protein build-up is accompanied by an increase in contractile protein (Blasius et al. 1956). Further animal experiments have shown that the norsteroids, like the testosterone esters, led to a build-up of the contractile elements of cardiac muscle, of actomyosin and of contractin (Blasius et al. 1957).

* nor-androstenolone decanoate = nandrolone decanoate = Deca-Durabolin, synthesized by N.V. Organon, Oss, Holland.
One problem in the treatment of progressive muscular dystrophy with sufficiently high doses of anabolic steroids is the occurrence of virilisation as a side effect. Norandrostenolone decanoate, with which the present therapeutic study was carried out, distinguished itself in animal experiments from the other anabolic steroids so far employed in the treatment of this condition, in that it proved to possess a more favourable ratio between anabolic and androgenic effect (de Visser & Overbeek 1960).

The only previous report on a clinical trial of norandrostenolone decanoate (NAD) in cases of progressive muscular dystrophy is a short publication on the treatment of two children (Huber 1961). The intention of the authors in undertaking the present study was to throw some light upon the actual mechanism of NAD's action in dystrophia musculorum progressiva, by the joint consideration of clinical and laboratory data.

**Experimental approach**

12 cases exhibiting various forms of progressive muscular dystrophy (see Fig. 2) were submitted to intensive treatment with nor-androstenolone decanoate. In order to obtain a sufficiently marked clinical anabolic effect it was decided to carry out treatment with high dosages over a prolonged period. Adults received an intramuscular injection of 50 mg nor-androstenolone decanoate twice weekly over a period of twelve weeks. The four child patients, all more than seven years of age, received twice weekly an intramuscular injection of 25 mg nor-androstenolone decanoate, also for a period of twelve weeks. The treatment was carried out during a sixteen week stay in hospital, two weeks being devoted to pre-treatment observation, twelve to treatment, and two more to follow-up observations. During the hospital stay a series of clinical and laboratory investigations were carried out at intervals of one or two weeks, and again after some nine months.

Alongside the relevant neurological examination we recorded especially the following clinical data: body weight, circumference of the extremities, subjective symptoms, objective signs; a series of specialized investigations of mobility and muscular strength, the selection of tests being made according to the severity of each individual case.

In every case a film was made before and after treatment showing the execution of such simple movements as walking, stair-climbing, lifting of the arms, sitting down and standing up again, lying down, and getting up from a supine position. Electromyograms were made before, during and after treatment. At the subsequent check-up examinations every two weeks, special attention was devoted during both questioning and physical examination to the subject of androgenic side effects (pubic hair, body hair, disturbance of the menstrual cycle,
changes of the voice, jaundice), and to palpation of the liver. The following blood tests were carried out at frequent intervals: red and white cell blood counts, haematocrit, blood sedimentation rate, liver function tests (bilirubin retention, Weltmann's test, thymol turbidity test), serum cholesterol level, determinations of various electrolytes (sodium, chloride, potassium), serum protein, serum albumin, serum electrophoresis, as also serum aldolase activity and serum transaminase activity (SGOT). The urine was repeatedly analysed for creatine, creatinine, 17-ketosteroids and ketogenic steroids.

The data obtained from the biochemical tests was processed simply. The average values obtained for a given substance in each patient were first traced graphically against the period of time during which observation and treatment took place. The chart was so designed that figures falling within the normal range of variation could be discarded and only readings showing an abnormally high or abnormally low level need be entered on the chart. The illustrations accompanying the present study and showing the rise and fall in the average deviations from the norm of the substances analysed are based on the composite readings of 12 patients in all.

Quite apart from the twelve patients with progressive muscular dystrophy we also studied three patients with dystrophia myotonica (Steinert); in addition, after observing a transient increase in the signs of myotony in these latter patients, we treated experimentally with nor-androstenolone decanoate 2 patients with Thomsen's myotonia congenita, using the same therapeutic plan.

Findings

At the end of the twelve-week period of treatment with nor-androstenolone decanoate 7 of the 12 cases of dystrophia musculorum progressiva had improved and 5 cases showed no change; in no case was any worsening of the condition recorded (Fig. 1). In deciding upon the degree of clinical improvement only objective criteria were employed.

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Summary of clinical improvement during a 12-week trial of intensive therapy with nor-androstenolone decanoate in cases of progressive muscular dystrophy.
Subjective impressions of "improvement" were not taken into account. We based our conclusions upon the patients' capabilities as regards power and movement, these physical capabilities being measured by appropriately graded tests, and by a comparison of the films made of the performance of various tasks before and after treatment. Of the 7 cases showing improvement at the end of the period of treatment, 2 showed good improvement, 2 further cases showed moderate improvement and in the 3 other cases a slight but undeniable amelioration could be detected. When the patients had a follow-up examination 9 months after the end of treatment, 3 cases still showed improvement as compared with their condition previous to treatment with nor-androstenolone decanoate, two of these showing very good improvement and the other moderate improvement. The remaining 9 cases showed at this final investigation no change as compared with their capacity for strength and movement before treatment (Fig. 1). In the following table (Fig. 2) the clinical data relevant to the treatment are classified according to age of onset, age at the time when treatment began, duration of the disease, sex, family history, groups of muscles affected, and degree of severity of the case.

The clinical course, as judged by strength and movement, showed in most cases a consistently alternating pattern during treatment. Most patients actually began to notice slight improvement within two weeks of the first injection. Between the second and the fourth week, on the other hand most patients reported a defi-

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<td>male</td>
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Fig. 2
Summary of clinical improvement during a 12-week trial of intensive therapy with nor-androstenolone decanoate, classified according to the various clinical criteria of dystrophia musculorum progressiva.

*Explanation of symbols:*

- O = unchanged
- + = slight but definite improvement
- ++ = moderate improvement
- +++ = good improvement

Heredity + = family history of dystrophia musculorum progressiva

Heredity - = No family history of dystrophia musculorum progressiva

p-f = pelvico-femoral type

s-f-h = scapulo-facio-humeral type
nite tendency to fatigue, together with a painful increase in tonus both in the proximal muscle groups of the extremities and in the calf muscles.

Sometimes during this same period a fine irregular tremor was present. (Those patients with myotonia congenita reported during this same period a strong increase in the myotonic symptoms, while the patients with myotonia dystrophica noticed a definite increase in their myotonic complaints). A few patients with progressive muscular dystrophy confirmed, in answer to leading questions, that they had difficulty in initiating muscular movements. The feeling of muscular tension could be reduced by exercise. As regards the clinical course after the fourth week of treatment, those cases exhibiting clinical improvement experienced a slowly progressive increase in strength, capacity for movement and general physical capabilities, which continued up to the end of the treatment. Those patients who were confined to bed, and the cases with pre-existing pes equinovarus or a tendency thereto showed at this stage an increase in pes equinovarus, irrespective of whether their condition generally was improving or unchanged, so that it proved necessary to abandon our original intention of allowing no massage or exercises during the period of treatment. By appropriate massage and exercises the tendency to pes equinovarus was minimized. All our cases showed during treatment an increase in body weight varying from more than 2 kg to 7 kg. We could not find any clear relationship between the degree of clinical improvement and this increase in body weight. The circumference of the extremities, measured at the middle of the upper arm and at the point of maximum circumference of the calf showed an increase varying from 0.5 cm to 2 cm. This led us to carry out muscle palpation, which showed an increase in the musculature.

The increase in the circumference of the extremities was more marked in those cases with atrophic than in those with pseudohypertrophic muscles. In cases showing a tendency to pes equinovarus, the increase in muscle bulk of the calf muscles was more clearly in evidence than the increase of the corresponding antagonists.

Investigations of the blood cell counts, blood sugar, blood sedimentation rate, haematocrit, blood electrolytes (chloride, sodium and potassium), liver function tests (bilirubin retention, Weltmann's test, thymol turbidity test) and blood cholesterol showed no characteristically abnormal findings during treatment. The regular examination of serum protein showed that in one of the 12 cases of dystrophia musculorum progressiva the protein level before treatment was low when compared with the normal range of variation.

Between the second and fourth week five cases in all showed serum protein levels lower than normal (Fig. 3). The regular determination of the serum albumin, expressed as a percentage of total serum protein, showed that between the second and fourth weeks of treatment 7 of the 12 patients with dystrophia mus-
Diagrammatic presentation of the serum proteins during observation and treatment of 12 cases of dystrophia musculorum progressiva undergoing 12 weeks of intensive treatment with nor-androstenolone decanoate. Of the 12 cases treated 5 show abnormally low readings during the whole course of observation (= "minimum levels") from the 2nd to the 4th week of therapy.

Explanation of symbols: The upper row of figures indicate weeks of treatment. Each dot above this row of figures indicates an intramuscular injection of nor-androstenolone decanoate (50 mg in adults, 25 mg in children). The area to the left of the figures represents the preliminary period of observation (two weeks). The field to the right of the figures represents the post-therapeutic period of observation, this also covering two weeks. The field on the extreme right represents the follow-up examination, 9 months after the end of treatment. Each heavy dot indicates the lowest reading of serum protein registered during the course of observation in one patient (= "minimum level"). All other marks are abnormal readings which were not "minimum levels". Normal readings are not marked in the diagram. In one case were serum protein levels higher than normal.

culorum progressiva had albumin levels below the normal range of variation. (Fig. 4). (As regards the 5 myotonic patients, 4 of these showed minimal levels of serum albumin between the second and fourth weeks of treatment, these levels falling equally below the range of normal variation). The serum globulins, as examined by electrophoresis, showed changes in different globulin fractions which will be discussed in a separate paper.

The serum aldolase activity was raised in 10 of the 12 patients with progressive muscular dystrophy before treatment began. During treatment, many cases showed a further rise in aldolase activity. This was especially marked in four patients who had been afflicted with the disease since early childhood. These four cases comprised two children, one older boy and one adult. Similarly, in these four patients the serum transaminase activity was raised before treatment began and showed a further increase during treatment, whilst in seven of the other eight
Diagrammatic presentation of the serum albumin readings (in percentages of total protein) obtained during the period of treatment and observation of 12 cases of progressive muscular dystrophy receiving a 12-week course of intensive treatment with nor-androstenolone decanoate. In 7 of the 12 cases treated the abnormal minimal readings were found to lie between the second and the fourth week of treatment.

Explanation of symbols: as in Fig. 3. The heavy dots represent the lowest readings registered for serum albumin. The small dots represent other abnormal serum albumin readings. All not marked readings lay within normal limits.

Diagrammatic representation of the range of urinary creatine readings obtained during the periods of treatment and observation of 12 cases of progressive muscular dystrophy receiving a 12-week course of intensive therapy with nor-androstenolone decanoate. In 7 of the 12 cases the creatine level was abnormally elevated before treatment began. During treatment a reduction in creatine levels occurred, so that by the end of the trial only three cases proved to have a persistently abnormally high creatine level. At the follow-up examination, 9 months after the end of treatment, 5 cases showed elevated creatinine levels.

Explanation of symbols: as in Fig. 3. The dots represent the abnormally high creatine levels with respect to sex. All not marked readings lay within normal limits.
patients the serum transaminase activity remained within normal limits. Of the four above-mentioned cases, three failed to react to treatment, but the fourth showed a slight but definite improvement.

The urinary creatine levels were in 7 of the 12 cases of dystrophia musculorum progressiva above the upper limits of normal at the beginning of treatment, if one takes the sex of the patients into consideration. In the course of treatment, four of these 7 patients showed a diminution of normal levels, so that when treatment ended only 3 patients continued to show abnormally high urinary creatine levels.

Nine months later, however, at the follow-up examination, 5 cases showed abnormally high levels of creatine in the urine. (Fig. 5). No firm correlation could be detected between the cases which showed a decline in urinary creatine during therapy and the cases exhibiting a positive clinical response to treatment. The urinary creatinine expressed as mg per kg bodyweight per 24 hours was in all our cases low at the beginning of our study and did not subsequently show any characteristic variations.

Nor did the urinary excretion of 17-ketosteroids and ketogenic steroids show any characteristic changes during treatment. We did not carry out an examination of the response of 17-ketosteroids and ketogenic steroids to ACTH administration during our investigations.

The electromyographic investigations which were carried out on our patients before, during and after treatment showed at the commencement of therapy the picture characteristic of progressive muscular dystrophy, i.e. a myogenic lesion without any decrease in the number of activated units on voluntary effort. The "pseudomyotonic showers" which have been described on several occasions in the literature as being produced by the mechanical stimulation of pseudohypertrophic muscle in cases of progressive muscular dystrophy could only occasionally be produced in our patients. The electromyographic investigations which were carried out routinely between the second and fourth weeks of intensive therapy with nor-androstenolone decanoate revealed "pseudomyotonic showers" in most of the cases examined not only in the pseudohypertrophic musculature but also in the atrophic musculature; these showers occurred not only following mechanical stimulation but also spontaneously, sometimes continuing for long periods. (Fig. 6). In the myotonic cases, the patients with dystrophia myotonica (Steinert) and even more markedly in the cases of myotonia congenita (Thomsen), the increase in myotonic symptoms during the same period of treatment was accompanied by a very considerable increase in myotonic showers.

In turning to the question of side effects we must point out that in view of the possibility of virilisation we had pre-selected our patients inasmuch as only
Electromyographic recordings taken in cases of clinically manifest progressive muscular dystrophy, from the atrophic musculature of the upper arm between the second and fourth week of intensive treatment with nor-androstenolone decanoate. The leads were derived by Adrian-Bronk needles inserted into the M. Biceps hum. In descending order:

Curve 1: Shower of discharges produced by movement of the needles.
Curve 2: Spontaneous and repetitive shower.
Curve 3: Shower provoked by voluntary movement.
Curve 4: Shower accompanying tremor.

Explanation of the symbols: the horizontal line above the upper curve represents one second (scale holds good for all the four curves).
The vertical line at the right of each curve represents 500 µV.

4 of the 12 were females, whilst all the 4 children selected for the study were males. Of these 12 patients, side effects were seen in 4 cases (2 women and 2 children). In the children there was an increase in pubic hair, whilst towards the end of the treatment masturbation was observed. In both of the affected women, the voice became coarser and deeper during the fourth week of treatment, whilst in the fifth or six weeks menstrual bleeding ceased. For these reasons, the treatment of both these cases was stopped after 6 and 8 weeks respectively. Two months after the termination of therapy with nor-androstenolone decanoate menstruation had once again become regular. At follow-up, nine months after the end of the treatment, both women still showed voice changes.

Discussion

In considering the extent to which improvement occurred in these cases it must be borne in mind that the selection of cases for study was made with a
strong negative bias, i.e. we purposely tended to choose patients in whom the condition was of long duration. In 6 of the 12 patients there was a history going back from 6 to 15 years, in 5 cases a history of more than 15 years, and only in one case was the condition of less than 5 years duration. When one bears this essential limitation in mind, the therapeutic results must be considered favourable when compared with other forms of treatment. The most favourable results were seen (see Fig. 2) in cases beginning at the juvenile stage, in male patients, and in cases showing the mildest dystrophic phenomena. On the other hand, of the four cases with what might reasonably be considered a poor prognosis, (disease beginning in early childhood, serum aldolase and serum transaminase activity raised previous to treatment and rising still further when therapy began) one case nevertheless showed a moderate degree of improvement.

In the majority of cases, a series of abnormal findings were registered between the second and fourth week of intensive treatment with NAD. The great majority of patients with dystrophia musculorum progressiva complained during this period of fatigue and raised tonus of the skeletal muscles which could be relieved by exercise.

At the same period of intensive treatment with nor-androstenolone decanoate the patients with myotonia dystrophica experienced a marked - and the patients with myotonia congenita, a severe - increase in their myotonic symptoms. At this same period the electromyographic investigations showed a great increase in myotonic showers in the myotonic patients and the occurrence of repetitive myotonic showers in the majority of the patients with dystrophia musculorum progressiva: the latter was to be observed not only in the pseudohypertrophic muscle but also in the atrophic musculature, and it occurred both following mechanical stimulation and spontaneously. Again, during this same period of treatment the serum protein fell in some patients below the normal minimum to a point lower than that registered at any other time during the period of observation, whilst the albumin levels showed in an even larger number of patients a decline at this time to levels below the normal minimum. These findings are capable of the following explanation: The intensive anabolic therapy with norandrosteno¬

The fall in serum albumin during intensive anabolic therapy may well be due to the migration of albumin or parts of it into the muscular tissue. Our findings would thus suggest that as a result of intensive anabolic therapy accompanied by raised membrane permeability a build-up of protein in the muscle-fibres occurs.
As regards the lessons to be learnt for the future treatment of dystrophia musculorum progressiva with nor-androstenolone decanoate, we can conclude from the above study that the same therapeutical effect can be obtained with a lower initial dosage and that one should continue at this lower level of dosage for maintenance therapy. For the initial period of treatment we would propose that adults receive 25 mg nor-androstenolone decanoate twice weekly, continuing for eight weeks, and subsequently as a maintenance therapy 50 mg nor-androstenolone decanoate every three weeks by injection. To prevent the occurrence of contractures during treatment it is advisable to combine physiotherapy - such as exercises and massage - with the drug therapy.

Whether one can expect a more favourable outcome with a combination of drug treatments is a question which the above study has not attempted to answer. The treatment of the infantile form of progressive muscular dystrophy is not entirely hopeless with nor-androstenolone decanoate, but for this indication the question of dosage will require special study.

Summary

12 cases of progressive muscular dystrophy were intensively treated with nor-androstenolone decanoate for a period of 12 weeks. Following this treatment, 7 cases showed definite clinical improvement; in 2 of these cases the improvement was good, in two other cases it was moderate, and in 3 other cases it was slight but quite definite. In three cases the improvement was still in evidence 9 months after treatment ended. Bearing in mind the deliberate preponderance of old-established cases among the patients selected these therapeutic results must be regarded as favourable. In spite of the high level of dosage only four patients showed virilizing side effects. From the clinical and laboratory data obtained at all stages of the trial certain conclusions have been drawn as to the mechanism of action of nor-androstenolone decanoate in dystrophia musculorum progressiva. In conclusion, dosage rules are suggested for the further treatment of dystrophia musculorum progressiva.

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**DISCUSSION**

*Tausk:* Thank you, Dr Pateisky. These two papers are now open for discussion.

*Kopera:* I think that we can only underestimate and not overestimate the results of the last four papers. It is true that muscular dystrophy is not a frequent disease but still we have to bear in mind that it is a disease characterized by a very bad prognosis and for which practically no effective therapy is known. The same holds true for diabetic retinopathy, although the great difference is that diabetic retinopathy is much more frequent. At present in America there are about 29,000 people blind from diabetic retinopathy and furthermore, most diabeticians are of the opinion that diabetic retinopathy will occur in practically all patients suffering from diabetes mellitus if only they live long enough. I think the results with Deca-Durabolin in both diseases are very encouraging indeed. One other comment I should like to make is in connection with a remark of Dr Prader. It was known that androgens had an effect on muscular dystrophy but as far as I am aware no significant effect at all was ever reported or observed with androgens in diabetic retinopathy. Now with Deca-Durabolin we have such a substance which really has an effect on diabetic retinopathy. It apparently is not an effect caused by the androgenic property of the substance but rather by another, most probably the anabolic property of the substance. So this should also be regarded as an indication of a dissociation of the two actions.

*De Toni:* Dr Kopera’s remarks have reminded me that there is another field in which these anabolic steroids have been used with very good results - the evolutive myopia of infancy. We treated some 25 cases between 1959 and 1960 (Ann. Oftal. (1960) 238). I think this is a very important new indication for hormone therapy and now in collaboration with the ophthalmological department of our pediatric
clinic in Genoa, we are treating every child who has some small signs of this infantile myopia, which can have a very bad prognosis, with these steroids. We have obtained very good results.

_Tausk:_ Which steroid did you employ?

_De Toni:_ Durabolin in very low doses. In children between 3 - 12 years we used a dose of 5 - 10 mg per week for a maximum of 2 to 3 months. Is there any one here who has had similar experience of this disease?

_Dardenne:_ I have never heard of this. Your results are very astonishing. I must ask: is this myopia progressiva or simple myopia? In myopia progressiva it is theoretically understandable because here the sclera of the bulbus is very weak and so the bulbus is growing and growing in size. It could be that the underdeveloped wall of the bulbus gets stronger with Durabolin treatment.

_De Toni:_ I am not an ophthalmologist but I think it is this disease. The children are always very asthenic but after treatment for 2 or 3 months they are completely changed and the ophthalmological condition is also improved.

_Dardenne:_ I am a little surprised that you have also found an objective improvement in the fundus.

_Bierich:_ I should be very glad to know what you think about the mechanisms involved in the improvement of muscular dystrophy following treatment.

_De Toni:_ It is very difficult to answer that as we know very little about the origin of the muscular dystrophy. Maybe this improvement is due to an increased protein synthesis but it is very difficult to explain as long as we believe that the origin of muscular dystrophy is an enzymatic defect. However, when the muscle fibres are not completely destroyed, I think it is possible to have some sort of improvement.

_Bierich:_ It is well-known of course that creatine is stored in the muscles as creatine phosphate. This storage is largely dependent on carbohydrate metabolism. Is it not possible that the same mechanism we heard of in a previous paper, namely that there is an improvement in carbohydrate metabolism apart from insulin production, would facilitate a larger storage of creatine?

_De Toni:_ Maybe.

_Prader:_ I would like to make a few remarks about the progressive infantile pseudo-hypertrophic form of muscular dystrophy (Duchenne). From Dr Pateisky’s paper I gained the impression that anabolic steroids are useful in those forms of muscular dystrophy with a later onset but not in the progressive infantile pseudo-hypertrophic form. In our own experience the small doses of anabolic steroids, which I recommended yesterday, have no effect in the infantile form. However, Prof. de Toni, who used much higher doses, has seen some good results. Did I understand this correctly?

_De Toni:_ We had some cases which started at a very young age; the first one began in the first month of life. The treatment began in the 9th year of life when we ad-
administered 30 mg Durabolin per day. The improvement was not so striking but we have to remember that the treatment began more than 8 years after the appearance of the first symptoms. I think the length of time between onset of the disease and onset of the treatment is a very important point.

Prader: I am wondering whether we have the right to recommend such treatment for young children, where we have to give huge doses to get only a very questionable clinical effect. We may do more harm than good to these patients. These children all die before the age of 20 and there is hardly any hope of prolonging their life with this treatment. I feel strongly that some clinical centres should collect more data about the treatment of the infantile form of muscular dystrophy with high doses of anabolic steroids before it can be recommended. Apparently this is different in older patients with other forms of muscular dystrophy where anabolic steroids seem to be at the moment the best available treatment.

Kopera: Is it necessary to use such a high dosage as Prof. de Toni recommends? Would it not be possible to reduce the dose?

Prof. de Toni: We tried to reduce this dosage but the creatinuria increased. Fortunately the signs of virilization in these patients disappeared almost completely after treatment. The only one that remained was the change of voice but this also disappeared slowly after some months.

Prof. Tausk: I am afraid I shall have to terminate this discussion now. I think with respect to what has just been said, it is obvious to everybody that we are dealing here with an extremely severe condition of which we still understand very little. Pioneers work is being done but I have very great respect for the sense of responsibility of the clinician who is cautious in using such a treatment before he has more information on it. I think all that can be done is to encourage further investigations by pediatricians and clinicians who share the serious sense of responsibility demonstrated here.

I should like to thank you all for your contributions. The meeting is over.